SIXTH EDITION

Small Animal Internal Medicine



RICHARD W. NELSON C. GUILLERMO COUTO

Kristen M. Couto
Eleanor C. Hawkins
Susan M. Taylor
Jodi L. Westropp
Autumn P. Davidson
Michael R Lappin
Jessica L. Ward
Michael D. Willard
Ann-Marie Della Maggiore
Jennifer A. Larsen
Wendy A. Ware
Andrew Woolcock
Stephen P. DiBartola
J. Catharine R. Scott-Moncrieff
Penny J. Watson

ELSEVIER

Contents

PART ONE CARDIOVASCULAR SYSTEM DISORDERS, 1

Wendy A. Ware and Jessica L. Ward

1 Clinical Manifestations of Cardiac Disease, 1
2 Diagnostic Tests for the Cardiovascular System, 13
3 Management of Heart Failure, 55
4 Cardiac Arrhythmias and Antiarrhythmic Therapy, 77
5 Congenital Cardiac Disease, 100
6 Acquired Valvular and Endocardial Disease, 119
7 Myocardial Diseases of the Dog, 141
8 Myocardial Diseases of the Cat, 158
9 Pericardial Disease and Cardiac Tumors, 174
10 Pulmonary Hypertension and Heartworm Disease, 190
11 Systemic Arterial Hypertension, 211
12 Thromboembolic Disease, 221

PART TWO RESPIRATORY SYSTEM DISORDERS, 240

Eleanor C. Hawkins

13 Clinical Manifestations of Nasal Disease, 240
14 Diagnostic Tests for the Nasal Cavity and Paranasal Sinuses, 247
15 Disorders of the Nasal Cavity, 257
16 Clinical Manifestations of Laryngeal and Pharyngeal Disease, 271
17 Diagnostic Tests for the Larynx and Pharynx, 273
18 Disorders of the Larynx and Pharynx, 277
19 Clinical Manifestations of Lower Respiratory Tract Disorders, 282
20 Diagnostic Tests for the Lower Respiratory Tract, 287
21 Disorders of the Trachea and Bronchi, 321
22 Disorders of the Pulmonary Parenchyma and Vasculature, 340
23 Clinical Manifestations and Diagnostic Tests of Pleural Cavity and Mediastinal Disease, 360
24 Disorders of the Pleural Cavity and Mediastinum, 371
25 Emergency Management of Respiratory Distress, 379

PART THREE DIGESTIVE SYSTEM DISORDERS, 389

Michael D. Willard

26 Clinical Manifestations of Gastrointestinal Disorders, 389
27 Diagnostic Tests for the Alimentary Tract, 412
28 General Therapeutic Principles, 432
29 Disorders of the Oral Cavity, Pharynx, and Esophagus, 447
30 Disorders of the Stomach, 462
31 Disorders of the Intestinal Tract, 474
32 Disorders of the Peritoneum, 510

PART FOUR HEPATOBILIARY AND EXOCRINE PANCREATIC DISORDERS, 518

Penny J. Watson

33 Clinical Manifestations of Hepatobiliary and Pancreatic Disease, 518
34 Diagnostic Tests for the Hepatobiliary and Pancreatic System, 531
35 Hepatobiliary Diseases in the Cat, 561
36 Hepatobiliary Diseases in the Dog, 584
37 The Exocrine Pancreas, 620

PART FIVE URINARY TRACT DISORDERS, 649

Stephen P. DiBartola and Jodi L. Westropp

38 Clinical Manifestations of Urinary Disorders, 649
39 Diagnostic Tests for the Urinary System, 658
40 Glomerular Disease, 675
41 Acute Kidney Injury and Chronic Kidney Disease, 686
42 Bacterial Cystitis, Pyelonephritis, and Prostatitis in the Dog and Cat, 704
43 Canine and Feline Urolithiasis, 712
44 Obstructive and Nonobstructive Feline Idiopathic Cystitis, 724
45 Disorders of Micturition, 730

PART SIX ENDOCRINE DISORDERS, 740

Richard W. Nelson and Ann-Marie Della Maggiore

46 Disorders of the Hypothalamus and Pituitary Gland, 740
47 Disorders of the Parathyroid Gland, 758
48 Disorders of the Thyroid Gland, 767
49 Disorders of the Endocrine Pancreas, 806
50 Disorders of the Adrenal Gland, 857

PART SEVEN METABOLIC AND ELECTROLYTE DISORDERS, 898

Jennifer A. Larsen and Ann-Marie Della Maggiore

51 Weight Loss and Obesity, 898
52 Hyperlipidemia, 908
53 Electrolyte Imbalances, 915

PART EIGHT REPRODUCTIVE SYSTEM DISORDERS, 935

Autumn P. Davidson

54 The Practice of Theriogenology, 935
55 Clinical Conditions of the Bitch and Queen, 953
56 Clinical Conditions of the Dog and Tom, 990
57 Neonatology and Pediatrics, 1007

PART NINE NERVOUS SYSTEM AND NEUROMUSCULAR DISORDERS, 1037

Susan M. Taylor

58 Lesion Localization and the Neurologic Examination, 1037
59 Diagnostic Tests for Nervous System and Neuromuscular Disorders, 1063
60 Intracranial Disorders, 1074
61 Loss of Vision and Pupillary Abnormalities, 1084
62 Seizures and Other Paroxysmal Events, 1093
63 Head Tilt, 1109
64 Encephalitis, Myelitis, and Meningitis, 1117
65 Disorders of the Spinal Cord, 1130
66 Disorders of Peripheral Nerves and the Neuromuscular Junction, 1157
67 Disorders of Muscle, 1174

PART TEN JOINT DISORDERS, 1187

Susan M. Taylor

68 Clinical Manifestations of and Diagnostic Tests for Joint Disorders, 1187
69 Disorders of the Joints, 1195

PART ELEVEN IMMUNE-MEDIATED DISORDERS, 1211

Andrew Woolcock and J. Catharine R. Scott-Moncrieff

70 Pathogenesis of Immune-Mediated Disorders, 1211
71 Diagnostic Testing for Immune-Mediated Disease, 1215
72 Treatment of Primary Immune-Mediated Diseases, 1220
73 Common Immune-Mediated Diseases, 1231

PART TWELVE ONCOLOGY, 1257

C. Guillermo Couto

74 Cytology, 1257
75 Principles of Cancer Treatment, 1265
76 Practical Chemotherapy, 1269
77 Complications of Cancer Chemotherapy, 1276
78 Approach to the Patient With a Mass, 1288
79 Lymphoma, 1294
80 Leukemias, 1311
81 Selected Neoplasms in Dogs and Cats, 1322

PART THIRTEEN HEMATOLOGY, 1340

C. Guillermo Couto

82 Anemia, 1340
83 Clinical Pathology in Greyhounds and Other Sighthounds, 1360
84 Erythrocytosis, 1368
85 Leukopenia and Leukocytosis, 1371
86 Combined Cytopenias and Leukoerythroblastosis, 1381
87 Disorders of Hemostasis, 1387
88 Lymphadenopathy and Splenomegaly, 1407
89 Hyperproteinemia, 1420
90 Fever of Undetermined Origin, 1423

PART FOURTEEN INFECTIOUS DISEASES, 1427

Michael R. Lappin

91 Laboratory Diagnosis of Infectious Diseases, 1427
92 Practical Antimicrobial Chemotherapy, 1436
93 Prevention of Infectious Diseases, 1448
94 Polysystemic Bacterial Diseases, 1457
95 Polysystemic Rickettsial Diseases, 1469
96 Polysystemic Viral Diseases, 1485
97 Polysystemic Mycotic Infections, 1502
98 Polysystemic Protozoal Infections, 1514
99 Zoonoses, 1532

Expert CONSULT Built with inkling | E books

Any screen. Any time. Anywhere.



Activate the eBook version
of this title at no additional charge.

Expert Consult eBooks give you the power to browse and find content, view enhanced images, share notes and highlights—both online and offline.

Unlock your eBook today.

1. Visit **expertconsult.inkling.com/redeem**
2. Scratch off your code
3. Type code into "Enter Code" box
4. Click "Redeem"
5. Log in or Sign up
6. Go to "My Library"

It's that easy!

Scan this QR code to redeem your eBook through your mobile device:

Place Peel Off Sticker Here

For technical assistance:
email expertconsult.help@elsevier.com
call 1-800-401-9962 (inside the US)
call +1-314-447-8200 (outside the US)

ELSEVIER

Use of the current edition of the electronic version of this book (eBook) is subject to the terms of the nontransferable, limited license granted on expertconsult.inkling.com. Access to the eBook is limited to the first individual who redeems the PIN, located on the inside cover of this book, at expertconsult.inkling.com and may not be transferred to another party by resale, lending, or other means.

2015v1.0

SMALL ANIMAL INTERNAL MEDICINE

This page intentionally left blank



SMALL ANIMAL INTERNAL MEDICINE

SIXTH EDITION

Richard W. Nelson, DVM, DACVIM
Professor Emeritus
Department of Medicine and Epidemiology
School of Veterinary Medicine
University of California, Davis
Davis, California

C. Guillermo Couto, DVM, DACVIM
President
Couto Veterinary Consultants
Hilliard, Ohio

ELSEVIER

Elsevier
3251 Riverport Lane
St. Louis, Missouri 63043

SMALL ANIMAL INTERNAL MEDICINE, EDITION 6 ISBN: 978-0-323-57014-5
Copyright © 2020, 2014, 2009, 2003, 1998, 1992 by Mosby, Inc., an imprint of Elsevier Inc.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

Notice

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

International Standard Book Number 978-0-323-57014-5

Senior Content Strategist: Jennifer Catando
Senior Content Development Manager: Ellen Wurm-Cutter
Content Development Specialist: Erin Garner
Publishing Services Manager: Julie Eddy
Senior Project Manager: Richard Barber
Designer: Brian Salisbury

Printed in Canada

Last digit is the print number: 9 8 7 6 5 4 3 2 1

ELSEVIER Book Aid International Working together to grow libraries in developing countries
www.elsevier.com • www.bookaid.org

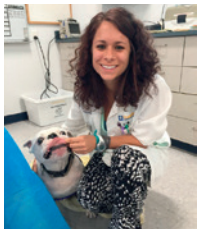
Section Editors



Richard W. Nelson, DVM, DACVIM (Internal Medicine), Professor Emeritus, Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis. Dr. Nelson received his DVM degree from the University of Minnesota in 1979; he completed a small animal internship at Washington State University in 1980 and a medicine residency at the University of California, Davis in 1982; he then joined the small animal medicine faculty at Purdue University. In 1989 he joined the small animal medicine faculty at UC Davis. Dr. Nelson's interests lie in clinical endocrinology, with a focus on the endocrine pancreas, thyroid gland, and adrenal gland. Dr. Nelson has authored numerous scientific publications and book chapters; has co-authored two textbooks, *Canine and Feline Endocrinology and Reproduction* with Dr. Ed Feldman and *Small Animal Internal Medicine* with Dr. C. Guillermo Couto; and has lectured extensively nationally and internationally. He served as an associate editor for the *Journal of Veterinary Internal Medicine* and served as a reviewer for several veterinary journals. Dr. Nelson is a co-founder and member of the Society for Comparative Endocrinology and has served as Chair of the Department of Medicine and Epidemiology and as Director of the Small Animal Clinic at UC Davis. He has received the Norden Distinguished Teaching Award at Purdue University and at UC Davis, the BSAVA Bourgelat Award, and the ACVIM Robert W. Kirk Award for Professional Excellence.



C. Guillermo Couto, DVM, Dipl. ACVIM (Internal Medicine and Oncology) graduated from Buenos Aires University, Argentina in 1976. He spent 5 years as a private practice small animal practitioner, and then completed a clinical oncology residency at the University of California-Davis. He is co-author of the textbook, *Small Animal Internal Medicine,* with Dr. Richard W. Nelson, and he has more than 350 peer-reviewed articles and book chapters in the areas of oncology, hematology, and Greyhound medicine. Dr. Couto served as editor-in-chief of the *Journal of Veterinary Internal Medicine,* and received numerous teaching and service awards while at the university. After 30 years in academia, he is now providing consultation and educational services through Couto Veterinary Consultants, Hilliard, Ohio.



Kristen M. Couto, DVM, DACVIM (ONCOLOGY)
Vista Veterinary Specialists by Ethos Veterinary Health, Sacramento, California. Dr. Couto received her BS in Biology at The Ohio State University in 2009 and went on to receive her DVM degree at Ohio State in 2013. She completed a Small Animal Medicine and Surgery internship at North Carolina State University in 2014, and a Medical Oncology residency at the University of California, Davis in 2017. Her clinical interests include multi-modal management of oncology patients, as well as fostering the human-animal bond, especially through all aspects of a cancer diagnosis and treatment. She routinely provides continuing education for local veterinary medical associations in California on various oncology topics.



Autumn P. Davidson, DVM, MS, DACVIM Clinical Professor, Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis. Dr. Davidson obtained her BS and MS at the University of California, Berkeley, with an emphasis in wildlife ecology and management. Dr. Davidson is a graduate of the School of Veterinary Medicine, University of California, Davis. She completed an internship in small animal medicine and surgery at Texas A&M University and a residency in small animal internal medicine at the University of California, Davis. She became board certified in internal medicine in 1992. Dr. Davidson specializes in small animal reproduction, pediatrics, and infectious disease. From 1998 to 2003, Dr. Davidson served as the Director of the San Rafael veterinary clinic at Guide Dogs for the Blind, Inc., overseeing the health care of 1000 puppies whelped annually, as well as a breeding colony of 350 and approximately 400 dogs in training. Dr. Davidson served on the board of directors for the Society for Theriogenology from 1996 to 1999, and the Institute for Genetic Disease Control from 1990 to 2002. Dr. Davidson consults with the Smithsonian Institution National Zoological Park in Washington, D.C., concerning theriogenology and internal medicine. She has authored numerous scientific publications and book chapters, and is a well-known international speaker on the topics of small animal theriogenology and infectious disease. She has traveled the world working with cheetahs, ring-tailed lemurs, and giant pandas in the field. Dr. Davidson was the 2003 recipient of the Hill's Animal Welfare and Humane Ethics Award, which recognizes an individual who has advanced animal welfare through extraordinary service or by furthering humane principles, education, and understanding.



Ann-Marie Della Maggiore, DVM, DACVIM (Internal Medicine) Mar-Queen Pet Emergency and Specialty Group, Roseville, California.

Dr. Della Maggiore earned her DVM degree from the University of California, Davis in 2008. She completed an internship in small animal medicine and surgery at Veterinary Medical and Surgical Group in Ventura, California. She then completed her small animal internal medicine residency at UC Davis and became ACVIM board certified in Internal Medicine. Following her residency, she took a clinical faculty position at UC Davis. In 2014 she transitioned to Assistant Professor of Clinical Internal Medicine in the Department of Medicine and Epidemiology. Her research and clinical interests are in small animal endocrinology. Dr. Della Maggiore now practices internal medicine at Mar-Queen Pet Emergency and Specialty Group in Roseville, California, a private referral practice. She has lectured both internationally and nationally in canine and feline internal medicine and primarily endocrinology.



Stephen P. DiBartola, DVM, DACVIM (Internal Medicine), Emeritus Professor of Medicine, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio. Dr. DiBartola received his DVM degree from the University of California, Davis in 1976. He completed an internship in small animal medicine and surgery at Cornell University in Ithaca, New York, in June 1977 and a residency in small animal medicine at The Ohio State University College of Veterinary Medicine from July 1977 to July 1979. He served as Assistant Professor of Medicine at the College of Veterinary Medicine, University of Illinois from July 1979 until August 1981. In August 1981, he returned to the Department of Veterinary Clinical Sciences at The Ohio State University as Assistant Professor of Medicine. He was promoted to Associate Professor in 1985 and to Professor in 1990. He received the Norden Distinguished Teaching Award in 1988 and the Zoetis Distinguished Teaching Award in 2014. His textbook *Fluid Therapy in Small Animal Practice* is in its fourth edition (2012). Dr. DiBartola currently serves as co-editor-in-chief for the *Journal of Veterinary Internal Medicine*. His clinical areas of interest include diseases of the kidney and fluid, acid-base, and electrolyte disturbances.



Eleanor C. Hawkins, DVM, Dipl. ACVIM (Internal Medicine), Professor, Department of Clinical Sciences and Director, Clinical Study Core, Comparative Medicine Institute North Carolina State University College of Veterinary Medicine. Dr. Hawkins has served as President and as Chair of the American College of Veterinary Internal Medicine (ACVIM), and as President of the Specialty of Small Animal Internal Medicine (ACVIM). She has been a board member of the Comparative Respiratory Society. She has been an invited lecturer in the United States, Europe, South America, and Japan. Dr. Hawkins is the author of many refereed publications and scientific proceedings. She has been a contributor or the respiratory editor for numerous well-known veterinary texts. Dr. Hawkins was the 2014 recipient of the ACVIM Distinguished Service Award. Her areas of research include canine chronic bronchitis, pulmonary function testing, and bronchoalveolar lavage as a diagnostic tool.



Michael R. Lappin, DVM, PhD, Dipl. ACVIM (Internal Medicine), is the Kenneth W. Smith Professor of Small Animal Clinical Veterinary Medicine at the College of Veterinary Medicine and Biomedical Sciences at Colorado State University and Director of the Center for Companion Animal Studies. After earning his DVM at Oklahoma State University in 1981, he completed a small animal internal medicine residency and earned his doctorate in parasitology at the University of Georgia. Dr. Lappin has studied feline infectious diseases and has authored more than 250 research papers and book chapters. Dr. Lappin is past associate editor for the *Journal of Veterinary Internal Medicine* and serves on the editorial board of *Journal of Feline Medicine and Surgery*. Dr. Lappin has received the Norden Distinguished Teaching Award, the Winn Feline Foundation Excellence in Feline Research Award, and the ESFM International Award for Outstanding Contribution to Feline Medicine.



Jennifer A. Larsen, DVM, MS, PHD, DACVN, Chief of Service, Nutrition Support Service, Veterinary Medicine Teaching Hospital, Professor of Clinical Nutrition, Department of Molecular Biosciences, School of Veterinary Medicine, UC Davis. Dr. Larsen holds bachelor's and master's degrees in Animal Science and a DVM from UC Davis. She completed one year in local private practice before accomplishing a clinical nutrition residency at UC Davis. In 2007, Dr. Larsen attained Diplomate status from the American College of Veterinary Nutrition and completed a PhD in Nutritional Biology in 2008. In her current role, Dr. Larsen provides clinical nutritional consulting through the Nutrition Support Service at the UC Davis Veterinary Medical Teaching Hospital. She also mentors residents and students, and she teaches in the veterinary curriculum as well as for the Graduate Group of Nutritional Biology.



J. Catharine R. Scott-Moncrieff, MA, VetMB, MS, DACVIM (SA), DECVIM (CA), Professor, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University. Dr. Scott-Moncrieff graduated from the University of Cambridge in 1985 and completed an internship in small animal medicine and surgery at the University of Saskatchewan and a residency in internal medicine at Purdue University. In 1989, she joined the faculty of Purdue University, where she is currently Professor of small animal internal medicine and Head of the Department of Veterinary Clinical Sciences. Her clinical and research interests include immune-mediated hematologic disorders and clinical endocrinology. She is the author of numerous manuscripts and book chapters and has lectured extensively nationally and internationally.



Susan M. Taylor, DVM, DACVIM (Internal Medicine), Professor of Small Animal Medicine, Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan. Dr. Taylor has received several awards for teaching excellence, including the Norden Distinguished Teaching Award. She has authored numerous refereed manuscripts and book chapters and one textbook (*Small Animal Clinical Techniques*, Elsevier 2016). She is also the co-creator of a web-based program for teaching clinical neurology and neuroanatomy (WCVM NeuroVet). Dr. Taylor has presented research and continuing education lectures throughout Canada, the United States, and abroad. Clinical, academic, and research interests include neurology, neuromuscular disease, clinical immunology, and infectious disease. Dr. Taylor has an active research program investigating medical and neurologic disorders affecting canine athletes, particularly the inherited syndromes of dynamin-associated exercise-induced collapse in Labrador Retrievers (d-EIC) and Border Collie collapse.



Jessica L. Ward, DVM, DACVIM (Cardiology), Assistant Professor, Department of Veterinary Clinical Sciences, Iowa State University. Dr. Ward obtained her DVM degree from North Carolina State University in 2011. After a small animal rotating internship at The Ohio State University, she returned to NC State to complete her residency training in Cardiology. Dr. Ward joined the faculty at Iowa State University in 2015, where she teaches clinical cardiology and recently received the college's Award for Early Achievement in Teaching. She has authored a number of manuscripts and scientific proceedings, and she has given invited lectures in the United States and China. Her research interests include point-of-care ultrasound, the cardiovascular effects of steroids, and the scholarship of teaching and learning.



Wendy A. Ware, DVM, MS, DACVIM (Cardiology), Professor, Departments of Veterinary Clinical Sciences and Biomedical Sciences, Iowa State University. Dr. Ware earned her DVM degree and completed her residency training at The Ohio State University. At Iowa State, she taught clinical cardiology and cardiovascular physiology, and she served as clinical cardiologist in the ISU Lloyd Veterinary Medical Center for many years. Dr. Ware authored the highly illustrated clinical textbook *Cardiovascular Disease in Small Animal Medicine* and is preparing an expanded second edition (*Cardiovascular Disease in Companion Animal Medicine*). She also has written and edited the case-based *Self-Assessment Color Review of Small Animal Cardiopulmonary Medicine* (2012, Manson Publishing), as well as numerous journal articles and more than 60 book chapters. Dr. Ware has been an invited speaker at many continuing education programs. Her other professional activities have included service as President and Chairman of the Board of Regents of the American College of Veterinary Internal Medicine, associate editor for Cardiology for the *Journal of Veterinary Internal Medicine*, and reviewer for several veterinary scientific journals.



Penny J. Watson, MA, Vet.MD, CertVR, DSAM, DECVIM, MRCVS, Senior Lecturer in Small Animal Medicine, Queen's Veterinary School Hospital, University of Cambridge, United Kingdom. Dr. Watson received her veterinary degree from the University of Cambridge. She spent four years in private veterinary practice in the United Kingdom before returning to Cambridge Veterinary School, where she now helps run the small animal internal medicine teaching hospital. She is both a member of the Royal College of Veterinary Surgeons and a European recognized specialist in small animal internal medicine. Dr. Watson was on the examination board of the European College of Veterinary Internal Medicine (ECVIM) for five years, two as Chair. Her clinical and research interests are focused on gastroenterology, hepatology, pancreatic disease, and comparative metabolism. She gained a doctorate for studies of canine chronic pancreatitis in 2009 and continues to research, lecture, and publish widely on aspects of canine and feline pancreatic and liver disease.



Jodi L. Westropp, DVM, PhD, DACVIM (Internal Medicine), Associate Professor, School of Veterinary Medicine, University of California, Davis. Dr. Westropp received her DVM degree, as well as her residency training in internal medicine, and PhD from The Ohio State University prior to joining the faculty at UC Davis in 2003. Her clinical and research interests include feline idiopathic cystitis, urinary tract infections, urinary incontinence, and urolithiasis. She is the author of numerous manuscripts and book chapters and has lectured extensively nationally and internationally. She is also the director of the G.V. Ling Urinary Stone Analysis Laboratory at UC Davis.



Michael D. Willard, DVM, MS, DACVIM (Internal Medicine), Senior Professor, Department of Veterinary Small Animal Medicine and Surgery, Texas A&M University. Dr. Willard is an internationally recognized veterinary gastroenterologist and endoscopist. He has received the National SCAVMA Teaching Award for clinical teaching and the National Teaching Award. A past President of the Comparative Gastroenterology Society and past Secretary of the specialty of Internal Medicine, his main interests are clinical gastroenterology and endoscopy (flexible and rigid). Dr. Willard has published more than 85 journal articles and 140 book chapters on these topics and has given more than 3600 hours of invited lectures on these subjects around the world. Dr. Willard is an associate editor for *Journal of Veterinary Internal Medicine*.



Andrew Woolcock, DVM, DACVIM (Internal Medicine), Assistant Professor, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Purdue University. Dr. Woolcock graduated from Michigan State University in 2011; he completed an internship in small animal medicine and surgery at North Carolina State University and a residency in small animal internal medicine at the University of Georgia. Dr. Woolcock joined the faculty of Purdue University in 2015, where he is currently Assistant Professor of small animal internal medicine. His clinical and research interests include immune-mediated hematologic disorders and oxidative stress in inflammatory disease states.

This page intentionally left blank

We dedicate this book to Kay and Graciela. This project would not have been possible without their continued understanding, encouragement, and patience. I (Guillermo) also dedicate this book to Jason and Kristen, who in following my path have made me the proudest dad. Having co-authored the oncology section with Kristen is one of the highlights of my career.

This page intentionally left blank

Preface

In the sixth edition of *Small Animal Internal Medicine*, we have retained our original goal of creating a practical text with a strong clinical slant that is useful for both practitioners and students. We have continued to limit authorship, with each author selected for her or his clinical expertise in their field, to ensure consistency within each section and allowing differences to be expressed when topics overlap between sections of the book; this illustrates that frequently different approaches get us to the same destination: a diagnosis. We have continued to focus on the clinically relevant aspects of the most common problems in internal medicine, presenting information in a concise, understandable, and logical format. Extensive use of tables, algorithms, cross-referencing within and among sections and a comprehensive index help make *Small Animal Internal Medicine* a quick, easy-to-use reference textbook.

ORGANIZATION

As before, the book contains 14 sections organized by organ systems (e.g., cardiology, respiratory) or when multiple systems are involved, by discipline (e.g., oncology, infectious diseases, immune-mediated disorders). Each section, when possible, begins with a chapter on clinical signs and differential diagnoses and is followed by chapters on indications, techniques, and interpretation of diagnostic tests; general therapeutic principles; specific diseases; and finally a table listing recommended drug dosages for drugs commonly used to treat disorders within the appropriate organ system or discipline. Each section is supported extensively by tables, photographs, schematic illustrations, videos, and algorithms, which address clinical presentations, differential diagnoses, diagnostic approaches, and treatment recommendations. Selected references and recommended readings are provided under the heading "Suggested Readings" at the end of each chapter. In addition, specific studies are cited in the text by author name and year of publication and are included in the Suggested Readings.

KEY FEATURES OF THE SIXTH EDITION

We have retained all of the features that were popular in the first five editions and have significantly updated and expanded the new sixth edition. Features in the sixth edition include:

- Thoroughly revised and updated content, with expanded coverage of hundreds of topics throughout the text
- The expertise of several new authors
- The addition of a new chapter on neonatology in the reproduction section of the book
- The addition of short video clips of physical examination, diagnostic, and treatment techniques
- The creation of a bank of multiple-choice questions to test student understanding of material contained in the book
- Extensive cross-referencing to other chapters and discussions, providing a helpful roadmap and reducing redundancy within the book
- Hundreds of functionally color-coded summary tables and boxes to draw the reader's eye to quickly accessible information such as:


Etiology


Differential Diagnoses


Drugs (appearing within chapters)


Drug formularies (appearing at the end of sections)


Treatment


General Information (e.g., formulas, clinical pathology values, manufacturer information, bred predispositions)

Finally, we are grateful to the many practitioners, faculty, and students worldwide who provided constructive comments on the first five editions, thereby making it possible to design an even stronger sixth edition. We believe the expanded content, features, and visual presentation will be positively received and will continue to make this book a valuable, user-friendly resource for all readers.

Richard W. Nelson
C. Guillermo Couto

This page intentionally left blank

Acknowledgments

We would like to extend our sincerest thanks to Wendy, Eleanor, Mike, Penny, Sean, Sue, Michael, Catharine, Jodi, and Autumn for their continued dedication and hard work to this project; to Kristen, Ann-Marie, Jennifer, Jessica, Michael, and Andrew for their willingness to become involved in this project; and to Jennifer Catando, Rich Barber, and many others at Elsevier for their commitment and latitude in developing this text.

This page intentionally left blank

Contents

PART ONE CARDIOVASCULAR SYSTEM DISORDERS, 1

Wendy A. Ware and Jessica L. Ward

1 Clinical Manifestations of Cardiac Disease, 1
Signs of Heart Disease, **1**
Signs of Heart Failure, **1**
Cardiovascular Examination, **3**

2 Diagnostic Tests for the Cardiovascular System, 13
Cardiac Biochemical Markers, **13**
Cardiac Radiography, **14**
Echocardiography, **18**
Electrocardiography, **34**
Other Techniques, **52**

3 Management of Heart Failure, 55
Overview of Heart Failure, **55**
Preclinical Cardiac Disease, **60**
Treatment for Acute Congestive Heart Failure, **61**
Management of Chronic Heart Failure, **66**

4 Cardiac Arrhythmias and Antiarrhythmic Therapy, 77
General Considerations, **77**
Diagnosis and Management of Common Arrhythmias, **78**
Antiarrhythmic Agents, **88**

5 Congenital Cardiac Disease, 100
General Considerations, **100**
Extracardiac Arteriovenous Shunt, **101**
Ventricular Outflow Obstruction, **105**
Intracardiac Shunt, **109**
Atrioventricular Valve Malformation, **112**
Cardiac Anomalies Causing Cyanosis, **113**
Other Cardiovascular Anomalies, **116**

6 Acquired Valvular and Endocardial Disease, 119
Degenerative Atrioventricular Valve Disease, **119**
Diagnosis, **122**
Preclinical (Stage B) CVMD, **126**
CHF Onset in CMVD (Stage C), **128**
Common Complications, **129**
Infective Endocarditis, **132**

7 Myocardial Diseases of the Dog, 141
Dilated Cardiomyopathy, **141**
Arrhythmogenic Right Ventricular Cardiomyopathy, **148**
Secondary Myocardial Disease, **150**
Hypertrophic Cardiomyopathy, **152**
Myocarditis, **153**

8 Myocardial Diseases of the Cat, 158
Hypertrophic Cardiomyopathy, **158**
Secondary Myocardial Hypertrophy, **167**
Restrictive Cardiomyopathy, **168**
Dilated Cardiomyopathy, **169**
Other Myocardial Diseases, **171**

9 Pericardial Disease and Cardiac Tumors, 174
Congenital Pericardial Disorders, **174**
Pericardial Effusion, **176**
Constrictive Pericardial Disease, **184**
Cardiac Tumors, **185**

10 Pulmonary Hypertension and Heartworm Disease, 190
Pulmonary Hypertension, **190**
Heartworm Disease, **193**
Heartworm Disease in Dogs, **194**
Heartworm Disease in Cats, **203**
Angiostrongylosis, **207**

11 Systemic Arterial Hypertension, 211
General Considerations, **211**

12 Thromboembolic Disease, 221
General Considerations, **221**
Pulmonary Thromboembolism, **224**
Systemic Arterial Thromboembolism in Cats, **224**
Systemic Arterial Thrombosis in Dogs, **230**
Venous Thrombosis, **233**

PART TWO RESPIRATORY SYSTEM DISORDERS, 240

Eleanor C. Hawkins

13 Clinical Manifestations of Nasal Disease, 240
General Considerations, **240**
Nasal Discharge, **240**
Sneezing, **244**
Stertor, **245**
Facial Deformity, **245**

14 Diagnostic Tests for the Nasal Cavity and Paranasal Sinuses, 247
Nasal Imaging, **247**
Rhinoscopy, **250**
Frontal Sinus Exploration, **252**
Nasal Biopsy: Indications and Techniques, **253**
Nasal Cultures: Sample Collection and Interpretation, **255**

15 Disorders of the Nasal Cavity, 257
Feline Upper Respiratory Infection, **257**
Bacterial Rhinitis, **259**
Nasal Mycoses, **260**
Nasal Parasites, **263**
Feline Nasopharyngeal Polyps, **264**
Canine Nasal Polyps, **264**
Nasal Tumors, **265**
Allergic Rhinitis, **266**
Idiopathic Rhinitis, **266**
16 Clinical Manifestations of Laryngeal and Pharyngeal Disease, 271
Clinical Signs, **271**
Differential Diagnoses for Laryngeal Signs in Dogs and Cats, **272**
Differential Diagnoses for Pharyngeal Signs in Dogs and Cats, **272**
17 Diagnostic Tests for the Larynx and Pharynx, 273
Radiography, **273**
Ultrasonography, **273**
Fluoroscopy, **273**
Computed Tomography and Magnetic Resonance Imaging, **273**
Laryngoscopy and Pharyngoscopy, **273**
18 Disorders of the Larynx and Pharynx, 277
Laryngeal Paralysis, **277**
Brachycephalic Airway Syndrome, **279**
Obstructive Laryngitis, **280**
Laryngeal Neoplasia, **281**
19 Clinical Manifestations of Lower Respiratory Tract Disorders, 282
Clinical Signs, **282**
Diagnostic Approach to Dogs and Cats With Lower Respiratory Tract Disease, **284**
20 Diagnostic Tests for the Lower Respiratory Tract, 287
Thoracic Radiography, **287**
Ultrasonography, **295**
Computed Tomography and Magnetic Resonance Imaging, **295**
Nuclear Imaging, **296**
Parasitology, **296**
Serology, **298**
Urine Antigen Tests, **298**
Polymerase Chain Reaction Tests, **298**
Tracheal Wash, **298**
Nonbronchoscopic Bronchoalveolar Lavage, **305**
Transthoracic Lung Aspiration and Biopsy, **310**
Bronchoscopy, **312**
Thoracotomy or Thoracoscopy With Lung Biopsy, **312**
Blood Gas Analysis, **313**
Pulse Oximetry, **318**
21 Disorders of the Trachea and Bronchi, 321
General Considerations, **321**
Canine Infectious Respiratory Disease Complex, Including Canine Influenza, **321**
Canine Chronic Bronchitis, **324**
Feline Bronchitis (Idiopathic), **328**
Tracheobronchomalacia (Collapsing Trachea), **333**
Allergic Bronchitis, **337**
Oslerus Osleri, **337**
22 Disorders of the Pulmonary Parenchyma and Vasculature, 340
Viral Pneumonias, **340**
Toxoplasmosis, **343**
Fungal Pneumonia, **344**
Pulmonary Parasites, **344**
Aspiration Pneumonia, **346**
Eosinophilic Lung Disease (Eosinophilic Bronchopneumopathy), **348**
Idiopathic Interstitial Pneumonias, **349**
Pulmonary Neoplasia, **352**
Pulmonary Hypertension, **353**
Pulmonary Thromboembolism (PTE), **354**
Pulmonary Edema, **356**
23 Clinical Manifestations and Diagnostic Tests of Pleural Cavity and Mediastinal Disease, 360
Clinical Signs, **360**
General Diagnostic Approach, **360**
Diagnostic Approach for Pleural Effusions Based on Fluid Cytology, **361**
Diagnostic Tests for the Pleural Cavity and Mediastinum, **364**
Chest Tubes: Indications and Placement, **367**
24 Disorders of the Pleural Cavity and Mediastinum, 371
Pyothorax, **371**
Chylothorax, **374**
Neoplastic Effusion, **375**
Pneumothorax, **376**
Mediastinal Masses, **377**
Pneumomediastinum, **378**
25 Emergency Management of Respiratory Distress, 379
General Considerations, **379**
Emergency Management Based on Localization, **379**
Oxygen Supplementation and Ventilation, **383**

PART THREE DIGESTIVE SYSTEM DISORDERS, 389
Michael D. Willard

26 Clinical Manifestations of Gastrointestinal Disorders, 389
Dysphagia, Halitosis, and Drooling, **389**
Distinguishing Regurgitation From Vomiting From Expectoration, **391**
Regurgitation, **392**
Vomiting, **394**
Hematemesis, **397**
Diarrhea, **398**
Hematochezia, **402**

Melena, 402
Tenesmus, 403
Constipation, 404
Fecal Incontinence, 405
Weight Loss, 405
Anorexia/Hyporexia, 407
Abdominal Effusion, 407
Acute Abdomen, 407
Abdominal Pain, 408
Abdominal Distention or Enlargement, 408

27 Diagnostic Tests for the Alimentary Tract, 412
Physical Examination, 412
Routine Laboratory Evaluation, 412
Fecal Parasitic Evaluation, 413
Fecal Digestion Tests, 413
Bacterial Fecal Culture, 414
ELISA, IFA, and PCR Fecal Analyses, 414
Cytologic Evaluation of Feces, 415
Electron Microscopy, 415
Radiography of the Alimentary Tract, 415
Ultrasonography of the Alimentary Tract, 415
Imaging of the Oral Cavity, Pharynx, and Esophagus, 416
Imaging of the Stomach and Small Intestine, 419
Peritoneal Fluid Analysis, 423
Digestion and Absorption Tests, 423
Serum Concentrations of Vitamins, 423
Endoscopy, 424
Biopsy Techniques and Submission, 429

28 General Therapeutic Principles, 432
Fluid Therapy, 432
Dietary Management, 434
Antiemetics, 437
Antacid Drugs, 438
Gastric and Cytoprotective Drugs, 439
Intestinal "Protectants", 440
Digestive Enzyme Supplementation, 440
Motility Modifiers, 440
Antiinflammatory and Antisecretory Drugs, 441
Antibacterial Drugs, 442
Probiotics/Prebiotics, 443
Fecal Transplantation, 443
Anthelmintic Drugs, 443
Enemas, Laxatives, and Cathartics, 443

29 Disorders of the Oral Cavity, Pharynx, and Esophagus, 447
Masses, Proliferations, and Inflammation of the Oropharynx, 447
Dysphagias, 451
Esophageal Weakness/Megaesophagus, 452
Esophageal Obstruction, 456

30 Disorders of the Stomach, 462
Gastritis, 462
Gastric Outflow Obstruction/Gastric Stasis, 465
Gastrointestinal Ulceration/Erosion, 470
Infiltrative Gastric Diseases, 471

31 Disorders of the Intestinal Tract, 474
Acute Diarrhea, 474
Infectious Diarrhea, 476
Bacterial Diseases: Common Themes, 480
Alimentary Tract Parasites, 485
Maldigestive Disease, 491
Non–Protein-Losing Malabsorptive Diseases, 491
Relation of Small Intestinal Dietary-Responsive Diarrhea and Antibiotic-Responsive Enteropathy, 492
Small Intestinal "Inflammatory Bowel Disease" (Chronic Enteropathy), 493
Protein-Losing Enteropathy, 495
Intestinal Obstruction, 498
Miscellaneous Intestinal Diseases, 502
Neoplasms of the Small Intestine, 502
Neoplasms of the Large Intestine, 503
Diseases of the Perineal Area and Anus, 504
Perianal Neoplasms, 506
Constipation, 506

32 Disorders of the Peritoneum, 510
Inflammatory Diseases, 510
Hemoabdomen, 513
Miscellaneous Peritoneal Disorders, 513

PART FOUR HEPATOBILIARY AND EXOCRINE PANCREATIC DISORDERS, 518

Penny J. Watson

33 Clinical Manifestations of Hepatobiliary and Pancreatic Disease, 518
General Considerations, 518
Gastrointestinal Signs, 518
Abdominal Pain, 519
Polyuria and Polydipsia, 519
Hepatic Encephalopathy, 522
Change in Liver Size, 524
Jaundice, Bilirubinuria, and Change in Fecal Color, 525
Coagulopathies, 527
Protein-Calorie Malnutrition, 529

34 Diagnostic Tests for the Hepatobiliary and Pancreatic System, 531
Diagnostic Approach, 531
Diagnostic Imaging, 545
Biopsy and Cytology, 553

35 Hepatobiliary Diseases in the Cat, 561
General Considerations, 561
Hepatic Lipidosis, 561
Biliary Tract Disease, 567
Extrahepatic Bile Duct Obstruction, 573
Ductal Plate Abnormalities, 574
Hepatic Amyloidosis, 575
Feline Copper Storage Disease, 576
Neoplasia, 576
Congenital Portosystemic Shunts, 577

Hepatobiliary Infections, 579
Toxic Hepatopathy, 580
Hepatobiliary Manifestations of Systemic Disease, 582
36 Hepatobiliary Diseases in the Dog, 584
General Considerations, 584
Chronic Hepatitis, 584
Acute Hepatitis, 598
Biliary Tract Disorders, 599
Congenital Vascular Disorders, 603
Focal Hepatic Lesions, 612
Hepatocutaneous Syndrome and Superficial Necrolytic Dermatitis, 615
Secondary Hepatopathies, 616
37 The Exocrine Pancreas, 620
General Considerations, 620
Pancreatitis, 620
Exocrine Pancreatic Insufficiency, 636
Exocrine Pancreatic Neoplasia, 641
Pancreatic Abscesses, Cysts, and Pseudocysts, 641

PART FIVE URINARY TRACT DISORDERS, 649

Stephen P. DiBartola and Jodi L. Westropp

38 Clinical Manifestations of Urinary Disorders, 649
Clinical Approach, 649
Presenting Problems, 650
39 Diagnostic Tests for the Urinary System, 658
Glomerular Function, 658
Tubular Function, 662
Urinalysis, 664
Microbiology, 670
Diagnostic Imaging, 671
Urodynamic Testing, 672
Urethrocystoscopy, 672
Renal Biopsy, 672
40 Glomerular Disease, 675
Normal Structure, 675
Pathogenesis, 676
Mechanisms of Immune Injury, 677
Progression, 677
Histopathologic Lesions of Glomerulonephritis, 678
Amyloidosis, 679
Clinical Findings, 680
Management of Patients With Glomerular Disease, 681
Complications, 684
41 Acute Kidney Injury and Chronic Kidney Disease, 686
Acute Kidney Injury, 686
Chronic Kidney Disease, 692
42 Bacterial Cystitis, Pyelonephritis, and Prostatitis in the Dog and Cat, 704
Introduction, 704
Classification of Bacterial Cystitis, 704
Bacterial Prostatitis, 710
43 Canine and Feline Urolithiasis, 712
Introduction, 712
Calcium Oxalate Calculi, 714
Ureterolithiasis in Dogs and Cats, 714
Conclusions, 722
44 Obstructive and Nonobstructive Feline Idiopathic Cystitis, 724
Introduction, 724
Pathophysiology, 724
Diagnostic Tests for Cats With Lower Urinary Tract Signs, 725
Treatment Options, 726
Conclusions, 729
45 Disorders of Micturition, 730
Anatomy and Physiology, 730
Definitions and Types of Urinary Incontinence, 730

PART SIX ENDOCRINE DISORDERS, 740

Richard W. Nelson and Ann-Marie Della Maggiore

46 Disorders of the Hypothalamus and Pituitary Gland, 740
Polyuria and Polydipsia, 740
Diabetes Insipidus, 741
Primary (Psychogenic) Polydipsia, 746
Endocrine Alopecia, 747
Feline Acromegaly, 749
Pituitary Dwarfism, 753
47 Disorders of the Parathyroid Gland, 758
Classification of Hyperparathyroidism, 758
Primary Hyperparathyroidism, 758
Primary Hypoparathyroidism, 763
48 Disorders of the Thyroid Gland, 767
Hypothyroidism in Dogs, 767
Hypothyroidism in Cats, 785
Hyperthyroidism in Cats, 788
Canine Thyroid Neoplasia, 800
49 Disorders of the Endocrine Pancreas, 806
Hyperglycemia, 806
Hypoglycemia, 806
Diabetes Mellitus in Dogs, 809
Diabetes Mellitus in Cats, 830
Diabetic Ketoacidosis, 840
Insulin-Secreting β-Cell Neoplasia, 847
Gastrin-Secreting Neoplasia, 853
50 Disorders of the Adrenal Gland, 857
Hyperadrenocorticism in Dogs, 857
Occult (Atypical) Hyperadrenocorticism in Dogs, 878
Hyperadrenocorticism in Cats, 878
Hypoadrenocorticism, 883
Atypical Hypoadrenocorticism, 889
Pheochromocytoma, 889
Incidental Adrenal Mass, 892

PART SEVEN METABOLIC AND ELECTROLYTE DISORDERS, 898

Jennifer A. Larsen and Ann-Marie Della Maggiore

51 Weight Loss and Obesity, 898
Polyphagia With Weight Loss, **898**
Obesity, **899**
52 Hyperlipidemia, 908
Hyperlipidemia, **908**
53 Electrolyte Imbalances, 915
Hypernatremia, **915**
Hyponatremia, **917**
Hyperkalemia, **919**
Hypokalemia, **921**
Hypercalcemia, **923**
Hypocalcemia, **927**
Hyperphosphatemia, **929**
Hypophosphatemia, **930**
Hypomagnesemia, **931**
Hypermagnesemia, **933**

PART EIGHT REPRODUCTIVE SYSTEM DISORDERS, 935

Autumn P. Davidson

54 The Practice of Theriogenology, 935
The Prebreeding Consultation, **935**
Estrous Cycle of the Bitch, **937**
Canine Ovulation Timing: Evaluation of the Estrous Cycle to Identify the Optimal Time to Breed, **940**
The Dog and Tom, **945**
Fresh, Fresh Chilled, and Frozen Artificial Inseminations (AI), **947**
Estrous Cycle of the Queen, **948**
Obstetrics, **949**
55 Clinical Conditions of the Bitch and Queen, 953
Normal Variations of the Estrous Cycle, **953**
Abnormalities of the Canine Estrous Cycle, **954**
Manipulation of the Estrous Cycle, **958**
Prepartum Disorders, **960**
Pregnancy Loss Associated With Infectious Disease, **963**
Abortion Associated With Other Bacteria, **965**
Metabolic Disorders, **966**
Parturition and Parturient Disorders, **968**
Postpartum Disorders, **974**
Disorders of the Reproductive Tract in Ovariohysterectomized Bitches and Queens, **979**
Infertility/Subfertility in the Bitch and Queen, **984**
Microbiology and Female Fertility, **984**
Cystic Endometrial Hyperplasia/Pyometra Complex, **985**
56 Clinical Conditions of the Dog and Tom, 990
Cryptorchidism, **990**
Testicular Torsion, **991**
Persistent Penile Frenulum, **992**
Urethral Prolapse, **992**
Scrotal Dermatitis, **992**
Balanoposthitis, **992**
Priapism, Paraphimosis, and Phimosis, **993**
Testicular Neoplasia in Stud Dogs, **996**
Microbiology and Male Fertility, **997**
Prostatic Disorders in the Valuable Stud Dog, **1001**
Congenital Infertility, **1005**
Disorders of Sexual Differentiation, **1005**
57 Neonatology and Pediatrics, 1007
Neonatal Resuscitation, **1007**
Anomalies Apparent at the Neonatal Exam, **1013**

PART NINE NERVOUS SYSTEM AND NEUROMUSCULAR DISORDERS, 1037

Susan M. Taylor

58 Lesion Localization and the Neurologic Examination, 1037
Functional Anatomy of the Nervous System and Lesion Localization, **1037**
Screening Neurologic Examination, **1043**
Diagnostic Approach, **1061**
59 Diagnostic Tests for Nervous System and Neuromuscular Disorders, 1063
Neurologic Examination, **1063**
Routine Laboratory Evaluation, **1063**
Immunology, Serology, and Microbiology, **1064**
Routine Systemic Diagnostic Imaging, **1064**
Diagnostic Imaging of the Nervous System, **1064**
Cerebrospinal Fluid Collection and Analysis, **1067**
Electrodiagnostic Testing, **1071**
Biopsy of Muscle and Nerve, **1073**
60 Intracranial Disorders, 1074
General Considerations, **1074**
Abnormal Mentation, **1074**
Hypermetria, **1074**
Diagnostic Approach to Animals With Intracranial Disease, **1075**
Intracranial Disorders, **1075**
61 Loss of Vision and Pupillary Abnormalities, 1084
General Considerations, **1084**
Neuroophthalmologic Evaluation, **1084**
Loss of Vision, **1087**
Horner Syndrome, **1089**
Protrusion of the Third Eyelid, **1091**
62 Seizures and Other Paroxysmal Events, 1093
Seizures, **1093**
Nonepileptic Paroxysmal Events, **1093**
Seizure Descriptions, **1093**
Seizure Classification and Localization, **1094**
Differential Diagnosis, **1095**
Diagnostic Evaluation, **1098**
Antiepileptic Drug Therapy, **1100**

Antiepileptic Drugs, 1101
Alternative Therapies, 1104
Emergency Therapy for Dogs and Cats in Status Epilepticus, 1104
Paroxysmal Events That Are Not Seizures, 1105
63 Head Tilt, 1109
General Considerations, 1109
Localization of Lesions, 1109
Disorders Causing Peripheral Vestibular Disease, 1111
Disorders Causing Central Vestibular Disease, 1115
64 Encephalitis, Myelitis, and Meningitis, 1117
General Considerations, 1117
Neck Pain, 1117
Noninfectious Inflammatory Disorders, 1119
Infectious Inflammatory Disorders, 1123
65 Disorders of the Spinal Cord, 1130
General Considerations, 1130
Localizing Spinal Cord Lesions, 1130
Peracute or Acute Spinal Cord Dysfunction, 1133
Progressive Spinal Cord Dysfunction, 1142
66 Disorders of Peripheral Nerves and the Neuromuscular Junction, 1157
General Considerations, 1157
Focal Neuropathies, 1157
Polyneuropathies, 1163
Disorders of the Neuromuscular Junction, 1168
Dysautonomia, 1172
67 Disorders of Muscle, 1174
General Considerations, 1174
Inflammatory Myopathies, 1174
Acquired Metabolic Myopathies, 1178
Noninflammatory Inherited Myopathies, 1179
Involuntary Alterations in Muscle Tone and Movement, 1181
Dyskinesias, 1183
Disorders Causing Exercise Intolerance or Collapse, 1183

PART TEN JOINT DISORDERS, 1187
Susan M. Taylor

68 Clinical Manifestations of and Diagnostic Tests for Joint Disorders, 1187
General Considerations, 1187
Clinical Manifestations, 1187
Diagnostic Approach, 1187
Diagnostic Tests, 1189
69 Disorders of the Joints, 1195
General Considerations, 1195
Noninflammatory Joint Disease, 1195
Infectious Inflammatory Joint Diseases, 1197
Noninfectious Polyarthritis: Nonerosive, 1201
Noninfectious Polyarthritis: Erosive, 1206

PART ELEVEN IMMUNE-MEDIATED DISORDERS, 1211
Andrew Woolcock and J. Catharine R. Scott-Moncrieff

70 Pathogenesis of Immune-Mediated Disorders, 1211
General Considerations and Definition, 1211
Immunopathologic Mechanisms, 1211
Pathogenesis of Immune-Mediated Disorders, 1212
Organ Systems Involved in Autoimmune Disorders, 1214
71 Diagnostic Testing for Immune-Mediated Disease, 1215
Clinical Diagnostic Approach, 1215
Specific Diagnostic Tests, 1215
Antiplatelet Antibodies, 1216
72 Treatment of Primary Immune-Mediated Diseases, 1220
Principles of Treatment of Immune-Mediated Diseases, 1220
Overview of Immunosuppressive Therapy, 1220
Glucocorticoids, 1221
Azathioprine, 1223
Chlorambucil, 1224
Cyclosporine (Ciclosporin), 1224
Leflunomide, 1226
Mycophenolate Mofetil, 1227
Splenectomy, 1228
Human Intravenous Immunoglobulin, 1228
Pentoxifylline, 1228
Vincristine, 1229
73 Common Immune-Mediated Diseases, 1231
Immune-Mediated Hemolytic Anemia, 1231
Feline Immune-Mediated Hemolytic Anemia, 1238
Pure Red Cell Aplasia, 1238
Idiopathic Aplastic Anemia, 1240
Immune-Mediated Thrombocytopenia, 1240
Immune-Mediated Neutropenia, 1244
Polyarthritis, 1245
Systemic Lupus Erythematosus, 1247
Glomerulonephritis, 1249
Acquired Myasthenia Gravis, 1250
Perianal Fistula, 1251
Immune-Mediated Myositis, 1252

PART TWELVE ONCOLOGY, 1257
C. Guillermo Couto

74 Cytology, 1257
General Considerations, 1257
Fine-Needle Aspiration, 1257
Impression Smears, 1258
Staining of Cytologic Specimens, 1258
Interpretation of Cytologic Specimens, 1258
75 Principles of Cancer Treatment, 1265
General Considerations, 1265

Patient-Related Factors, 1265
Family-Related Factors, 1265
Treatment-Related Factors, 1266
76 Practical Chemotherapy, 1269
Cell and Tumor Kinetics, 1269
Basic Principles of Chemotherapy, 1270
Indications and Contraindications of Chemotherapy, 1272
Mechanism of Action of Anticancer Drugs, 1272
Types of Anticancer Drugs, 1272
Metronomic Chemotherapy, 1273
Safe Handling of Anticancer Drugs, 1274
77 Complications of Cancer Chemotherapy, 1276
General Considerations, 1276
Hematologic Toxicity, 1276
Gastrointestinal Toxicity, 1280
Hypersensitivity Reactions, 1281
Dermatologic Toxicity, 1282
Pancreatitis, 1283
Cardiotoxicity, 1283
Urotoxicity, 1284
Hepatotoxicity, 1285
Neurotoxicity, 1285
Pulmonary Toxicity, 1285
Acute Tumor Lysis Syndrome, 1286
78 Approach to the Patient With a Mass, 1288
Approach to the Cat or Dog With a Solitary Mass, 1288
Approach to the Patient With Metastatic Lesions, 1289
Approach to the Patient With a Mediastinal Mass, 1290
79 Lymphoma, 1294
80 Leukemias, 1311
Definitions and Classification, 1311
Leukemias in Dogs, 1313
Leukemias in Cats, 1319
81 Selected Neoplasms in Dogs and Cats, 1322
Hemangiosarcoma in Dogs, 1322
Osteosarcoma, 1325
Mast Cell Tumors in Dogs and Cats, 1328
Injection Site Sarcomas in Cats, 1334

PART THIRTEEN HEMATOLOGY, 1340

C. Guillermo Couto

82 Anemia, 1340
Definition, 1340
Clinical and Clinicopathologic Evaluation, 1340
Management of the Anemic Patient, 1345
Transfusion Therapy, 1355
83 Clinical Pathology in Greyhounds and Other Sighthounds, 1360
Hematology, 1360
Hemostasis, 1361
Clinical Chemistry, 1361
Clinical Pathology in Greyhounds: The Author's Experience, 1364
Conclusions, 1366
84 Erythrocytosis, 1368
Definition and Classification, 1368
85 Leukopenia and Leukocytosis, 1371
General Considerations, 1371
Normal Leukocyte Morphology and Physiology, 1371
Leukocyte Changes in Disease, 1372
86 Combined Cytopenias and Leukoerythroblastosis, 1381
Definitions and Classification, 1381
Clinicopathologic Features, 1381
87 Disorders of Hemostasis, 1387
General Considerations, 1387
Physiology of Hemostasis, 1387
Clinical Manifestations of Spontaneous Bleeding Disorders, 1388
Clinicopathologic Evaluation of the Bleeding Patient, 1389
Management of the Bleeding Patient, 1393
Primary Hemostatic Defects, 1394
Secondary Hemostatic Defects, 1399
Mixed (Combined) Hemostatic Defects, 1400
Thrombosis, 1405
88 Lymphadenopathy and Splenomegaly, 1407
Applied Anatomy and Histology, 1407
Function, 1407
Lymphadenopathy, 1407
Splenomegaly, 1411
Approach to Patients With Lymphadenopathy or Splenomegaly, 1414
Management of Lymphadenopathy or Splenomegaly, 1418
89 Hyperproteinemia, 1420
90 Fever of Undetermined Origin, 1423
Fever and Fever of Undetermined Origin, 1423
Disorders Associated With Fever of Undetermined Origin, 1423
Diagnostic Approach to the Patient With Fever of Undetermined Origin, 1424

PART FOURTEEN INFECTIOUS DISEASES, 1427

Michael R. Lappin

91 Laboratory Diagnosis of Infectious Diseases, 1427
Demonstration of the Organism, 1427
Antibody Detection, 1433
Antemortem Diagnosis of Infectious Diseases, 1435
92 Practical Antimicrobial Chemotherapy, 1436
Anaerobic Infections, 1438
Bacteremia and Bacterial Endocarditis, 1440
Central Nervous System Infections, 1442
Gastrointestinal Tract and Hepatic Infections, 1442
Musculoskeletal Infections, 1443

Respiratory Tract Infections, **1444**
Skin and Soft Tissue Infections, **1445**
Urogenital Tract Infections, **1445**
93 Prevention of Infectious Diseases, 1448
Biosecurity Procedures for Small Animal Hospitals, **1448**
Biosecurity Procedures for Clients, **1450**
Vaccination Protocols, **1451**
94 Polysystemic Bacterial Diseases, 1457
Canine Bartonellosis, **1457**
Feline Bartonellosis, **1458**
Feline Plague, **1460**
Leptospirosis, **1462**
Mycoplasma and Ureaplasma, **1464**
95 Polysystemic Rickettsial Diseases, 1469
Canine Granulocytotropic Anaplasmosis, **1469**
Feline Granulocytotropic Anaplasmosis, **1471**
Canine Thrombocytotropic Anaplasmosis, **1472**
Canine Monocytotropic Ehrlichiosis, **1473**
Feline Monocytotropic Ehrlichiosis, **1477**
Canine Granulocytotropic Ehrlichiosis, **1478**
Rocky Mountain Spotted Fever, **1479**
Other Rickettsial Infections, **1481**
96 Polysystemic Viral Diseases, 1485
Canine Distemper Virus, **1485**
Feline Coronavirus, **1488**
Feline Immunodeficiency Virus, **1491**
Feline Leukemia Virus, **1494**
97 Polysystemic Mycotic Infections, 1502
Blastomycosis, **1502**
Coccidioidomycosis, **1505**
Cryptococcosis, **1507**
Histoplasmosis, **1510**
98 Polysystemic Protozoal Infections, 1514
Babesiosis, **1514**
Cytauxzoonosis, **1516**
Hepatozoonosis, **1517**
Leishmaniosis, **1518**
Neosporosis, **1520**
Feline Toxoplasmosis, **1521**
Canine Toxoplasmosis, **1525**
American Trypanosomiasis, **1525**
99 Zoonoses, 1532
Enteric Zoonoses, **1532**
Bite, Scratch, or Exudate Exposure Zoonoses, **1539**
Respiratory Tract and Ocular Zoonoses, **1542**
Genital and Urinary Tract Zoonoses, **1542**
Shared Vector Zoonoses, **1543**
Shared Environment Zoonoses, 1543

Index, 1547

Video Contents

PART ONE CARDIOVASCULAR SYSTEM DISORDERS

1 Clinical Manifestations of Cardiac Disease
- Video 1.1 Tips for Cardiac Auscultation

2 Diagnostic Tests for the Cardiovascular System
- Video 2.1 Attaching a Holter Monitor
- Video 2.2 Smartphone-Based ECG Recording
- Video 2.3 Introduction to Some Basic Echocardiographic Views

11 Systemic Arterial Hypertension
- Video 11.1 Blood Pressure Measurement Using the Doppler Method

PART TWO RESPIRATORY SYSTEM DISORDERS

13 Clinical Manifestations of Nasal Disease
- Video 13.1 Reverse Sneeze

16 Clinical Manifestations of Laryngeal and Pharyngeal Disease
- Video 16.1 Laryngeal Paralysis

19 Clinical Manifestations of Lower Respiratory Tract Disorders
- Video 19.1 Cat Cough

21 Disorders of the Trachea and Bronchi
- Video 21.1 Canine Bronchitis – Bronchoscopy
- Video 21.2 Tracheobronchomalacia (Tracheal Collapse) in Dogs

PART THREE DIGESTIVE SYSTEM DISORDERS

26 Clinical Manifestations of Gastrointestinal Disorders
- Video 26.1 Cat with Severe Esophageal Weakness

27 Diagnostic Tests for the Alimentary Tract
- Video 27.1 Colonoscopy in a Dog with Severe Colitis
- Video 27.2 Colonoscopy on a Dog with Lymphosarcomatous Infiltrates in the Mucosa
- Video 27.3 Colonoscopy Performed in a Cat

29 Disorders of the Oral Cavity, Pharynx and Esophagus
- Video 29.1 Esophagoscopy of a Dog with Severe, Acquired Esophageal Weakness
- Video 29.2 Barium Contrast Fluoroscopic Examination of the Esophagus
- Video 29.3 Barium Contrast Fluoroscopic Examination of the Lower Esophageal Region
- Video 29.4 Foley Catheter Used to Retrieve a Foreign Body in the Esophagus
- Video 29.5 Esophagoscopy in a Dog with a Chronic, Benign Stricture

30 Disorders of the Stomach
- Video 30.1 Endoscopic Examination that Begins in the Duodenum.
- Video 30.2 Endoscopic Examination of the Stomach of a Dog that has had a Billroth I Procedure
- Video 30.3 Endoscopic Examination of the Stomach showing a Large Benign Ulcer in the Antrum

PART FIVE URINARY TRACT DISORDERS

38 Clinical Manifestations of Urinary Disorders
- Video 38.1 Idiopathic Hematuria Cystoscopy (Courtesy Dr. Dennis Chew)

39 Diagnostic Tests for the Urinary System
- Video 39.1 Laparoscopic Renal Biopsy (Courtesy Dr. William Culp)

42 Bacterial Cystitis and Pyelonephritis
- Video 42.1 Proliferative Urethritis
- Video 42.2 Transitional Cell Carcinoma in the Apex, Bladder Biospy
- Video 42.3 Bladder Biopsy

43 Canine and Feline Urolithiasis
- Video 43.1 Voiding Urohydropropulsion
- Video 43.2 Basket Retrieval of a Stone via the Cystoscope
- Video 43.3 Holmium:YAG Laser Lithotripsy
- Video 43.4 Antegrade Ureteral Stent (Courtesy Dr. William Culp)

44 Obstructive and Nonobstructive Feline Idiopathic Cystitis
- Video 44.1 Cystoscopy of Feline Idiopathic Cystitis Cat

45 Diagnostic Approach and Management for the Incontinent Patient
- Video 45.1 Abdominal Ultrasonography
- Video 45.2 Cystoscopy
- Video 45.3 Cystoscopic Laser Ablation
- Video 45.4 Collagen Injection
- Video 45.5 Cystoscopy and Placement of Urethral Stent

PART SIX ENDOCRINE DISORDERS

47 Disorders of the Parathyroid Gland
- Video 47.1 Ultrasound Scan of Parathyroid Mass (Courtesy Dr. Craig Long, DVM, DACVR)

48 Disorders of the Thyroid Gland
Video 48.1 Cat with Hyperthyroidism
49 Disorders of the Endocrine Pancreas
Video 49.1 Diabetic Cat with Peripheral Neuropathy
50 Disorders of the Adrenal Gland
Video 50.1 CT Scan of the Region of the Pituitary Gland in a Dog
Video 50.2 Laparoscopic Surgery to Remove an Adrenal Tumor (Courtesy Dr. Phil Mayhew BVMS, DACVS)

PART EIGHT REPRODUCTIVE SYSTEM DISORDERS

54 The Practice of Theriogenology
Video 54.1 Canine Flagging Behavior Displayed During Estrus
Video 54.2 Estrus Behavior
Video 54.3 Transcervical Catheterization
Video 54.4 Gestational Aging-Based Biparietal Skull Measurement
55 Clinical Conditions of the Bitch and Queen
Video 55.1 Abdominal Ultrasound Technique to Localize an Ovarian Remnant
56 Clinical Conditions of the Dog and Tom
Video 56.1 Transabdominal Ultrasound for Pediatric Canine Cryptorchidism (Courtesy T.W. Baker)
57 Neonatology and Pediatrics
Video 57.1 Steps in Neonatal Resuscitation Following a Cesarean Section
Video 57.2 Vocalization Indicating Successful Cardiopulmonary Resuscitation of the Neonate
Video 57.3 Sagittal Ultrasound Imaging Illustrating the Presence of an Ectopic Ureter (Courtesy T.W. Baker)
Video 57.4 Endoscopic Cystoscopic Laser Ablation of an Intramural Ectopic Ureter
Video 57.5 Transverse Intercostal Ultrasound Imaging of an Intrahepatic Ductal Portocaval Shunt (Courtesy T.W. Baker)
Video 57.6 Transverse Abdominal Ultrasound Imaging of a Small Bowel Intussusception (Courtesy T.W. Baker)

PART NINE NERVOUS AND NEUROMUSCULAR DISORDERS

58 Lesion Localization and the Neurologic Examination
Video 58.1 General Proprioceptive Ataxia in a Great Dane
Video 58.2 Vestibular Ataxia in a Golden Retriever with Geriatric Canine Vestibular Disease
Video 58.3 Cerebellar Ataxia in an Adult Cat with Cerebellar Hypoplasia
Video 58.4 Postural Reaction Testing
Video 58.5 Spinal Manipulation and Palpation
Video 58.6 Rapid Regional Cranial Nerve Examination
59 Diagnostic Tests for Neurologic and Neuromuscular Disorders
Video 59.1 Cisternal Collection of Cerebrospinal Fluid

PART TEN JOINT DISORDERS

68 Clinical Manifestation of and Diagnostic Tests for Joint Disorders
Video 68.1 Collection of Synovial Fluid from the Radiocarpal Joint

PART ELEVEN IMMUNE-MEDIATED DISORDERS

70 Immune-Mediated Disorders
Video 70.1 Canine Blood Donation
Video 70.2 Canine Joint Tap
Video 70.3 Feline Blood Typing
Video 70.4 Canine Slide Agglutination Test

PART ONE ▪ Cardiovascular System Disorders

Wendy A. Ware and Jessica L. Ward

CHAPTER 1

Clinical Manifestations of Cardiac Disease



SIGNS OF HEART DISEASE

Several signs can indicate the presence of heart disease, even if the animal is not clinically in "heart failure." So-called objective signs of heart disease are, for the most part, cardiac specific. These are cardiac murmurs, rhythm disturbances, jugular pulsations, and cardiac enlargement. Notable exceptions to this generalization include murmurs that are functional (nonpathologic) in nature and the normal rhythm irregularity of sinus arrhythmia. Other clinical signs may indicate heart disease but can occur with noncardiac diseases as well. These include syncope, excessively weak or strong arterial pulses, cough or respiratory difficulty, exercise intolerance, abdominal distention, and cyanosis. Further evaluation using thoracic radiography, cardiac biomarker tests, echocardiography, electrocardiography (ECG), and sometimes other tests usually is indicated when signs consistent with cardiovascular (CV) disease are present.

SIGNS OF HEART FAILURE

Heart failure generally is considered to occur when the heart cannot adequately meet the body's circulatory needs or can do so only with high filling (venous) pressures. Not all animals with heart disease will develop heart failure. Of those that do, the majority show clinical signs (Box 1.1) related to high venous pressure behind one or both ventricles (congestive signs), and some also manifest signs of inadequate blood ejection from the heart (low output signs). Congestive signs associated with right-sided heart failure stem from systemic venous hypertension and the resulting increase in systemic capillary hydrostatic pressure. High left-heart filling pressure causes pulmonary venous engorgement and edema. Signs of biventricular failure develop in some animals. Chronic left-sided congestive heart failure (CHF) can promote the development of right-sided congestive signs when pulmonary venous hypertension markedly raises pulmonary arterial pressure. Signs of low cardiac output are similar regardless of which ventricle is affected, because output from the left heart is coupled to that from the right heart. Heart failure is discussed further in Chapter 3 and within the context of specific diseases.

WEAKNESS AND EXERCISE INTOLERANCE

Animals with heart failure often cannot adequately raise cardiac output to sustain increased levels of activity. Furthermore, vascular and metabolic changes that occur over time impair skeletal muscle perfusion during exercise and contribute to reduced exercise tolerance. Increased pulmonary vascular pressure and edema also lead to poor exercise ability. Episodes of exertional weakness or collapse can relate to these changes or to an acute decrease in cardiac output caused by arrhythmias (Box 1.2).

SYNCOPE

Syncope is characterized by transient unconsciousness, with loss of postural tone (collapse), from insufficient oxygen or glucose delivery to the brain. Various cardiac and noncardiac abnormalities can cause syncope and intermittent weakness (see Box 1.2). Syncope can be confused with seizure episodes. A careful description of the animal's behavior or activity before the collapse event, during the event itself, and following the collapse, as well as a drug history, can help the clinician differentiate among syncopal attacks, episodic weakness, and true seizures. Syncope often is associated with exertion or excitement. The actual event can include rear limb weakness or sudden collapse, lateral recumbency, stiffening of the forelimbs with opisthotonos, and micturition (Fig. 1.1). Vocalization is common; however tonic/clonic motion, facial fits, and defecation are not. An aura (which often occurs before seizure activity), postictal dementia, and neurologic deficits are not expected in dogs and cats with CV syncope. Sometimes profound hypotension or asystole causes hypoxic "convulsive syncope," with seizure-like

BOX 1.1

Clinical Signs of Heart Failure

Congestive Signs—Left (↑ Left Heart Filling Pressure)

Pulmonary venous congestion
Pulmonary edema (causes tachypnea, ↑ respiratory effort, cough, orthopnea, pulmonary crackles, tiring, cyanosis, hemoptysis)
Postcapillary pulmonary hypertension
Secondary right-sided heart failure
Cardiac arrhythmias

Congestive Signs—Right (↑ Right Heart Filling Pressure)

Systemic venous congestion (causes ↑ central venous pressure, jugular vein distention)
Hepatic ± splenic congestion
Pleural effusion (causes ↑ respiratory effort, orthopnea, cyanosis)
Ascites
Small pericardial effusion
Subcutaneous edema
Cardiac arrhythmias

Low Cardiac Output Signs

Tiring
Exertional weakness
Syncope
Prerenal azotemia
Cyanosis (from poor peripheral circulation)
Cardiac arrhythmias



FIG 1.1
Syncope in a Doberman Pinscher with paroxysmal ventricular tachycardia. Note the extended head and neck with stiffened forelimbs. Involuntary micturition also occurred, followed shortly by return of consciousness and normal activity.

activity or twitching; however, these convulsive syncopal episodes are preceded by loss of muscle tone. Presyncope, where reduced brain perfusion (or substrate delivery) is not severe enough to cause unconsciousness, may appear as transient "wobbliness" or weakness, especially in the rear limbs.

BOX 1.2

Causes of Syncope or Intermittent Weakness

Cardiovascular Causes

Bradyarrhythmias (second- or third-degree AV block, sinus arrest, sick sinus syndrome, atrial standstill)
Tachyarrhythmias (paroxysmal atrial or ventricular tachycardia, reentrant supraventricular tachycardia, atrial fibrillation)
Congenital ventricular outflow obstruction (pulmonic stenosis, subaortic stenosis)
Acquired ventricular outflow obstruction (heartworm disease and other causes of pulmonary hypertension, hypertrophic obstructive cardiomyopathy, intracardiac tumor, thrombus)
Cyanotic heart disease (tetralogy of Fallot, pulmonary hypertension, and "reversed" shunt)
Impaired forward cardiac output (severe valvular insufficiency, dilated cardiomyopathy, myocardial infarction or inflammation)
Impaired cardiac filling (e.g., cardiac tamponade, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, intracardiac tumor, thrombus)
Cardiovascular drugs (diuretics, vasodilators)
Neurocardiogenic reflexes (vasovagal, cough-syncope, other situational syncope)

Pulmonary Causes

Diseases causing hypoxemia
Pulmonary hypertension
Pulmonary thromboembolism

Metabolic and Hematologic Causes

Hypoglycemia
Hypoadrenocorticism
Electrolyte imbalance (especially potassium, calcium)
Anemia
Sudden hemorrhage

Neurologic Causes

Cerebrovascular accident
Brain tumor
(Seizures)

Neuromuscular Disease

(Narcolepsy, cataplexy)

AV, Atrioventricular.

Tests to explore the cause of intermittent weakness or syncope usually include ECG recordings (during rest, exercise, and/or after exercise or a vagal maneuver), complete blood count (CBC), serum biochemical analysis (including electrolytes and glucose), heartworm testing, neurologic examination, thoracic radiographs, and echocardiography. Other studies for neuromuscular or neurologic disease also may be valuable. Intermittent cardiac arrhythmias that are not apparent on resting ECG may be uncovered by ambulatory ECG monitoring, using a 24-hour Holter, event, or

implantable loop recording device. In-hospital continuous ECG monitoring for a period of time sometimes reveals a culprit arrhythmia also.

Cardiovascular Causes of Syncope

Various arrhythmias, obstruction to ventricular outflow, cyanotic congenital heart defects, and acquired diseases that impair cardiac output are the usual causes of CV syncope. Activation of vasodepressor reflexes and excessive dosages of CV drugs also can induce syncope. Arrhythmias that provoke syncope usually are associated with either very fast or very slow heart rates and can occur with or without identifiable underlying organic heart disease. Ventricular outflow obstruction can provoke syncope or sudden weakness if cardiac output becomes inadequate during exercise or if high systolic pressure activates ventricular mechanoreceptors, causing inappropriate reflex bradycardia and hypotension. Both dilated cardiomyopathy and severe mitral insufficiency can impair forward cardiac output, especially during exertion. Vasodilator and diuretic drugs can induce syncope if given in excess.

Syncope caused by abnormal peripheral vascular and/or neurologic reflex responses is not well defined in animals, but is thought to occur in some patients. Syncope associated with sudden bradycardia after a burst of sinus tachycardia has been documented, especially in small breed dogs with advanced atrioventricular (AV) valve disease; excitement often precipitates such an episode. Doberman Pinschers and Boxers similarly may experience syncope after sudden bradycardia. Postural hypotension and hypersensitivity of carotid sinus receptors infrequently can provoke syncope by inappropriate peripheral vasodilation and bradycardia.

Fainting associated with a coughing fit (cough syncope or "cough-drop") occurs in some dogs with marked left atrial (LA) enlargement and bronchial compression, as well as in dogs with primary respiratory disease. Several mechanisms have been proposed, including an acute decrease in cardiac filling and output during the cough, peripheral vasodilation after the cough, and increased cerebrospinal fluid pressure with intracranial venous compression. Severe pulmonary disease, anemia, certain metabolic abnormalities, and primary neurologic diseases also can cause collapse that resembles CV syncope.

COUGH AND OTHER RESPIRATORY SIGNS

CHF in dogs produces tachypnea, respiratory distress, and sometimes coughing. These signs also can occur with the pulmonary vascular pathology and pneumonitis of heartworm disease in both dogs and cats. Noncardiac conditions, including diseases of the upper and lower airways, pulmonary parenchyma (including noncardiogenic pulmonary edema), pulmonary vasculature, and pleural space, as well as certain nonrespiratory conditions, also should be considered in patients with cough, tachypnea, or dyspnea (see Chapter 19).

The cough associated with cardiogenic pulmonary edema in dogs often is soft and moist; it sometimes sounds like gagging. Cats, in contrast, rarely cough from pulmonary edema. Tachypnea progressing to dyspnea occurs in both species. Pleural and pericardial effusions occasionally are associated with coughing as well. Mainstem bronchus collapse or compression associated with severe LA enlargement can stimulate a dry or hacking cough in dogs with chronic mitral valve disease, even when pulmonary edema or congestion is absent. Concurrent bronchomalacia is likely to be a contributing factor in these cases. A heart base tumor, enlarged hilar lymph nodes, or other masses that impinge on an airway also can stimulate this type of cough.

When respiratory signs have a cardiac cause, other evidence of heart disease usually is evident, such as generalized cardiomegaly, LA enlargement, pulmonary venous congestion, lung infiltrates that resolve with diuretic therapy, or a positive heartworm test. Findings on physical examination, thoracic radiographs, cardiac biomarker assays, echocardiogram, and sometimes an ECG, help in differentiating cardiac from noncardiac causes.

CARDIOVASCULAR EXAMINATION

The medical history (Box 1.3) is an important part of the CV evaluation and can help guide the choice of diagnostic tests because it may suggest various cardiac or noncardiac diseases. The patient's signalment is useful because some



BOX 1.3

Important Historic Information

- Signalment (age, breed, gender)?
- Vaccination status?
- What is the diet? Have there been any recent changes in food or water consumption?
- Where was the animal obtained?
- Is the pet housed indoors or outdoors?
- How much time is spent outdoors? Supervised?
- What activity level is normal? Does the animal tire easily now?
- Has there been any coughing? When? Describe episodes.
- Has there been any excessive or unexpected panting or heavy breathing?
- Has there been any vomiting or gagging? Diarrhea?
- Have there been any recent changes in urinary habits?
- Have there been any episodes of fainting or weakness?
- Do the tongue/mucous membranes always look pink, especially during exercise?
- Have there been any recent changes in attitude or activity level?
- Are medications being given for this problem? What? How much? How often? Do they help?
- Have medications been used in the past for this problem? What? How much? Were they effective?

congenital and acquired abnormalities are more prevalent in certain breeds or life stages, or because specific findings are common in individuals of a given breed (such as a soft left basilar ejection murmur in normal Greyhounds and other sighthounds).

Physical evaluation of the patient with suspected heart disease includes observation (for example, of attitude, posture, body condition, level of anxiety, respiratory pattern) and a general physical examination. The CV examination itself consists of evaluating the peripheral circulation (mucous membranes), systemic veins (especially the jugular veins), systemic arterial pulses (usually the femoral arteries), and the precordium (left and right chest wall over the heart), as well as auscultation of the heart and lungs, and palpating or percussing for abnormal fluid accumulation (e.g., ascites, subcutaneous edema, pleural effusion). Proficiency in all aspects of the CV examination requires practice but is important for accurate patient assessment and monitoring.

RESPIRATORY PATTERNS

Respiratory difficulty (dyspnea) usually causes the animal to appear anxious. Increased respiratory effort, flared nostrils, and often a rapid rate of breathing are evident (Fig. 1.2). Increased depth of respiration (hyperpnea) can result from hypoxemia, hypercarbia, or acidosis. Pulmonary edema (or other pulmonary infiltrates) increases lung stiffness; the rapid and shallow breathing (tachypnea) that results helps minimize the work of breathing. In the absence of primary lung disease, an increase in resting respiratory rate often is an early indicator of pulmonary edema. Lung stiffness also increases with pleural fluid or air accumulation and can produce tachypnea, too. However, with large-volume pleural effusion or pneumothorax, respiratory motions become increasingly labored and exaggerated as the animal struggles to expand the collapsed lungs; the respiratory rate often is not elevated in these cases.

It is important to note whether the respiratory difficulty is more intense during a particular phase of respiration. Prolonged, labored inspiration usually is associated with upper airway obstructive disorders, whereas prolonged expiration occurs with lower airway obstruction as well as pulmonary infiltrative disease (including edema). Animals with severely compromised ventilation may refuse to lie down; rather, they stand or sit with elbows abducted to allow maximal rib expansion, and they resist being positioned in lateral or dorsal recumbency (orthopnea). Cats with dyspnea often crouch in a sternal position with elbows abducted. Open-mouth breathing usually is a sign of severe respiratory distress in cats (Fig. 1.3). The increased respiratory rate associated with excitement, fever, fear, or pain generally can be differentiated from dyspnea by careful observation and physical examination.

MUCOUS MEMBRANES

Mucous membrane color and capillary refill time (CRT) are used to evaluate peripheral perfusion. The oral mucosa usually is assessed, although caudal mucous membranes (prepuce or vagina) also can be evaluated. The CRT is determined by applying digital pressure to blanch the membrane; color should return within 2 seconds. Slower refill times occur as a result of dehydration and other causes of decreased cardiac output because of high peripheral sympathetic tone and vasoconstriction. Pale mucous membranes occur with either anemia or peripheral vasoconstriction. The CRT is normal in anemic animals unless hypoperfusion also is present. However, the CRT can be difficult to assess in severely anemic animals because of the lack of color contrast. In animals with polycythemia (erythrocytosis) or exercise-induced rear limb weakness, the color of the caudal membranes should be compared with that of the oral membranes for evidence of differential cyanosis (see p. 115 in Chapter 5). If oral membranes are heavily pigmented, the ocular



FIG 1.2
Dyspnea in an older male Golden Retriever with dilated cardiomyopathy and fulminant pulmonary edema. The dog appeared highly anxious, with rapid labored respirations and hypersalivation. Respiratory arrest occurred within minutes of this photograph being taken, but the dog was resuscitated.



FIG 1.3
Severe dyspnea is manifested in this cat by open-mouth breathing, infrequent swallowing (drooling saliva), and reluctance to lie down. Note also the dilated pupils associated with heightened sympathetic tone.

BOX 1.4

Abnormal Mucous Membrane Color

Pale Mucous Membranes

Anemia
Poor cardiac output/high sympathetic tone

Injected, Brick-Red Membranes

Polycythemia (erythrocytosis)
Sepsis
Excitement
Other causes of peripheral vasodilation

Cyanotic Mucous Membranes*

Pulmonary parenchymal disease
Airway obstruction
Pleural space disease
Pulmonary edema
Right-to-left shunting congenital cardiac defect
Hypoventilation
Shock
Cold exposure
Methemoglobinemia

Differential Cyanosis

Reversed patent ductus arteriosus (head and forelimbs receive normally oxygenated blood, but caudal part of body receives desaturated blood via the ductus, which arises from the descending aorta)

Icteric Mucous Membranes

Hemolysis
Hepatobiliary disease
Biliary obstruction

*Anemic animals might not appear cyanotic even with marked hypoxemia because 5 g/dL of desaturated hemoglobin is necessary for visible cyanosis.

conjunctiva can be evaluated. Box 1.4 outlines causes for abnormal mucous membrane color. Petechiae in the mucous membranes might be evident in animals with platelet disorders (see Chapter 87). In addition, oral and ocular membranes often are areas where icterus (jaundice) is first detected; a yellowish cast to these membranes should prompt further evaluation for hemolysis (see Chapter 82) or hepatobiliary disease (see Chapter 33).

JUGULAR VEINS

Systemic venous and right heart filling pressures are reflected at the jugular veins. These veins should not be distended when the animal is standing with its head in a normal position (jaw parallel to the floor). Persistent jugular vein distention occurs in patients with right-sided CHF (because of high right heart filling pressure), external compression of the cranial vena cava (as from a cranial mediastinal mass), and jugular vein or cranial vena cava thrombosis (Fig. 1.4).

Jugular pulsations that extend higher than one third of the way up the neck from the thoracic inlet also are



FIG 1.4
Prominent jugular vein distention in a cat with signs of right-sided congestive heart failure from dilated cardiomyopathy.

abnormal. Sometimes the carotid pulse wave is transmitted through adjacent soft tissues, mimicking a jugular pulse in thin or excited animals. To differentiate a true jugular pulse from carotid transmission, lightly occlude the jugular vein below the area of visible pulsation. If the pulse disappears, it is a true jugular pulsation; if the pulse continues, it is being transmitted from the carotid artery. Jugular pulse waves are related to atrial contraction and filling. Visible pulsations occur in animals with tricuspid insufficiency (after the first heart sound, during ventricular contraction), conditions causing a stiff and hypertrophied right ventricle (just before the first heart sound, during atrial contraction), or arrhythmias that cause the atria to contract against closed AV valves (so-called cannon "a" waves). Specific causes of jugular vein distention and pulsations are listed in Box 1.5. Impaired right ventricular (RV) filling, reduced pulmonary blood flow, or tricuspid regurgitation can cause a positive *hepatojugular* (*abdominojugular*) *reflux* test even in the absence of jugular distention or pulsations at rest. To test for this reflux, apply firm pressure to the cranial abdomen while the animal stands quietly with head and neck in normal position. This transiently increases venous return. Jugular distention that persists while abdominal pressure is applied constitutes a positive (abnormal) test. Normal animals have little to no change in the jugular vein with this maneuver.

ARTERIAL PULSES

The strength and regularity of the peripheral arterial pressure waves and the pulse rate are assessed by palpating the femoral or other peripheral arteries (Box 1.6). Subjective evaluation of pulse strength is based on the difference between the systolic and diastolic arterial pressures (that is,

BOX 1.5

Causes of Jugular Vein Distention/Pulsation

Distention Alone

Pericardial effusion/tamponade
Right atrial mass/inflow obstruction
Dilated cardiomyopathy
Cranial mediastinal mass
Jugular vein/cranial vena cava thrombosis

Pulsation ± Distention

Tricuspid regurgitation of any cause (degenerative, cardiomyopathy, congenital, secondary to diseases causing right ventricular pressure overload)
Pulmonic stenosis
Heartworm disease
Pulmonary hypertension
Ventricular premature contractions
Complete (third-degree) heart block
Constrictive pericarditis
Hypervolemia

BOX 1.6

Abnormal Arterial Pulses

Weak Pulses

Dilated cardiomyopathy
(Sub) aortic stenosis
Pulmonic stenosis
Shock
Dehydration

Strong Pulses

Excitement
Hyperthyroidism
Fever
Hypertrophic cardiomyopathy

Very Strong, Bounding Pulses

Patent ductus arteriosus
Fever/sepsis
Severe aortic regurgitation

the pulse pressure). When the difference is wide, the pulse feels strong on palpation; abnormally strong pulses are termed *hyperkinetic.* When the pressure difference is small, the pulse feels weak *(hypokinetic).* If the rise to maximum systolic arterial pressure is prolonged, as with severe subaortic stenosis, the pulse also tends to feel weak *(pulsus parvus et tardus).* Both femoral pulses should be palpated and compared; absence of pulse or a weaker pulse on one side could be caused by thromboembolic disease. Femoral pulses can be difficult to palpate in cats, even when normal. Often an elusive pulse can be found by gently working a fingertip between the dorsomedial thigh muscles toward the femur, in the area of the femoral triangle, where the femoral artery enters the leg.

The femoral arterial pulse rate should be evaluated simultaneously with the direct heart rate, which is obtained by auscultation or chest wall palpation. Fewer femoral pulses than heartbeats constitute a pulse deficit. Various cardiac arrhythmias induce pulse deficits by causing the heart to beat before adequate ventricular filling has occurred. Consequently, minimal or even no blood is ejected for those beats, and a palpable pulse is absent. Other arterial pulse variations also occur occasionally. Alternately weak then strong pulsations can result from severe myocardial failure *(pulsus alternans)* or from a normal heartbeat alternating with a premature beat *(bigeminy),* which causes reduced ventricular filling and ejection. An exaggerated decrease in systolic arterial pressure during inspiration occurs from cardiac tamponade *(pulsus paradoxus)*; a weak arterial pulse strength may be detectable during inspiration in those patients.

PRECORDIUM

The term "precordium" refers to the area of the chest wall that overlies the heart on both sides of the thorax. To palpate the precordium, place the palm and fingers of each hand on the corresponding side of the animal's chest wall over the heart (e.g., right hand over the right precordial area and left hand over the left precordial area). Normally the strongest systolic impulse is felt over the area of the left cardiac apex (located at approximately the fifth intercostal space near the costochondral junction). Cardiomegaly or a space-occupying mass within the chest can shift the precordial impulse to an abnormal location. Decreased intensity of the precordial impulse can be caused by obesity, weak cardiac contractions, pericardial effusion, intrathoracic masses, pleural effusion, or pneumothorax. The precordial impulse should be stronger on the left chest wall than on the right. A stronger right precordial impulse can result from RV hypertrophy or displacement of the heart into the right hemithorax by a mass lesion, lung atelectasis, or chest deformity. Very loud cardiac murmurs cause palpable vibrations on the chest wall known as a *precordial thrill.* This feels like a "buzzing" sensation to the hand. A precordial thrill usually is localized to the area of maximum murmur intensity.

EVALUATION FOR FLUID ACCUMULATION

Right-sided CHF promotes abnormal fluid accumulation within body cavities (Fig. 1.5; see also Fig. 9.3) and occasionally in the subcutis of dependent areas. Palpation and ballottement of the abdomen, percussion of the chest in the standing animal, and palpation of dependent areas are used to detect effusions and subcutaneous edema. Fluid accumulation secondary to right-sided heart failure usually is accompanied by abnormal jugular vein distention with or without pulsations, unless the animal's circulating blood volume is diminished from diuretic administration or other cause. Hepatomegaly and splenomegaly also may be noted in cats and dogs with right-sided CHF.



FIG 1.5
Abdominal distention caused by ascites from right heart failure in a 7-year-old Golden Retriever.



FIG 1.6
During cardiac auscultation, respiratory noise and purring often can be decreased or eliminated by gently placing a finger over one or both nostrils for brief periods of time.

AUSCULTATION

Thoracic auscultation is used to assess heart rate and rhythm, identify normal heart sounds, determine the presence or absence of abnormal sounds, and evaluate pulmonary sounds. Heart sounds are created by turbulent blood flow and associated vibrations in adjacent tissue during the cardiac cycle. Although many of these sounds are too low in frequency or intensity to be audible, others can be heard with the stethoscope or even palpated. Heart sounds are classified as transient sounds (those of short duration) and cardiac murmurs (longer sounds occurring during a normally silent part of the cardiac cycle). Cardiac murmurs and transient sounds are described by their timing within the cardiac cycle and by general characteristics of sound: frequency (pitch), amplitude of vibrations (intensity/loudness), duration, and quality (timbre). Sound quality is affected by the physical characteristics of the vibrating structures.

Because many heart sounds can be difficult to hear, a cooperative animal and a quiet room are important during auscultation. The animal should be standing, if possible, so that the heart is in its normal position. Panting in dogs is discouraged by holding the animal's mouth shut. Respiratory noise can be decreased further by placing a finger over one or both nostrils for a short time. Purring in cats often can be stopped by briefly holding a finger over one or both nostrils (Fig. 1.6), gently pressing the cricothyroid ligament region with a fingertip, waving an alcohol-soaked cotton ball near the cat's nose, or turning on a water faucet near the animal. Various other artifacts can interfere with auscultation, including respiratory clicks, air movement sounds, shivering, muscle twitching, hair rubbing against the stethoscope, gastrointestinal sounds, and extraneous room noises.

The traditional stethoscope has both a stiff, flat diaphragm and a bell on the chestpiece. The diaphragm, when applied firmly to the chest wall, allows better auscultation of higher-frequency heart sounds than those of low frequency. The bell, applied lightly to the chest wall, facilitates auscultation of lower-frequency sounds such as S_3 and S_4 (see the section on Gallop Sounds). Stethoscopes with a single-sided chestpiece are designed to function as a diaphragm when used with firm pressure against the skin and as a bell when used with light pressure. Ideally the stethoscope should have short double tubing and comfortable eartips. The binaural eartubes should be angled rostrally to align with the examiner's ear canals (Fig. 1.7).



FIG 1.7
Note the angulation of the stethoscope binaurals for optimal alignment with the clinician's ear canals (top of picture is rostral). The flat diaphragm of the chestpiece faces left, and the concave bell faces right.

Both sides of the chest should be carefully auscultated, with special attention to the valve areas (Fig. 1.8). The stethoscope is moved gradually to all areas of the chest. The examiner should concentrate on the various heart sounds, correlating them to the events of the cardiac cycle, and listen for any abnormal sounds in systole and diastole successively. The normal heart sounds (S_1 and S_2) are used as a framework for timing abnormal sounds. The point of maximal intensity (PMI) of any abnormal sounds should be located. The examiner should focus on cardiac auscultation separately from

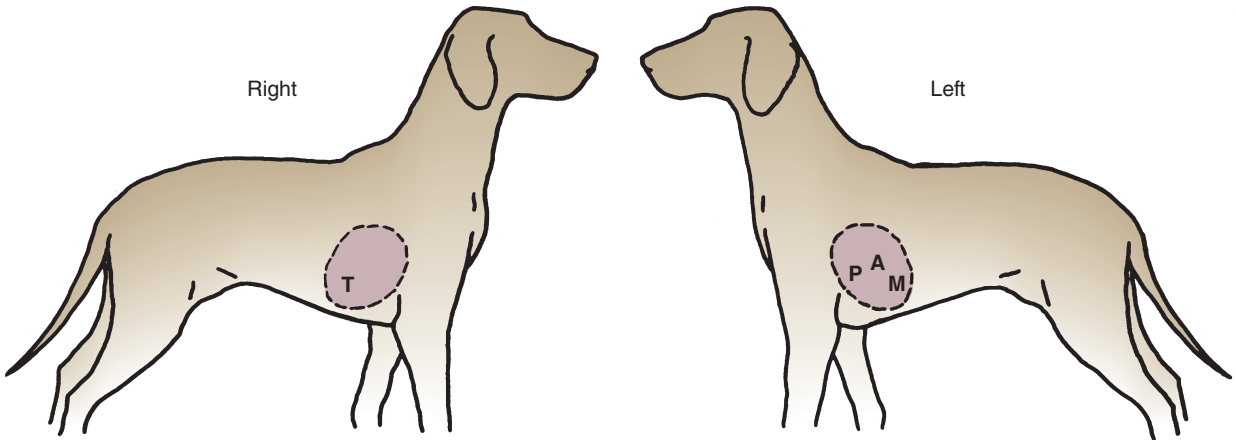


FIG 1.8
Approximate locations of various valve areas on the chest wall. *T,* Tricuspid; *P,* pulmonic; *A,* aortic; *M,* mitral.

pulmonary auscultation because full assimilation of sounds from both systems simultaneously is unlikely. Pulmonary auscultation is described further in Chapter 20.

Transient Heart Sounds

The heart sounds heard normally in dogs and cats are S_1 (associated with closure and tensing of the AV valves and associated structures at the onset of systole) and S_2 (associated with closure of the aortic and pulmonic valves following ejection). The diastolic sounds (S_3 and S_4) are not audible in normal dogs and cats. Fig. 1.9 correlates the hemodynamic events of the cardiac cycle with the ECG and timing of the heart sounds. It is important to understand these events and identify the timing (from a clinical perspective) of systole (between S_1 and S_2) and diastole (after S_2 until the next S_1) in the animal. The precordial impulse occurs just after S_1 (systole), and the arterial pulse occurs between S_1 and S_2.

Sometimes the first (S_1) and second (S_2) heart sounds are altered in intensity. The normal heart sounds may be louder in dogs and cats with a thin chest wall, high sympathetic tone, tachycardia, or systemic arterial hypertension. Shortened PR intervals increase the intensity of S_1. Muffled sounds can result from obesity, pericardial effusion, diaphragmatic hernia, dilated cardiomyopathy, hypovolemia/poor ventricular filling, or pleural effusion. A split or sloppy-sounding S_1 may be normal, especially in large dogs, or it may result from ventricular premature contractions or an intraventricular conduction delay. The intensity of S_2 can be increased by pulmonary hypertension of any cause (see Chapter 10). Cardiac arrhythmias often cause variation in the intensity (or even absence) of heart sounds.

Normal physiologic splitting of S_2 occasionally is heard in some (larger) dogs because of variation in stroke volume during the respiratory cycle. During inspiration, increased venous return to the right ventricle tends to delay closure of the pulmonic valve, whereas reduced filling of the left

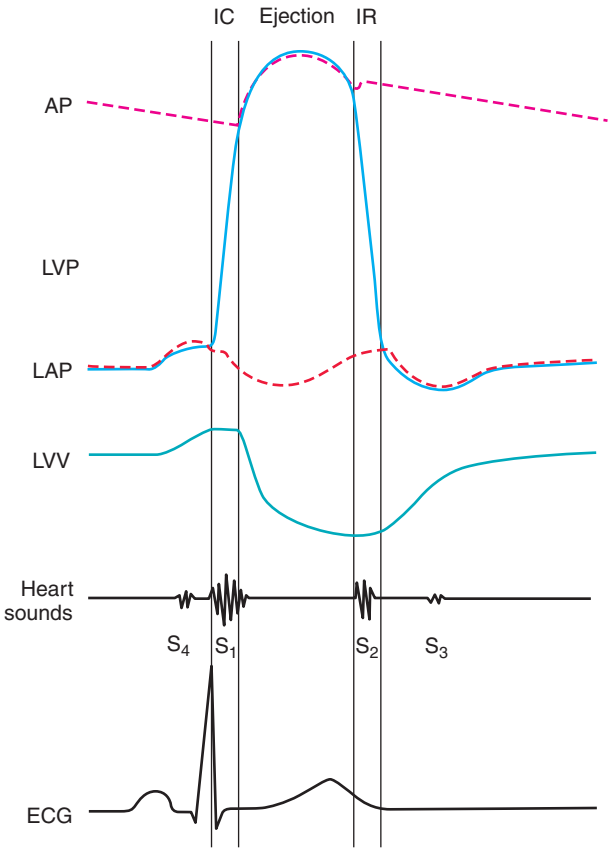


FIG 1.9
Cardiac cycle diagram depicting relationships among great vessel, ventricular and atrial pressures, ventricular volume, heart sounds, and electrical activation. *AP,* Aortic pressure; *ECG,* electrocardiogram; *IC,* isovolumic contraction; *IR,* isovolumic relaxation; *LAP,* left atrial pressure; *LVP,* left ventricular pressure; *LVV,* left ventricular volume.

ventricle accelerates aortic closure. Pathologic splitting of S_2 can result from delayed ventricular activation or prolonged RV ejection secondary to ventricular premature beats, right bundle branch block, a ventricular or atrial septal defect, or pulmonary hypertension.

Gallop Sounds

The third (S_3) and fourth (S_4) heart sounds occur during diastole (see Fig. 1.9) and are not normally audible in dogs and cats. When an S_3 or S_4 sound is heard, the heart can sound like a galloping horse, hence the term *gallop rhythm.* This term can be confusing because the presence or absence of an audible S_3 or S_4 has nothing to do with the heart's rhythm (that is, the origin of cardiac electrical activation and the intracardiac conduction process). Gallop sounds usually are heard best with the bell of the stethoscope (or by light pressure applied to a single-sided chestpiece) because they are of lower frequency than S_1 and S_2. At very fast heart rates, differentiation of S_3 from S_4 may be impossible. If both sounds are present, they may be superimposed, which is called a *summation gallop.*

The S_3 gallop, also known as an *S_3 gallop* or *ventricular gallop,* is associated with low-frequency vibrations at the end of the rapid ventricular filling phase. An audible S_3 in the dog or cat usually indicates ventricular dilation with myocardial failure. The extra sound often is very subtle although sometimes it can be fairly loud and easily detected; it is heard best over the cardiac apex. This sound may be the only auscultable abnormality in an animal with dilated cardiomyopathy. An S_3 gallop also may be audible in dogs with advanced mitral valve disease and CHF.

The S_4 gallop, also called an *atrial* or *presystolic gallop,* is associated with low-frequency vibrations triggered by blood flow into the ventricles during atrial contraction (just after the P wave of the ECG). An audible S_4 in the dog or cat usually is associated with increased ventricular stiffness and hypertrophy, such as with hypertrophic cardiomyopathy or hyperthyroidism in cats. A transient S_4 gallop of unclear significance sometimes is heard in stressed or anemic cats.

Other Transient Sounds

Other brief abnormal sounds are audible in some cases. Systolic clicks are mid-to-late systolic sounds that usually are heard best over the mitral valve area. These sounds have been associated with degenerative valvular disease (endocardiosis), mitral valve prolapse, and congenital mitral dysplasia; a concurrent mitral insufficiency murmur can be present. In dogs with degenerative valvular disease, a mitral click might be the first abnormal sound noted, with a murmur developing over time. An early systolic, high-pitched ejection sound at the left base can occur in animals with valvular pulmonic stenosis or other diseases that cause dilation of a great artery. The sound is thought to arise from either the sudden checking of a fused pulmonic valve or the rapid filling of a dilated vessel during ejection. Rarely, constrictive pericardial disease causes an audible pericardial knock. This diastolic sound arises from sudden checking of ventricular filling by the constrictive pericardium; its timing is similar to the S_3.

Cardiac Murmurs

There are many causes for cardiac murmurs. Most involve a structural cardiac abnormality and are considered pathologic murmurs. However, some murmurs do not and are considered nonpathologic. Nonpathologic murmurs are systolic in timing. They can occur for physiologic reasons, for example, when blood viscosity is reduced by anemia, or when cardiac output is increased from fever, hyperthyroidism, etc.; these are known as *functional* murmurs. Sometimes a soft murmur is heard in an animal without evidence for structural cardiac disease or physiologic alteration. These are considered *innocent* murmurs and often are found in young puppies. Many animals with a pathologic murmur also have other clinical signs consistent with heart disease. However, pathologic as well as nonpathologic murmurs often are discovered as incidental findings on physical examination. In these cases, it is important to determine if a clinically important cardiac disease or physiologic abnormality is the cause or not. Careful physical examination and auscultation can help the clinician decide how aggressively (or whether) to immediately pursue additional diagnostic testing.

Cardiac murmurs are described by their timing within the cardiac cycle (systolic or diastolic, or portions thereof), intensity, PMI on the precordium, radiation over the chest wall, quality, and pitch. Systolic murmurs can occur in early (protosystolic), middle (mesosystolic), or late (telesystolic) systole or throughout systole (holosystolic). Diastolic murmurs generally occur in early diastole (protodiastolic) or throughout diastole (holodiastolic). Murmurs at the end of diastole are termed *presystolic.* Continuous murmurs begin in systole and extend through S_2 into all or part of diastole. Murmur intensity generally is graded on a scale of 1 to 6 (sometimes written I to VI) (Table 1.1). The PMI usually is indicated by the hemithorax (right or left) and valve area or intercostal space where it is located, or by the terms *apex* or *base.* Because murmurs can radiate extensively, the entire thorax, thoracic inlet, and carotid artery areas should be auscultated. The pitch and quality of a murmur relate to its frequency and subjective assessment. "Noisy" or "harsh" murmurs contain mixed frequencies. "Musical" murmurs are of essentially one frequency with its overtones; these can sound like a "whoop" or "honk."

Murmurs also can be described by their phonocardiographic configuration (Fig. 1.10). A plateau-shaped or "regurgitant" murmur begins at the time of S_1 and remains of fairly uniform intensity throughout systole. Sometimes this murmur configuration also is called *holosystolic*, because it generally is consistent throughout systole. Loud regurgitant/holosystolic murmurs can mask the S_1 and S_2 sounds. AV valve insufficiency and interventricular septal defects commonly cause this type of murmur because turbulent blood flow begins at the time of AV valve closing and continues throughout ventricular systole. A crescendo-decrescendo or diamond-shaped murmur starts softly, builds intensity in

midsystole, and then diminishes; the S_1 and S_2 sounds usually can be heard before and after the murmur, respectively. This type is also called an *ejection murmur* because it occurs during ventricular ejection, usually because of a ventricular outflow obstruction. A decrescendo murmur tapers from its initial intensity over time; it may occur in systole or diastole. Continuous (machinery) murmurs occur throughout systole and (well into or) throughout diastole.

TABLE 1.1

Grading of Heart Murmurs

GRADE	MURMUR
1	Very soft murmur; heard only over its site of origin, after prolonged listening in quiet surroundings
2	Soft murmur but easily heard over its site of origin (usually a particular valve area)
3	Moderate-intensity murmur; usually radiates to other precordial/valve areas too
4	Loud murmur but without a precordial thrill; radiates widely and usually can be heard over most precordial regions
5	Loud murmur with a palpable precordial thrill; radiates widely and usually can be heard clearly over all precordial regions
6	Very loud murmur with a precordial thrill; radiates widely, generally is heard clearly over all precordial areas, and also can be heard with the stethoscope chestpiece lifted slightly (~1 cm) from the chest wall (at the murmur PMI)

Systolic murmurs

Systolic murmurs can be decrescendo, holosystolic (plateau-shaped), or ejection (crescendo-decrescendo) in configuration. It can be difficult to differentiate these by auscultation alone. However, the most important steps toward diagnosis include establishing that the murmur occurs in systole (rather than diastole), determining its PMI, and grading its intensity. Fig. 1.11 depicts the typical PMI of various murmurs over the chest wall.

Functional, nonpathologic murmurs usually are heard best over the left heart base. They are soft to moderate in intensity and of decrescendo or crescendo-decrescendo configuration. Functional murmurs have no apparent CV structural cause and can accompany physiologic

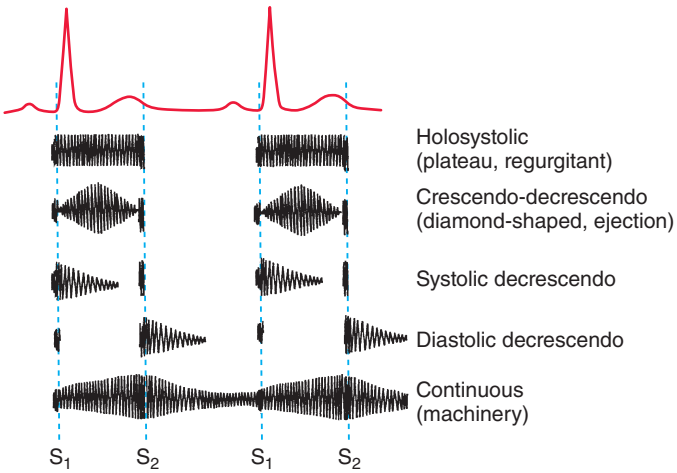


FIG 1.10
The phonocardiographic shape (configuration) and the timing of different murmurs are illustrated in this diagram.

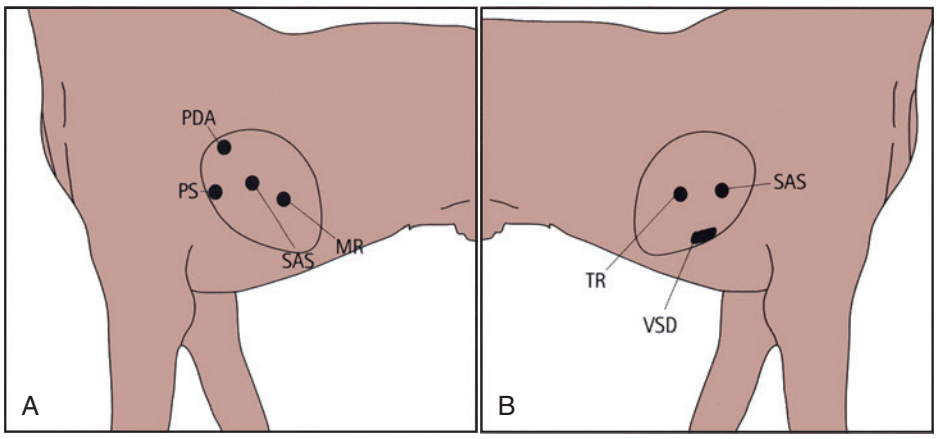


FIG 1.11
The usual point of maximal intensity (PMI) and configuration for murmurs typical of various congenital and acquired causes are depicted on left **(A)** and right **(B)** chest walls. *MR,* Mitral regurgitation (insufficiency); *PDA,* patent ductus arteriosus; *PS,* pulmonic stenosis; *SAS,* subaortic stenosis; *TR,* tricuspid regurgitation (insufficiency); *VSD,* ventricular septal defect. (From Ware WA: *Cardiovascular disease in small animal medicine,* London, 2011, Manson Publishing.)

abnormalities (and also are called *physiologic murmurs*). Physiologic murmurs have been associated with anemia, fever, high sympathetic tone, hyperthyroidism, marked bradycardia, peripheral arteriovenous fistulae, hypoproteinemia, and athletic hearts. Aortic dilation (for example, from hypertension) and dynamic RV outflow obstruction are other conditions associated with systolic murmurs in cats. Innocent puppy murmurs also are nonpathologic and generally disappear by the time the animal is about 6 months old.

The murmur of mitral insufficiency (regurgitation) most often is heard best at the left apex, in the area of the mitral valve. It radiates well dorsally and often to the left base and right chest wall. Mitral insufficiency characteristically causes a plateau-shaped murmur (holosystolic timing), but in its early stages the murmur may be protosystolic, tapering to a decrescendo configuration. Occasionally this murmur has a musical or "whoop-like" quality. With degenerative mitral valve disease, murmur intensity usually relates to disease severity.

Systolic ejection murmurs most often are heard at the left base. Ventricular outflow obstruction, usually from a fixed narrowing (e.g., subaortic or pulmonic valve stenosis) or dynamic muscular obstruction, is the typical cause. Ejection murmurs become louder as cardiac output or contractile strength increases. The subaortic stenosis murmur is heard well at the low left base and also at the right base, because the murmur radiates up the aortic arch, which curves toward the right. This murmur also radiates up the carotid arteries and, when loud, occasionally can be heard on the calvarium. Soft (grade 1-2/6), nonpathologic (functional) systolic ejection murmurs are common in sighthounds, Boxers, and certain other large breeds; these can be related to a large stroke volume, as well as breed-related left ventricular (LV) outflow tract characteristics. The murmur of pulmonic stenosis is best heard at the cranial left base. Relative pulmonic stenosis occurs when flow volume through a structurally normal valve is abnormally increased (as with a large left-to-right shunting atrial or ventricular septal defect).

Most murmurs heard on the right chest wall are holosystolic, plateau-shaped murmurs, except for the subaortic stenosis murmur (discussed earlier). The tricuspid insufficiency murmur is loudest at the right apex over the tricuspid valve. Its pitch or quality may be noticeably different from a concurrent mitral insufficiency murmur. Moderate to severe tricuspid insufficiency often is accompanied by jugular pulsations. Ventricular septal defects also cause holosystolic murmurs. The PMI usually is at the right sternal border, reflecting the direction of the intracardiac shunt. A large ventricular septal defect can also cause the murmur of relative pulmonic stenosis.

In the general population of apparently healthy cats, the prevalence of systolic murmurs is estimated at up to 40%, and is even higher in older cats. Although a systolic murmur can accompany subclinical structural cardiac disease, especially in older cats where the prevalence of cardiomyopathy can be almost 30%, the presence of a murmur alone is not a highly sensitive predictor of cardiomyopathy. This is especially true in young cats. The PMI of most feline murmurs is near the sternal border. Many of these murmurs are associated with dynamic left (or right) ventricular outflow obstruction. Congenital cardiac malformations are another potential cause of murmurs in cats. NT-proBNP measurement can help with screening for structural disease in cats. However, an echocardiogram performed by a veterinary cardiologist or other person with advanced echocardiography training is the most sensitive tool for detecting structural disease in cats with a murmur.

Diastolic murmurs

Diastolic murmurs are uncommon in dogs and cats. They are always pathologic. Aortic valve insufficiency from infective endocarditis is the most common cause, although congenital malformation or degenerative aortic valve disease occasionally occurs. Clinically relevant pulmonic valve insufficiency is rare, but an audible pulmonic insufficiency murmur would be more likely in the face of pulmonary hypertension. These diastolic murmurs begin at the time of S_2 and are heard best at the left base. They are decrescendo in configuration and extend a variable time into diastole, depending on the pressure difference between the associated great vessel and ventricle. Some aortic insufficiency murmurs have a musical quality.

Continuous murmurs

As implied by the name, continuous ("machinery") murmurs occur throughout the cardiac cycle. They indicate that a substantial pressure gradient exists continuously between two connecting vessels. The murmur is not interrupted at the time of S_2; rather, its intensity often is greater at that time. The murmur becomes softer toward the end of diastole, and at slow heart rates it may even become inaudible by mid- or late-diastole. Patent ductus arteriosus (PDA) is by far the most common cause of a continuous murmur. The PDA murmur is loudest high at the left base, dorsal to the pulmonic valve area; it tends to radiate cranially, ventrally, and to the right. The systolic component usually is louder and heard well all over the chest. The diastolic component often is more localized to the left base. The diastolic component (and the correct diagnosis) may be missed if only the cardiac apical area is auscultated.

Continuous murmurs can be confused with concurrent systolic ejection and diastolic decrescendo murmurs (the so-called *to-and-fro* murmur). However, with to-and-fro murmurs, the ejection (systolic) component tapers in late systole, and the S_2 usually can be heard as a distinct sound. The most common cause of a to-and-fro murmur is the combination of subaortic stenosis and aortic valve insufficiency (usually as a result of aortic valve endocarditis). Rarely, stenosis and insufficiency of the pulmonic valve cause this type of murmur. Likewise, both a holosystolic and a diastolic decrescendo murmur can occur together occasionally (such as with a ventricular septal defect and aortic insufficiency from loss of aortic root support); this also is not considered a true *continuous* murmur.

Suggested Readings

Côté E, et al. Management of incidentally detected heart murmurs in dogs and cats. *J Am Vet Med Assoc*. 2015;246:1076–1088. Also published in *J Vet Cardiol* 2015;17:245–261.

Côté E, et al. Assessment of the prevalence of heart murmurs in overtly healthy cats. *J Am Vet Med Assoc*. 2004;225:384–388.

Dirven MJ, et al. Cause of heart murmurs in 57 apparently healthy cats. *Tijdschr Diergeneeskd*. 2010;135:840–847.

Fabrizio F, et al. Left basilar systolic murmur in retired racing greyhounds. *J Vet Intern Med*. 2006;20:78–82.

Ferasin L, et al. Risk factors for coughing in dogs with naturally acquired myxomatous mitral valve disease. *J Vet Intern Med*. 2013;27:286–292.

Hoglund K, et al. A prospective study of systolic ejection murmurs and left ventricular outflow tract in Boxers. *J Small Anim Pract*. 2011;52:11–17.

Koplitz SL, Meurs KM, Bonagura JD. Echocardiographic assessment of the left ventricular outflow tract in the Boxer. *J Vet Intern Med*. 2006;20:904–911.

Paige CF, et al. Prevalence of cardiomyopathy in apparently healthy cats. *J Am Vet Med Assoc*. 2009;234:1398–1403.

Payne JR, Brodbelt DC, Fuentes VL. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). *J Vet Cardiol*. 2015;17:S244–S257.

Rishniw M, Thomas WP. Dynamic right ventricular outflow obstruction: a new cause of systolic murmurs in cats. *J Vet Intern Med*. 2002;16:547–552.

Szatmari V, van Leeuwn MW, Teske E. Innocent cardiac murmur in puppies: prevalence, correlation with hematocrit, and auscultation characteristics. *J Vet Intern Med*. 2015;29:1524–1528.

Wagner T, et al. Comparison of auscultatory and echocardiographic findings in healthy adult cats. *J Vet Cardiol*. 2010;12:171–182.

Ware WA. The cardiovascular examination. In: Ware WA, ed. *Cardiovascular disease in small animal medicine*. London: Manson Publishing; 2011:26–33.

Ware WA. Syncope or intermittent collapse. In: Ware WA, ed. *Cardiovascular disease in small animal medicine*. London: Manson Publishing; 2011:139–144.

CHAPTER 2

Diagnostic Tests for the Cardiovascular System



CARDIAC BIOCHEMICAL MARKERS

Certain cardiac biomarkers have potential diagnostic and prognostic utility in dogs and cats, especially the cardiac troponins and natriuretic peptides. Cardiac troponins are regulatory proteins attached to the cardiac actin (thin) contractile filaments. Circulating concentrations of cardiac troponin proteins normally are very low; however, myocyte injury allows their leakage into the cytoplasm and extracellular fluid. Cardiac troponin I (cTnI) is the protein usually measured clinically. It is more sensitive for detecting myocardial injury than other biochemical markers of muscle damage (such as cardiac-specific creatine kinase), although it usually does not differentiate the underlying cause. Serum cTnI increases relatively rapidly with severe injury. Because the half-life of this biomarker is short, it can decrease rapidly; the half-life in dogs has been estimated at about 6 hours. Persistently increased cTnI indicates ongoing myocardial damage. Moderate elevations in cTnI can occur in chronic heart disease, although levels often are normal with mild disease. This is thought to reflect myocardial remodeling. Myocardial inflammation, trauma, various acquired and congenital cardiac diseases, and congestive heart failure (CHF) are associated with increased cTnI concentrations, although there can be overlap with clinically normal animals. Strenuous exercise and some noncardiac disease, such as gastric dilatation/volvulus, can be associated with minimal cTnI increases. Renal dysfunction can falsely elevate cTnI, and older animals may have mildly elevated cTnI. Normal Greyhounds appear to have slightly higher cTnI concentration than other breeds. Human assays for cTnI can be used in dogs and cats. Standard (older) cTnI tests have a lower limit of detection of about 0.02 ng/mL with an upper detection limit of about 40 ng/mL. Some labs consider a cTnI concentration of 0.09 ng/mL as the upper limit of normal. Others indicate that cTnI concentrations <0.2 ng/mL are to be considered normal (Troponin I Canine/Feline, IDEXX). A high-sensitivity cTnI test (with a detection range of 0.006-50 ng/mL) has been validated in dogs and cats; this can detect milder cTnI elevation in early to moderate cardiac disease (such as with canine chronic mitral valve disease), although clinical utility remains to be defined.

The natriuretic peptides (or their precursors) can be useful biomarkers for identifying the presence and possibly prognosis of heart disease and CHF. Increased circulating concentrations occur with vascular volume expansion, decreased renal clearance, and when their production is stimulated (as with atrial stretch, ventricular strain and hypertrophy, hypoxia, tachyarrhythmias, and occasionally from ectopic noncardiac production). The natriuretic peptides (atrial [ANP] and brain [BNP]) help regulate blood volume and pressure and antagonize the renin-angiotensin-aldosterone axis, among other effects. They are synthesized as preprohormones, then cleaved to a prohormone, and finally to their inactive amino terminal (NT-pro-) and active carboxyterminal (C-) fragments. The N-terminal fragments remain in circulation longer and reach higher plasma concentrations than the active hormone molecules.

NT-proBNP is measured most often, and the degree of its elevation generally correlates with cardiac disease severity. In animals with dyspnea, NT-proBNP measurement can help the clinician decide whether it is more likely due to CHF or a noncardiac cause. Similar to cTnI, natriuretic peptides are better used as functional markers of cardiac disease rather than of specific pathology. However, circulating (NT-pro)BNP concentrations also can rise with certain noncardiac abnormalities, including renal dysfunction, pulmonary hypertension, and hyperthyroidism (in cats). Species-specific assays are required. Canine and feline NT-proBNP measurement is commercially available (Cardiopet proBNP, Canine and Feline; IDEXX). Plasma concentrations of less than (800-) 900 pmol/L (dogs) and less than 100 pmol/L (cats) are associated with a low risk of clinically significant heart disease. However, some Doberman Pinschers with occult cardiomyopathy have had NT-proBNP concentrations below this cut-off. Dogs with respiratory signs, especially with a murmur, and a plasma NT-proBNP concentration >(1400-)1800 pmol/L are more likely to have

CHF as the underlying cause. Plasma NT-proBNP between 901-1800 pmol/L in dogs represents a "gray" zone, where increased stress on the heart is likely but CHF cannot be reliably differentiated. When NT-proBNP is elevated, additional diagnostic tests (such as thoracic radiography and echocardiography) are recommended. Small breed dogs with chronic mitral valve disease that have a NT-proBNP >1500 pmol/L are at high risk for developing CHF within the next 12 months. An assay for canine plasma C-BNP (Cardio-BNP; ANTECH) is also available; the manufacturer reports a cut-off value of 6 pg/mL as being highly sensitive and specific for CHF in dyspneic dogs.

In cats, a NT-proBNP >100 pmol/L is likely to indicate increased stress or stretch on the myocardium, and follow-up testing with echocardiography, and blood pressure and T4 (in older cats) measurement, is recommended. Hypertension, hyperthyroidism, and renal dysfunction can elevate NT-proBNP levels. Cats with respiratory signs and a NT-proBNP >270 pmol/L are likely to have CHF. For cats with NT-proBNP between 100 and 269 pmol/L, respiratory signs are less likely to be caused by CHF; however, additional testing, as previously noted, is advised to screen for preclinical cardiovascular disease. A point of care (POC), SNAP Feline proBNP test (IDEXX), can be helpful for differentiating CHF from noncardiac causes of dyspnea, although caution with interpretation is advised. For example, a negative POC proBNP SNAP test in a cat with pleural effusion strongly suggests a noncardiac cause; however, a positive test can be less specific. This POC test is better at identifying the absence of moderate to severe cardiac disease (high negative predictive value) in cats, whether symptomatic or not.

CARDIAC RADIOGRAPHY

Thoracic radiographs are important for assessing overall heart size and shape, pulmonary vessels, and lung parenchyma, as well as surrounding structures. Both lateral and dorsoventral (DV) or ventrodorsal (VD) views should be obtained; a three-view study, with both left and right lateral images, usually is preferred. On lateral views, the ribs should be aligned with each other dorsally. On DV or VD views, the sternum, vertebral bodies, and dorsal spinous processes should be superimposed. Consistency in views chosen is important because slight changes in cardiac shadow appearance occur with different positions. For example, the heart tends to look more elongated on VD view in comparison to its appearance on DV view. In general, the DV view yields better definition of the hilar area and caudal pulmonary arteries. Careful (not obliquely tilted) patient positioning is important. Exposure should be made at the time of peak inspiration. On expiration, the lungs appear denser, the heart is relatively larger, the diaphragm may overlap the caudal heart border, and pulmonary vessels are poorly delineated.

Chest conformation must be considered when evaluating cardiac size and shape in dogs because normal cardiac appearance may vary from breed to breed. The cardiac shadow in dogs with a round or barrel-shaped chest has greater sternal contact on lateral view and an oval shape on DV or VD view. In contrast, the heart has an upright, elongated appearance on lateral view and a small, almost circular shape on DV or VD view in narrow- and deep-chested dogs. Because of variations in chest conformation and the influences of respiration, cardiac cycle, and positioning on the apparent size of the cardiac shadow, mild cardiomegaly may be difficult to identify. Also, excess pericardial fat may mimic the appearance of cardiomegaly. The cardiac shadow in puppies normally appears slightly large relative to thoracic size compared with that of adult dogs. Radiographic suggestion of abnormal cardiac size or shape should be considered within the context of the physical examination and other test findings in all cases.

The vertebral heart score (VHS) is one widely used means of assessing cardiomegaly in dogs and cats because there is good correlation between body length and heart size, although chest conformation may have some influence. Measurements for the VHS are obtained using the lateral view (Fig. 2.1) in adult dogs and puppies. The cardiac long axis is measured from the ventral border of the left mainstem bronchus to the most ventral aspect of the cardiac apex. This same distance is compared with the thoracic spine beginning at the cranial edge of T4; length is estimated to the nearest 0.1

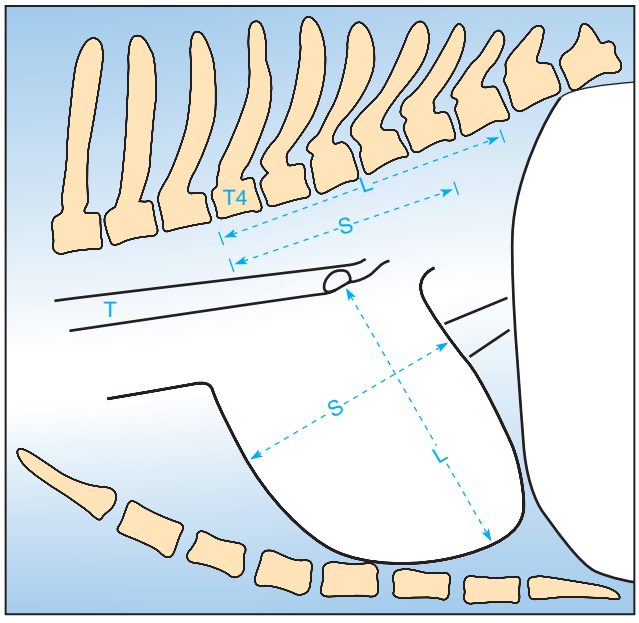


FIG 2.1
Diagram illustrating the vertebral heart score (VHS) measurement method using the lateral chest radiograph. The long-axis (L) and short-axis (S) heart dimensions are transposed onto the vertebral column and recorded as the number of vertebrae beginning with the cranial edge of T4. These values are added to obtain the VHS. In this example, L = 5.8 v, S = 4.6 v; therefore VHS = 10.4 v. *T,* Trachea. (Modified from Buchanan JW, Bücheler J: Vertebral scale system to measure canine heart size in radiographs, *J Am Vet Med Assoc* 206:194, 1995.)

vertebra. The maximum perpendicular short axis is measured in the central third of the heart shadow; the short axis is also measured in number of vertebrae (to the nearest 0.1) beginning with T4. Both measurements are added to yield the VHS. A VHS between 8.5 and 10.5 vertebrae (v) is considered normal for most breeds. However, some variation exists among breeds. In dogs with a short thorax (e.g., Miniature Schnauzer), an upper limit of 11 v may be normal. The VHS in normal Greyhounds, Whippets, and some other breeds such as the Labrador Retriever may normally exceed 11 v, and the VHS range in normal Boxers is thought to extend to 12.6 v. In contrast, an upper limit of 9.5 v may be normal in dogs with a long thorax (e.g., Dachshund).

In cats, the cardiac silhouette on lateral view is aligned more parallel to the sternum than in dogs; this often is accentuated in older cats. Radiographic positioning can influence the relative size, shape, and position of the heart because the feline thorax is so flexible. On lateral view, the normal cat heart is less than or equal to two intercostal spaces (ICSs) in width and less than 70% of the height of the thorax. On DV view the heart is normally no more than one half the width of the thorax. Measurement of VHS is useful in cats as well. From lateral radiographs in cats, mean VHS in normal cats is 7.3 to 7.5 vertebrae (range 6.7-8.1 v). A VHS over 9 v strongly suggests heart disease in cats. In normal cats, the mean short-axis cardiac dimension taken from DV or VD view, compared with the thoracic spine beginning at T4 on lateral view, is 3.4 to 3.5 v, with 4 v identified as the upper limit of normal. In kittens, as in puppies, the relative size of the heart compared with that of the thorax is larger than in adults because of smaller lung volume.

An abnormally small heart shadow (microcardia) usually is caused by markedly reduced venous return from severe hypovolemia. The cardiac apex appears more pointed and may be elevated from the sternum.

CARDIOMEGALY

Generalized enlargement of the cardiac silhouette on plain thoracic radiographs may indicate true cardiomegaly or pericardial distention. With cardiac enlargement, the contours of different chambers usually are still evident, although massive right ventricular (RV) and right atrial (RA) dilation can cause a rounded cardiac silhouette. Fluid, fat, or viscera within the pericardium tends to obliterate these contours and can create a globoid heart shadow (see Fig. 9.1, p. 175 and Fig. 9.4, p. 179). Common differential diagnoses for cardiac enlargement patterns are listed in Box 2.1. A clock-face analogy is often used to identify regions on cardiac silhouette where specific chamber or vascular enlargement typically are seen, especially on DV/VD view.

CARDIAC CHAMBER ENLARGEMENT PATTERNS

Most diseases that cause cardiac dilation or hypertrophy affect two or more chambers. For example, mitral insufficiency leads to left ventricular (LV) and left atrial (LA) enlargement; pulmonic stenosis causes RV enlargement, a main pulmonary artery bulge, and often RA dilation. Even when only one side of the heart is affected, the cardiac silhouette may appear generally enlarged because of chamber superimposition. For descriptive purposes, however, specific chamber enlargement patterns are presented in the following sections. Fig. 2.2 illustrates various patterns of chamber enlargement.

BOX 2.1

Common Differential Diagnoses for Radiographic Signs of Cardiomegaly

Generalized Enlargement of the Cardiac Shadow

Dilated cardiomyopathy
Chronic mitral and tricuspid insufficiency
Pericardial effusion
Peritoneopericardial diaphragmatic hernia
Tricuspid dysplasia
Ventricular or atrial septal defect
Patent ductus arteriosus

Left Atrial Enlargement Alone

Early mitral insufficiency
Hypertrophic cardiomyopathy
Early dilated cardiomyopathy (especially in Doberman Pinschers)
(Sub)aortic stenosis

Left Atrial and Ventricular Enlargement

Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Mitral insufficiency
Aortic insufficiency
Ventricular septal defect
Patent ductus arteriosus
(Sub)aortic stenosis
Systemic hypertension
Hyperthyroidism

Right Atrial and Ventricular Enlargement

Advanced heartworm disease
Chronic, severe pulmonary disease
Tricuspid insufficiency
Pulmonic stenosis
Tetralogy of Fallot
Atrial septal defect
Pulmonary hypertension
Mass lesion within the right heart

Left Atrium

The left atrium (LA) is the most dorsocaudal chamber of the heart, although its auricular appendage extends to the left and craniad. On lateral view, an enlarged LA bulges dorsally and caudally, elevating the left and sometimes right mainstem bronchus. Severe LA enlargement may be associated with collapse or compression of the left mainstem bronchus.

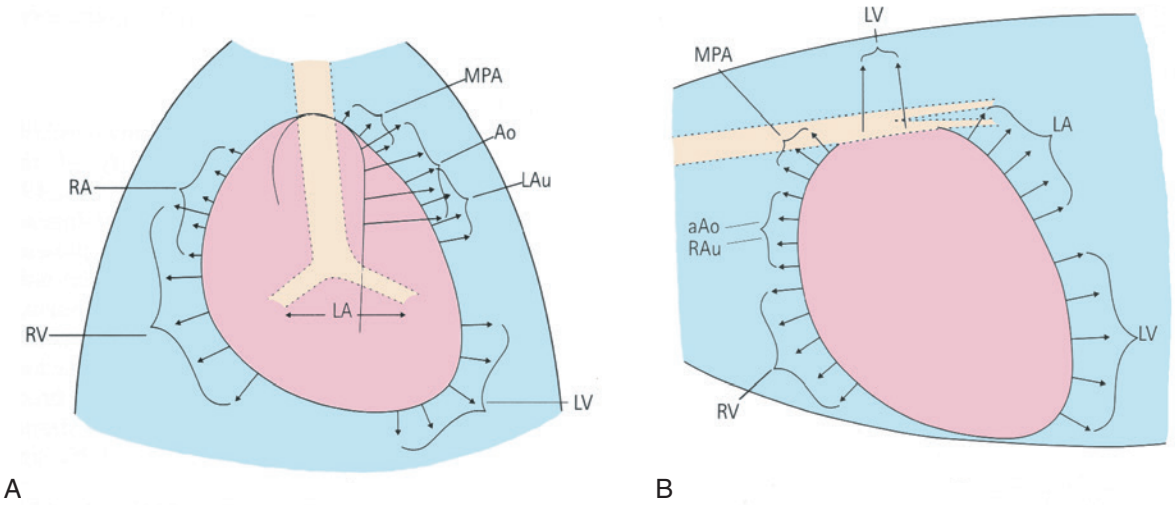


FIG 2.2
Common radiographic enlargement patterns. Diagrams indicating direction of enlargement of cardiac chambers and great vessels in the dorsoventral **(A)** and lateral **(B)** views. *Ao,* Aorta (descending); *LA,* left atrium; *LAu,* left auricle; *LV,* left ventricle; *MPA,* main pulmonary artery; *RA,* right atrium; *RAu,* right auricle; *RV,* right ventricle. (Modified from Ware WA: *Cardiovascular disease in small animal medicine*, London, 2011, Manson Publishing.)

In cats, the caudal heart border is normally quite straight on lateral view; LA enlargement causes subtle to marked convexity of the dorsocaudal heart border with elevation of the mainstem bronchi.

On DV or VD view, the mainstem bronchi tend to be displaced laterally and may curve slightly around a markedly enlarged LA (sometimes referred to as the "bowed-legged cowboy sign"). Concurrent left auricular enlargement causes a bulge in the 2- to 3-o'clock area of the cardiac silhouette. Massive LA enlargement sometimes appears as a large, rounded soft tissue opacity superimposed over the LV apical area on DV (VD) view (Fig. 2.3). In some cats, marked LA enlargement creates a "valentine"-shaped cardiac silhouette (see Fig. 8.7, p. 169) because it causes widening of the cranial aspect of the heart. LA size is influenced by the pressure or volume load imposed, as well as by its duration. For example, mitral regurgitation of gradually increasing severity can cause massive LA enlargement without pulmonary edema, if chamber dilation occurs slowly at relatively low pressure. Conversely, chordae tendineae rupture can acutely cause severe valvular regurgitation with rapid and marked LA pressure increase, leading to pulmonary edema with relatively normal LA size.

Left Ventricle

LV enlargement is manifested on lateral view by a taller cardiac silhouette with elevation of the carina and caudal vena cava (CaVC). The caudal heart border becomes convex, but cardiac apical sternal contact is maintained. On DV/VD view, rounding and enlargement occur in the 2- to 5-o'clock position. Some cats with hypertrophic cardiomyopathy maintain a pointed LV apical appearance.

Right Atrium

RA enlargement expands the cranial heart border and widens the cardiac silhouette on lateral view. Tracheal elevation may occur over the cranial portion of the heart shadow. Bulging of the cardiac shadow on DV/VD view occurs in the 9- to 11-o'clock position. The right atrium (RA) is largely superimposed over the right ventricle (RV), so differentiation from RV enlargement is difficult; however, concurrent enlargement of both chambers is common.

Right Ventricle

RV enlargement (dilation or hypertrophy) usually causes increased convexity of the cranioventral heart border and elevation of the trachea over the cranial heart border on lateral view. With severe RV enlargement and relatively normal left heart size, the apex is elevated from the sternum (see Fig. 10.1, p. 191); the carina and CaVC are also elevated. The degree of sternal contact of the heart shadow is not, by itself, a reliable sign of RV enlargement because of breed variation in chest conformation. On DV/VD view, the heart tends to take on a reverse-D configuration, especially without concurrent left-sided enlargement. The apex may be shifted leftward, and the right heart border bulges to the right.

INTRATHORACIC BLOOD VESSELS

Great Vessels

The aorta and main pulmonary artery dilate in response to chronic arterial hypertension or increased turbulence (poststenotic dilation). Subaortic stenosis causes dilation of the ascending aorta. Because of its location within the mediastinum, dilation here is not easily detected, although widening and increased opacity of the dorsocranial heart

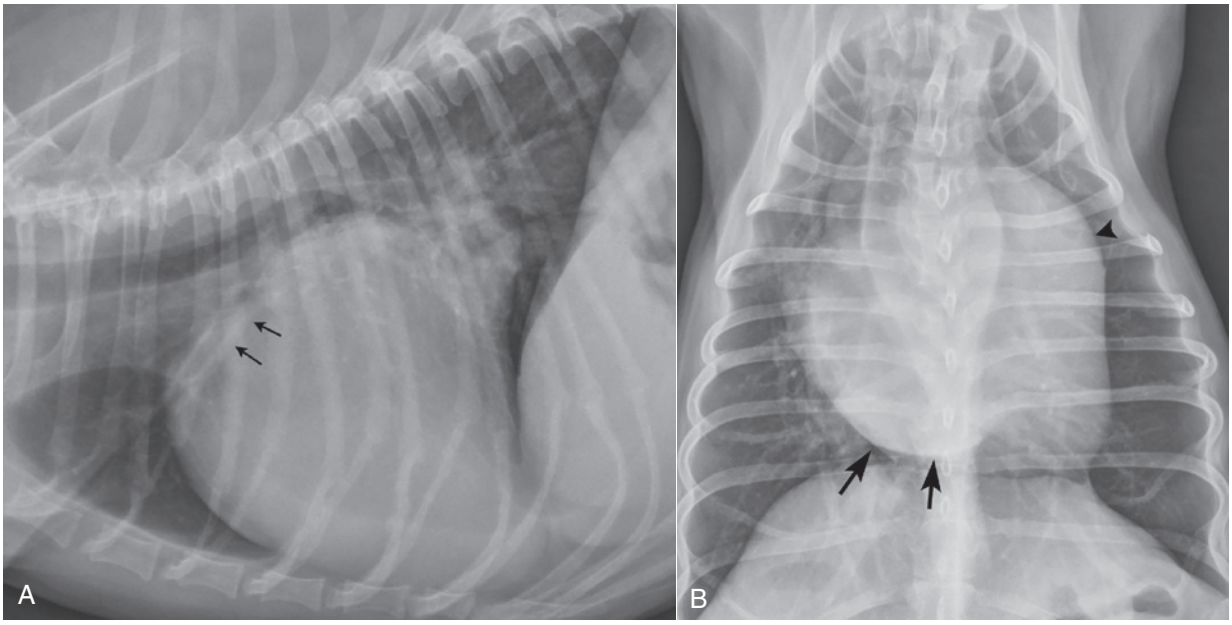


FIG 2.3
Lateral **(A)** and dorsoventral **(B)** views from a dog with chronic mitral regurgitation. Marked left ventricular and atrial enlargement are evident. Dorsal displacement of the carina and pulmonary venous distension *(arrows)* are seen in **A;** the caudal edge of the left atrium *(arrows),* superimposed over the ventricular shadow, and a prominent left auricular bulge *(arrowhead)* are seen in **B.**

shadow may be observed. Patent ductus arteriosus causes a localized dilation in the descending aorta just caudal to the arch where the ductus exits; this "ductus bump" is seen on DV or VD view in the 2- to 3-o'clock position. A prominent aortic arch is more common in cats than dogs. The thoracic aorta of older cats also may have an undulating appearance. Systemic hypertension should be a consideration in these cases.

Severe dilation of the main pulmonary trunk (usually associated with pulmonic stenosis or pulmonary hypertension) can appear as a bulge superimposed over the trachea on lateral radiograph. On DV view in the dog, main pulmonary trunk enlargement causes a bulge in the 1- to 2-o'clock position. In the cat, the main pulmonary trunk is slightly more medial and is usually obscured within the mediastinum.

The CaVC normally angles cranioventrally from the diaphragm to the heart. The width of the CaVC is approximately that of the descending thoracic aorta, although its size changes with respiration. The CaVC-cardiac junction is pushed dorsally with enlargement of either ventricle. Persistent widening of the CaVC could indicate RV failure, cardiac tamponade, pericardial constriction, or other obstruction to right heart inflow. The following comparative findings suggest CaVC distention: CaVC/aortic diameter (at same ICS) greater than 1.5; CaVC/length of the thoracic vertebra directly above the tracheal bifurcation greater than 1.3; and CaVC/width of right fourth rib (just ventral to the spine) greater than 3.5. A thin CaVC can indicate hypovolemia, poor venous return, or pulmonary overinflation.

Lobar Pulmonary Vessels

Pulmonary arteries are located dorsal and lateral to their accompanying veins and bronchi. In other words, pulmonary veins are "ventral and central." On lateral view, the cranial lobar vessels in the nondependent ("up-side") lung are more ventral and larger than those in the dependent lung. The width of the cranial lobar vessels is measured where they cross the fourth rib in dogs or at the cranial heart border (fourth to fifth rib) in cats. These vessels are normally 0.5 to 1 times the diameter of the proximal one third of the fourth rib. The DV view is best for evaluating the caudal pulmonary vessels. The caudal lobar vessels that are 0.5 to 1 times the width of the ninth (dogs) or tenth (cats) rib at the point of intersection are normal. However, in many normal dogs, the right caudal pulmonary vessels are slightly wider than the ninth rib. This may be true in cats as well. Four pulmonary vascular patterns are usually described: overcirculation, undercirculation, prominent pulmonary arteries, and prominent pulmonary veins.

An overcirculation pattern occurs when the lungs are hyperperfused, as occurs with left-to-right shunts, overhydration, and other hyperdynamic states. Pulmonary arteries and veins are both prominent. The increased perfusion also generally increases lung opacity.

Pulmonary undercirculation is characterized by thin pulmonary arteries and veins, along with increased pulmonary lucency. Severe dehydration, hypovolemia, obstruction to RV inflow, right-sided CHF, and tetralogy of Fallot can cause this pattern. Some animals with pulmonic stenosis appear to

have pulmonary undercirculation. Overinflation of the lungs or overexposure of radiographs also minimizes the appearance of pulmonary vessels.

Pulmonary arteries that are larger than their accompanying veins indicate pulmonary arterial hypertension. The pulmonary arteries become dilated, tortuous, and blunted, and visualization of the terminal portions is lost. Heartworm disease often causes this pulmonary vascular pattern, in addition to patchy to diffuse interstitial pulmonary infiltrates.

Prominent pulmonary veins are a sign of pulmonary venous congestion, usually from left-sided CHF. On lateral view, the cranial lobar veins are larger and denser than their accompanying arteries and may sag ventrally. Dilated, tortuous pulmonary veins may be seen entering the dorsocaudal aspect of the enlarged LA in dogs and cats with chronic pulmonary venous hypertension. However pulmonary venous dilation is not always visualized in patients with left-sided heart failure. In cats with acute cardiogenic pulmonary edema, enlargement of both pulmonary veins and arteries is common.

PATTERNS OF PULMONARY EDEMA

Pulmonary interstitial fluid accumulation increases pulmonary opacity. Pulmonary vessels appear ill-defined, and bronchial walls look thick as interstitial fluid accumulates around vessels and bronchi. As pulmonary edema worsens, areas of fluffy or mottled fluid opacity progressively become more confluent. Alveolar edema causes greater opacity in the lung fields and obscures vessels and outer bronchial walls. The air-filled bronchi appear as lucent, branching lines surrounded by fluid density (air bronchograms). Interstitial and alveolar patterns of pulmonary infiltration can be caused by many pulmonary diseases, as well as by cardiogenic edema. The distribution of these pulmonary infiltrates is important, especially in dogs. Cardiogenic pulmonary edema in dogs classically is located in dorsal and perihilar areas and is often bilaterally symmetric. Nevertheless, some dogs develop an asymmetric or concurrent ventral distribution of cardiogenic edema. The distribution of cardiogenic edema in cats is usually uneven and patchy, although some cats have a diffuse, uniform pattern. The infiltrates can be distributed throughout the lung fields or concentrated in ventral, middle, or caudal zones. Both the radiographic technique and the phase of respiration influence the apparent severity of interstitial infiltrates. Other abnormalities on thoracic radiographs are discussed in Chapter 20.

OTHER IMAGING TECHNIQUES

Cardiac Computed Tomography and Magnetic Resonance Imaging

Cardiac computed tomography (CT) and magnetic resonance imaging (MRI) are now more widely available in veterinary practice and provide greater anatomic detail than plain radiographs. Their requirements for greater technical expertise, study duration, and expense, as well as the need for heavy sedation or general anesthesia, may be limitations in some cases. CT combines multiple radiographic image slices to produce detailed cross-sectional images from reconstructed three-dimensional (3-D) orientations. MRI uses radio waves and a magnetic field, rather than ionizing radiation, to create detailed tissue images. These techniques can allow greater differentiation among cardiovascular structures, varying tissue types, and the blood pool. Identification of pathologic morphology, such as from cardiac congenital malformations or mass lesions, is a major application. These modalities also are more sensitive than plain radiographs for detecting pulmonary nodules. Because cardiac movement during the imaging sequence reduces image quality, physiologic (electrocardiographic) gating is used for optimal cardiac imaging. Evaluation of cardiac volumes, myocardial function, perfusion, or valve function also may be performed. Different cardiac MRI imaging sequences are used depending on the application or type of information desired. For example, "black blood" MRI scans allow better assessment of anatomical details and abnormalities, whereas "bright blood" sequences are used to evaluate cardiac function.

Nuclear Cardiology

Radionuclide, or nuclear, methods of evaluating cardiopulmonary function are available at some veterinary referral centers. These techniques can provide noninvasive assessment of cardiac output, ejection fraction, and other measures of cardiac performance, as well as myocardial blood flow and metabolism.

ECHOCARDIOGRAPHY

Echocardiography (cardiac ultrasonography) is an important noninvasive tool for imaging the heart and surrounding structures. Anatomic relationships and cardiac function can be assessed by evaluating cardiac chamber size, wall thickness, wall motion, valve configuration and motion, and proximal great vessels and other parameters. Pericardial and pleural fluid are easily detected, and mass lesions within and adjacent to the heart can be identified. This section provides an overview of the basic echocardiographic examination, and an introduction to Doppler echocardiography and other modalities. Readers looking for more detail are referred to the excellent, in-depth Echocardiography chapter by Bonagura and Luis-Fuentes (see Suggested Readings list).

Like other diagnostic modalities, echocardiography is best used within the context of a thorough history, cardiovascular examination, and other appropriate tests. Technical expertise is essential to adequately perform and interpret a complete echocardiographic examination. The importance of the echocardiographer's skill and understanding of normal and abnormal cardiovascular anatomy and physiology cannot be overemphasized. Yet often, some important information is attainable with even rudimentary echocardiographic or "thoracic focused assessment with sonography for trauma" (TFAST) training and experience. For example, a large pericardial effusion, marked LA enlargement, and severe LV dilation with poor versus vigorous ventricular wall

motion are readily detectable and can guide initial management. Nevertheless, follow-up evaluation by a veterinary cardiologist or other individual with advanced echocardiographic training usually is advisable. In addition, a lung ultrasound examination (see p. 33) could rapidly narrow the differential diagnosis list and help guide initial therapy in patients with respiratory signs.

BASIC PRINCIPLES

Echocardiography uses pulsed, high-frequency sound waves that are reflected, refracted, and absorbed by body tissue interfaces. Only the reflected portion can be received and processed for display. Transducer frequency, power output, and various processing controls influence the intensity and clarity of the displayed echo images. Individual patient characteristics also affect the quality of images obtained. Sound waves do not travel well through bone (ribs) and air (lungs); these structures may preclude good visualization of the entire heart. Several echo modalities commonly are used for clinical examinations: two-dimensional (2-D, real-time), M-mode, and Doppler modalities. Each has important applications (described later).

Sound waves are propagated through soft tissue at a characteristic speed (≈1540 m/sec), which allows the location and size of various structures to be determined in relation to the origin of the ultrasound beam at any point in time. With 2-D and M-mode echocardiography, stronger echoes are returned when the ultrasound beam is oriented perpendicular to the imaged structure. Stronger echoes also result when there is greater mismatch in acoustic impedance (related to tissue density) between two adjacent tissues, because this produces a more reflective boundary. Very reflective interfaces such as bone/tissue or air/tissue interfere with imaging of weaker echoes from deeper tissue interfaces. The ultrasound beam decreases in intensity as it penetrates through the body's tissues (because of beam divergence, absorption, scatter, and reflection of wave energy at tissue interfaces); echoes returning from deeper structures tend to be weaker.

In general, higher frequency ultrasound energy permits better resolution of small structures because of the beam's characteristics (longer near field and lesser far field divergence). However, higher frequencies have less penetrating ability as more energy is absorbed and scattered by the soft tissues. Conversely, a transducer that produces lower frequencies provides greater penetration depth but less well-defined images. Frequencies generally used for small animal echocardiography range from about 3.5 megahertz (MHz) for large dogs to greater than 10 MHz for cats and small dogs. However, image optimization also involves many other technical factors and settings that can vary among manufacturers and are beyond the scope of this chapter.

Strongly reflective tissues are referred to as being *hyperechoic* or *of increased echogenicity.* Poorly reflecting tissues are *hypoechoic*; fluid, which does not reflect sound, is *anechoic* or sonolucent. Tissue behind an area of sonolucency appears hyperechoic because of acoustic enhancement. On the other hand, through-transmission of the ultrasound beam is blocked by a strongly hyperechoic object (such as a rib), and an acoustic shadow (where no image appears) is cast behind the object.

For most echocardiographic examinations, the animal is gently restrained in lateral recumbency; better-quality images usually are obtained when the heart is imaged from the recumbent side. For this the animal is placed on a table or platform with an edge cut out, which allows the echocardiographer to position and manipulate the transducer from the animal's dependent side. Some animals can be adequately imaged while standing; however, patient movement often is challenging. Shaving a small area of hair over the transducer placement site improves skin contact and usually image clarity. Coupling gel is applied to produce air-free contact between skin and transducer. The transducer is placed over the area of the precordial impulse (or other appropriate site), and its position is adjusted to find a good "acoustic window" that allows clear visualization of the heart. The right and left parasternal transducer positions are used most often. Minor adjustment of the animal's forelimb or torso position may be required to obtain a good acoustic window. Once the heart is located, the transducer is angled or rotated to obtain the desired views. Controls for factors such as beam strength, focus, and postprocessing parameters are adjusted as needed to optimize the image. For 2-D and M-mode studies, better image definition is achieved when the ultrasound beam is oriented perpendicular to the cardiac structures. Image artifacts are common and can mimic a cardiac abnormality. Sometimes a lesion is suspected that is not truly present; other times an actual abnormality is obscured. If a suspected lesion can be visualized in more than one imaging plane, this provides greater assurance that it is real.

A basic echocardiographic examination is obtained from the right parasternal position and includes standard 2-D imaging planes and carefully obtained M-mode views. A more complete examination includes standard left parasternal views as well as any other modified views needed to further evaluate specific lesions. Doppler evaluation provides important additional information. A complete examination may be quite time consuming in some patients.

Echocardiography usually can be performed with minimal or no chemical restraint. For animals that will not lie quietly with gentle manual restraint, light sedation is helpful. Sedation protocols for dogs include either butorphanol (0.2-0.3 mg/kg, IV or IM), or butorphanol (same dose) mixed with acepromazine (0.02-0.03 mg/kg, IV or IM), or buprenorphine (0.005-0.01 mg/kg, IV or IM) combined with acepromazine (0.02-0.03 mg/kg, IV or IM). For cats, butorphanol (0.2-0.25 mg/kg IM) mixed with acepromazine (0.05-0.1 mg/kg IM) or midazolam (0.2 mg/kg IM) often is adequate after a 20 to 30 minute rest period in a quiet room. However, some cats require more intense sedation. A combination of butorphanol (0.2-0.4 mg/kg IM) and alfaxalone (1-2 mg/kg IM) can be effective and does not raise heart rate like ketamine does. Predictably fractious cats also can be pretreated at home (~2-3 hours before the echo appointment) with gabapentin at 50 mg (for small cats) to 150 mg

(for very large cats); have the owner mix the contents of the appropriately sized capsule with a tiny amount of wet food and administer on an empty stomach. If additional sedation is required to perform the echo, a light dose of butorphanol can be effective. Other strategies have included acepromazine (0.1 mg/kg IM) followed in 15 minutes by ketamine (2 mg/kg [or 5-10 mg/cat] IV), although this can undesirably increase heart rate.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography displays a plane of tissue (depth and width). Anatomic structure and motion, including changes caused by various acquired or congenital abnormalities, are evident; actual blood flow is not visualized with 2-D or M-mode imaging alone.

Common Two-Dimensional Echocardiographic Views

A variety of planes can be imaged from several chest wall locations. Most standard views are obtained from either the right or left parasternal positions (directly over the heart and close to the sternum). Images sometimes are obtained from the subxiphoid (subcostal) position. Long-axis views are obtained with the imaging plane parallel to the long axis of the heart; short-axis views are perpendicular to this plane (Figs. 2.4 to 2.9). Images are described by the location of the transducer and the imaging plane used (for example, right

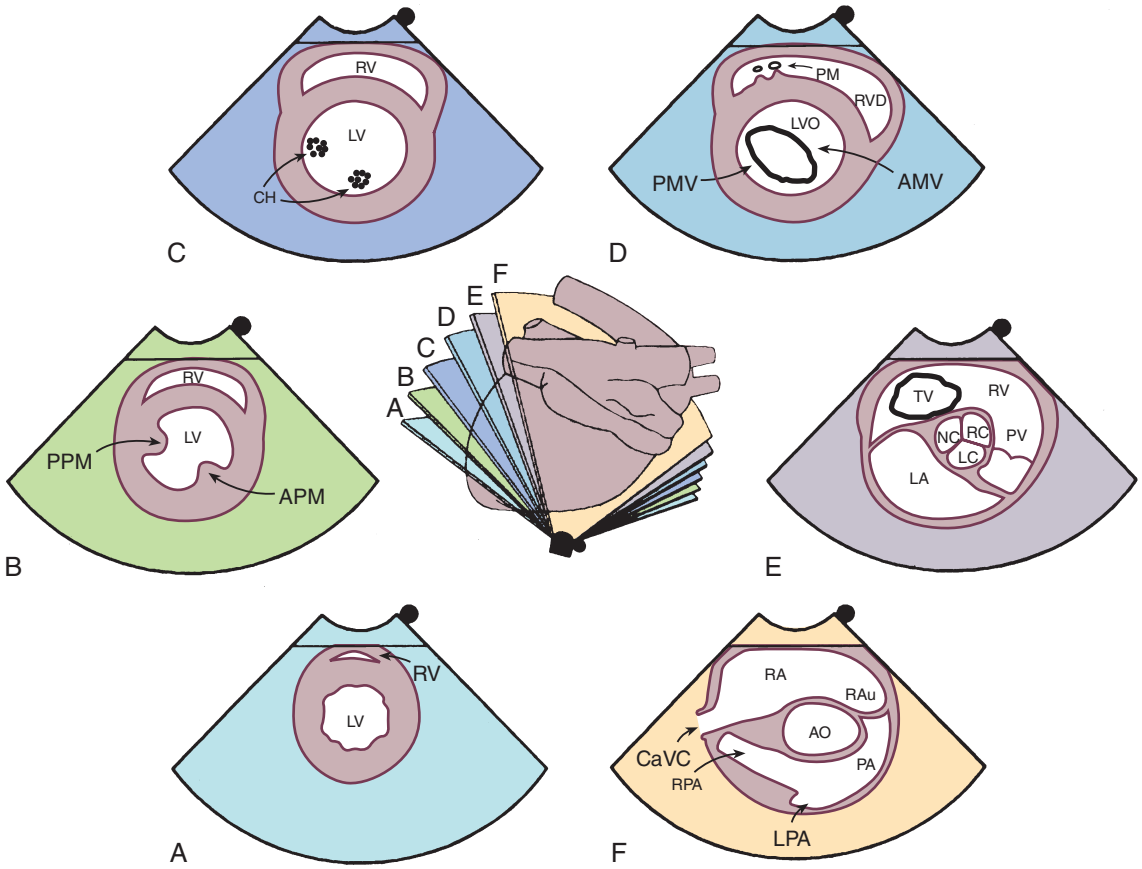


FIG 2.4
Two-dimensional short-axis echocardiographic views from the right parasternal position. The center diagram indicates the orientation of the ultrasound beam used to image cardiac structures at the six levels shown. Several of these positions guide M-mode beam placement, and occasionally can be used for Doppler evaluation of tricuspid and pulmonary flows. Corresponding echo images are shown clockwise from the bottom. **(A)** Apex. **(B)** Papillary muscle. **(C)** Chordae tendineae. **(D)** Mitral valve. **(E)** Aortic valve. **(F)** Pulmonary artery. *AMV,* Anterior (septal) mitral valve cusp; *AO,* aorta; *APM,* anterior papillary muscle; *CaVC,* caudal vena cava; *CH,* chordae tendineae; *LA,* left atrium; *LPA,* left pulmonary artery; *LV,* left ventricle; *LVO,* left ventricular outflow tract; *PA,* pulmonary artery; *PM,* papillary muscle; *PMV,* posterior mitral valve cusp; *PPM,* posterior papillary muscle; *PV,* pulmonary valve; *RA,* right atrium; *RAu,* right auricle; *RC, LC, NC,* right, left, and noncoronary cusps of aortic valve; *RPA,* right pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow tract; *TV,* tricuspid valve. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

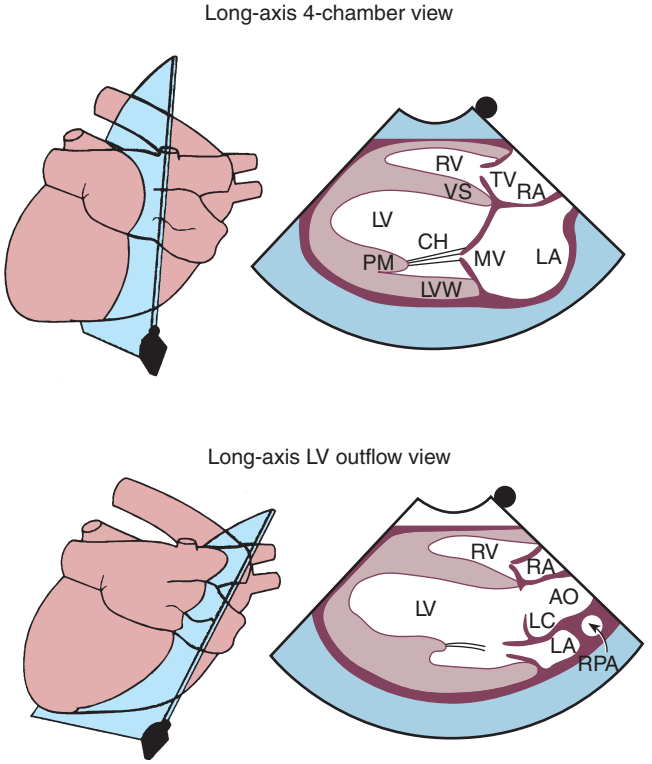


FIG 2.5
Two-dimensional long-axis echocardiographic views from right parasternal position. Each diagram on the left indicates the location of the ultrasound beam as it transects the heart from the right side, resulting in the corresponding echo image on the right. Long-axis four-chamber (left ventricular inflow) view is above. Long-axis view of the left ventricular outflow region is below. *AO,* Aorta; *CH,* chordae tendinae; *LA,* left atrium; *LC,* left coronary cusp of aortic valve; *LV,* left ventricle; *LVW,* left ventricular wall; *MV,* mitral valve; *PM,* papillary muscle; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *TV,* tricuspid valve; *VS,* interventricular septum. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

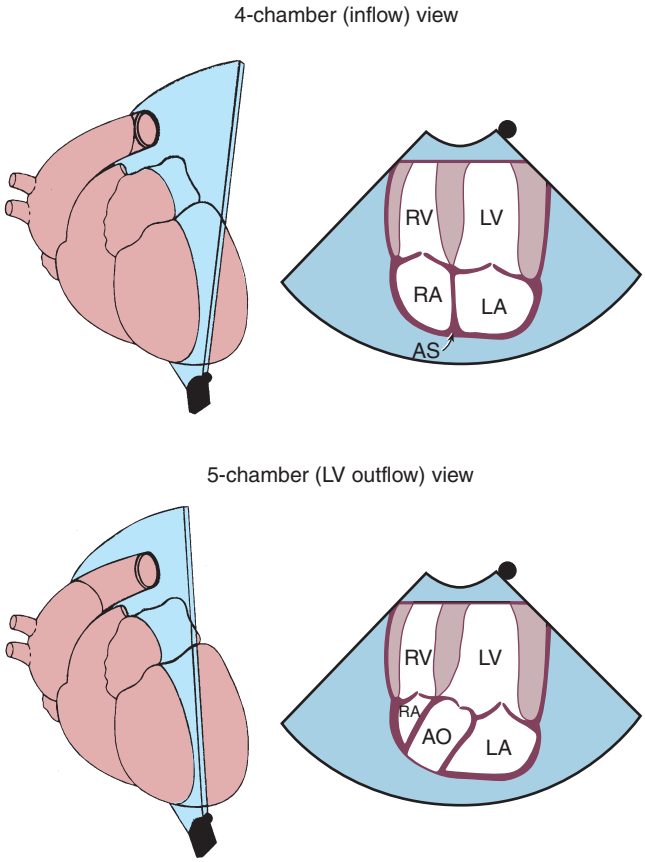


FIG 2.6
Left caudal (apical) parasternal position. Four-chamber view optimized for ventricular inflow is above. Five-chamber view optimized for left ventricular outflow is below. These views provide good Doppler velocity signals from the mitral and sometimes the aortic valve regions. *AO,* Aorta; *AS,* interatrial septum; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

parasternal short-axis view, left cranial parasternal long-axis view). Two-dimensional imaging allows an overall assessment of cardiac chamber orientation, size, and wall thickness. The RV wall normally is about one third the thickness of the LV free wall and should be no greater than half its thickness. The size of the RA and RV chambers is compared with that of the LA and LV; the right parasternal long axis and left apical four-chamber views are most useful for this. All valves and related structures, as well as the great vessels, also are systematically examined. Any suspected abnormality should be scanned using multiple planes to further verify and delineate it.

End diastolic and peak systolic LV internal dimensions and wall thicknesses usually are obtained using M-mode, but appropriately timed 2-D frames also can be used. Several methods can be used to estimate LV volume and wall mass. LA size should be assessed from 2-D rather than M-mode images. Several methods for measuring LA size have been described, and they are not interchangeable. The method used should be specified, to minimize variability in results, especially for comparative and repeated studies.

One method is to measure the end-systolic LA (LAs) internal cranial-caudal diameter (top-to-bottom on screen), just before mitral valve opening, using a right parasternal long-axis four-chamber view optimized for the mitral valve/LV inflow tract and excludes the aortic root. The measurement line should be positioned mid-atrium and aligned parallel to the mitral annulus. In cats, this LAs dimension normally is less than 16 mm, although adjustment of this cut-off up or down is appropriate in very small or very large cats, respectively. A LAs diameter in cats greater than ~22 mm is considered severe LA enlargement and indicates greater risk for thromboembolism. Because dogs have greater

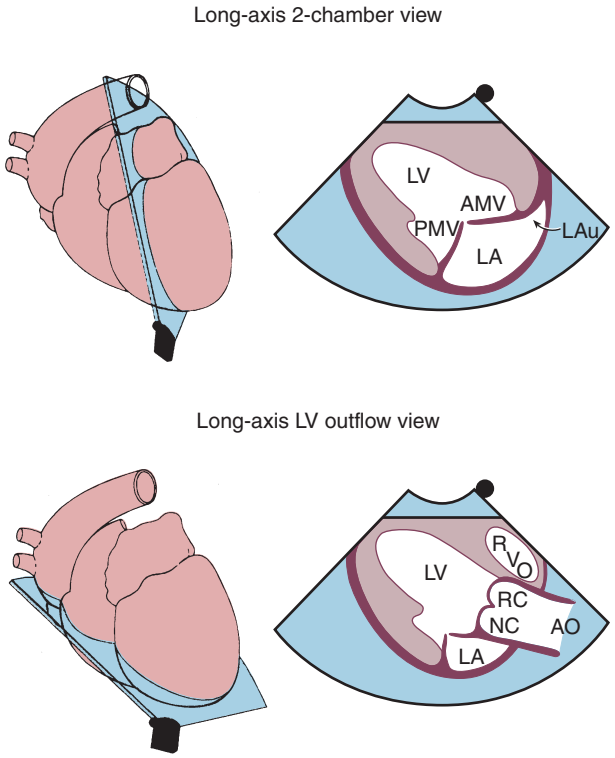


FIG 2.7
Left caudal (apical) parasternal two-dimensional views optimized for left ventricular inflow and left auricle (2-chamber view; above) and left ventricular outflow (3-chamber view; below); the outflow view sometimes is obtained with the aorta pointing to the lower left of the image. The 3-chamber view can provide good alignment with left ventricular outflow velocity (although the subcostal position [not illustrated here] is often better). *AMV,* Anterior (septal) mitral valve cusp; *AO,* aorta; *LA,* left atrium; *LAu,* left auricle; *LV,* left ventricle; *PMV,* posterior mitral valve cusp; *RC, NC,* right and noncoronary cusps of aortic valve; *RVO,* right ventricular outflow tract. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

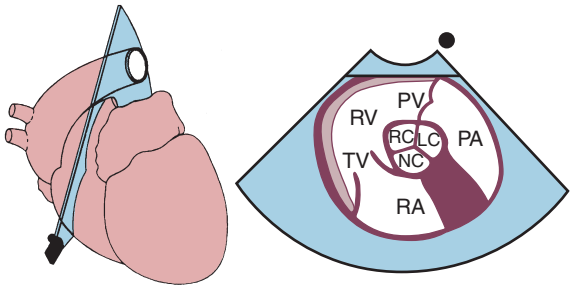


FIG 2.8
Left cranial parasternal short-axis view optimized for right ventricular inflow and outflow. This view is useful for Doppler interrogation of tricuspid and pulmonary artery flows. *PA,* Pulmonary artery; *PV,* pulmonary valve; *RA,* right atrium; *RC, LC, NC,* right, left, and noncoronary cusps of aortic valve; *RV,* right ventricle; *TV,* tricuspid valve. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

body size variation, the LA dimension usually is compared with an aortic measurement, both for the long-axis, systolic dimension as well as for the short-axis, diastolic dimension (see next paragraph). Regarding the long axis, LAs comparison, some clinicians advocate using the distance between the open aortic leaflets (at the valve hinge points) during midsystole (AoVs), measured from a right long-axis view optimized for the LV outflow tract and aortic valve. The ratio of Las:AoVs in normal dogs is thought to be <2.6. However, if the 2-D aortic root diameter is measured across the sinuses of Valsalva, the ratio of LAs:aortic root in normal dogs usually is ≤1.9.

Another LA size assessment method, often used in dogs, employs the right parasternal short-axis view and compares the LA dimension in diastole (LAd) to the aortic diameter. This sometimes is called the "Scandinavian" method. The 2-D image is optimized to include the LA and auricle, as well as the aortic valve. The internal LA dimension is measured in early diastole, along a line extending from and parallel to the commissure formed by the closed left and noncoronary aortic valve cusps. The aortic dimension measurement, from the same frozen 2-D frame, also aligns with the same valve commissure and includes only one sinus of Valsalva. The LAd:aortic root ratio using this short-axis method in normal dogs usually is between 1.3 to 1.4. Ratios over 1.5 to 1.6 indicate LA enlargement. However, LA size evaluation using this short-axis method can be confounded by the fact that maximal LA size is not measured, by variability in the imaging plane used among echocardiographers, and by inconsistent measurement timing, especially when the aortic valve leaflets are not clearly imaged.

M-MODE ECHOCARDIOGRAPHY

This modality provides a one-dimensional (depth) view into the heart. M-mode images represent echoes from various tissue interfaces along the axis of the beam (displayed vertically on the screen). These echoes, which move during the cardiac cycle, are displayed against time (on the horizontal axis). Thus the "wavy" lines seen on these recordings correspond to the positions of specific structures in relation to the transducer, as well as to each other at any point in time. Accurate M-mode beam placement, using a moveable cursor line superimposed on an appropriate 2-D (real-time) image, is essential for measurement purposes. M-mode images usually provide cleaner resolution of cardiac borders than 2-D images because of their higher sampling rate. Measurements of cardiac dimensions and motion throughout the cardiac cycle often are more accurately obtained from M-mode tracings, especially when coupled with a simultaneously recorded ECG (or phonocardiogram). Difficulty in achieving consistent and accurate

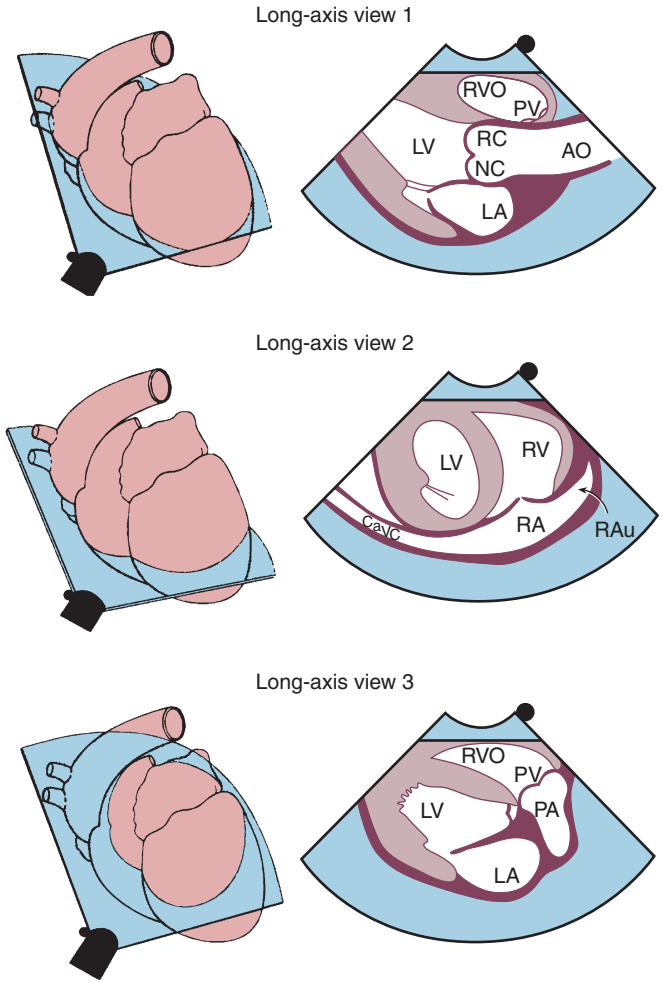


FIG 2.9
Left cranial parasternal long-axis views optimized for aortic root (above), right atrium and auricle (middle), and right ventricular outflow and main pulmonary artery (below). These views are used to evaluate the heart base and can provide good Doppler signals for tricuspid and pulmonary flows. *AO,* Aorta; *CaVC,* caudal vena cava; *LA,* left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *PV,* pulmonary valve; *RA,* right atrium; *RAu,* right auricle; *RC, NC,* right and noncoronary cusps of aortic valve; *RV,* right ventricle; *RVO,* right ventricular outflow tract. (Modified from Thomas WP et al.: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, *J Vet Intern Med* 7:247, 1993.)

beam placement for standard measurements and calculations can be a limitation.

M-Mode Views

Standard M-mode views are obtained from the right parasternal transducer position. The M-mode cursor is positioned with 2-D guidance using the right parasternal short-axis view; angling the transducer so that the LV appears as round as possible helps ensure the ultrasound beam is oriented perpendicular to the axis of the LV. Some clinicians prefer using the long-axis view to obtain images for ventricular measurements; however, it may be more difficult to verify that the beam is transecting the LV at its maximum dimension. Precise positioning of the ultrasound beam within the heart (perpendicular to the structures to be measured) and clear endocardial images are essential for accurate M-mode measurements and calculations. For example, papillary muscles within the LV must be avoided when measuring free-wall thickness. Fig. 2.10 illustrates standard M-mode views. In cases where the M-mode cursor cannot be optimally aligned (e.g., in animals with focal or asymmetric hypertrophy), wall thickness measurements from 2-D images are preferred, although in animals with a high heart rate, obtaining true end-diastolic frames can be uncertain.

Common Measurements and Normal Values

The standard dimensions measured with M-mode and their timing also are indicated in Fig. 2.10. The "leading edge" technique is used when possible (i.e., from the edge closest to the transducer [leading edge] of one side of the dimension to the leading edge of the other). In this way, only one endocardial thickness is included in the measurement. LV wall and interventricular septal thicknesses, as well as LV chamber dimensions, should be determined at the level of the chordae tendineae rather than the apex or mitral valve level. Measurements also may be taken from 2-D images if they are of high resolution, and frames from the appropriate times in the cardiac cycle are used. Body size greatly influences echocardiographic measurements, especially in dogs. However, the relationship between body weight or surface area and cardiac dimensions is not linear. Rather, cardiac linear dimensions are more closely related to body length, which is proportional to body weight to the ⅓ power ($BW^{⅓}$). Allometric scaling has been used to generate guidelines for common cardiac dimension measurements in normal dogs (see Table 2.1). Mean values are listed for selected weights along with 95% prediction intervals. However, these prediction intervals are quite wide, especially for larger dogs, and may encompass some degree of LV enlargement. Somatotype and breed may have additional influence on normal echo values in some dogs. For example, healthy Boxers can have increased LV wall thickness and smaller aortic dimensions relative to nonBoxer dogs, although chamber dimensions are comparable. Slightly higher LV wall thickness and chamber dimensions have been observed in Greyhounds compared with other dogs of comparable weight. Endurance training also affects measured parameters, reflecting the increased cardiac mass and volume associated with frequent and sustained strenuous exercise. Normal measurements in cats are more uniform but also are influenced by body size (Table 2.2). Chamber volume and ejection fraction are better estimated from optimized 2-D frames using the modified Simpsons' method rather than M-mode images because of the greater potential for inaccurate geometric assumptions from one-dimensional measurements (see Suggested Readings for further information). The right parasternal four-chamber

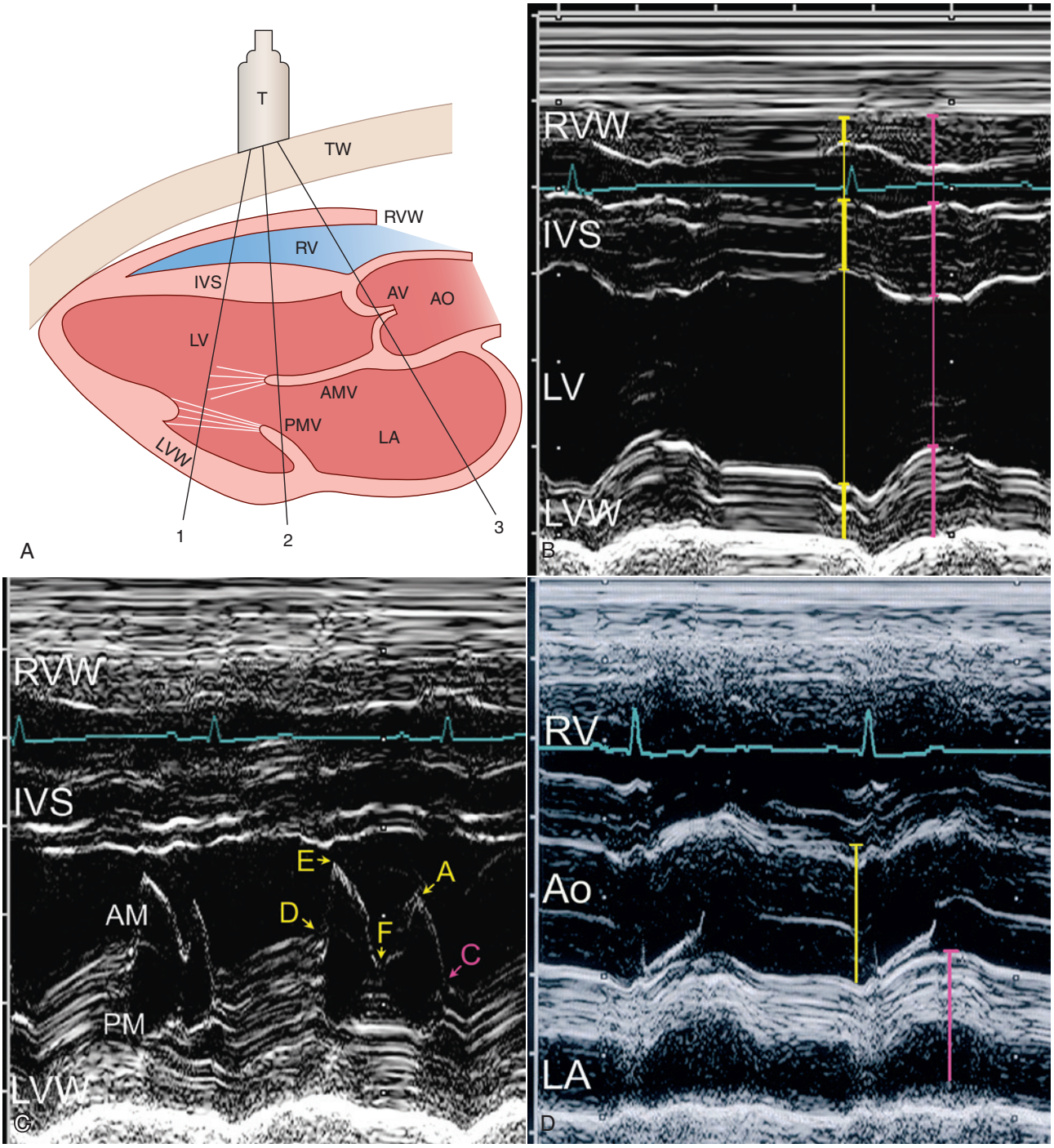


FIG 2.10
Common M-mode views. **(A)** Diagram indicates the approximate orientation of the one-dimensional ultrasound beam through the heart to achieve the corresponding M-mode images. **(B)** Image at the level of the chordae tendineae within the left ventricular lumen (LV), corresponding to cursor line "1" in **A.** A lead II ECG is recorded with the echo images for timing within the cardiac cycle. End diastole occurs at the onset of the QRS complex (yellow time/measure line); end systole (pink time/measure line) is the time when the dimension between the interventricular septum (IVS) and left ventricular free wall (LVW) is smallest. Internal dimensions of the LV are measured from the leading (anterior) edge of the left endocardial wall of the IVS to the leading edge (luminal surface) of the posterior LVW. The thickness of the IVS is measured from the right endocardial surface of the IVS to the leading edge of the left endocardial septal wall at end diastole and end systole; the posterior LVW is measured at the same times from the endocardial surface to (but not including) the leading edge of the epicardial echoes. **(C)** Image at the mitral valve level, cursor line "2" in **A.** The motion of the anterior (AM) and posterior (PM) mitral leaflets is described by the letters shown. Diastolic opening of the valve occurs at point D, and systolic closing occurs at point C (see text for more information). **(D)** Image at the aortic root (Ao) level "3" (where valve cusps are seen). Diameter is measured at end diastole from the leading (anterior) edge of the anterior aortic wall to the leading edge of the posterior wall. The left atrium (LA; usually the auricular region) is below the aorta (pink measure line, in systole); however, the M-mode dimension underestimates LA size in most animals (see text). *RV,* Right ventricular lumen; *RVW,* right ventricular wall.

TABLE 2.1

Echocardiographic Measurement Guidelines for Dogs*

BW (kg)	$LVID_D$ (cm)	$LVID_S$ (cm)	LVW_D (cm)	LVW_S (cm)	IVS_D (cm)	IVS_S (cm)	AO (cm)	LA† (M-mode; cm)
3	2.1 (1.8-2.6)	1.3 (1.0-1.8)	0.5 (0.4-0.8)	0.8 (0.6-1.1)	0.5 (0.4-0.8)	0.8 (0.6-1.0)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
4	2.3 (1.9-2.8)	1.5 (1.1-1.9)	0.6 (0.4-0.8)	0.9 (0.7-1.2)	0.6 (0.4-0.8)	0.8 (0.6-1.1)	1.3 (1.0-1.5)	1.2 (1.0-1.6)
6	2.6 (2.2-3.1)	1.7 (1.2-2.2)	0.6 (0.4-0.9)	1.0 (0.7-1.3)	0.6 (0.4-0.9)	0.9 (0.7-1.2)	1.4 (1.2-1.8)	1.4 (1.1-1.8)
9	2.9 (2.4-3.4)	1.9 (1.4-2.5)	0.7 (0.5-1.0)	1.0 (0.8-1.4)	0.7 (0.5-1.0)	1.0 (0.7-1.3)	1.7 (1.3-2.0)	1.6 (1.3-2.1)
11	3.1 (2.6-3.7)	2.0 (1.5-2.7)	0.7 (0.5-1.0)	1.1 (0.8-1.5)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	1.8 (1.4-2.2)	1.7 (1.3-2.2)
15	3.4 (2.8-4.1)	2.2 (1.7-3.0)	0.8 (0.5-1.1)	1.2 (0.9-1.6)	0.8 (0.6-1.1)	1.1 (0.8-1.5)	2.0 (1.6-2.4)	1.9 (1.6-2.5)
20	3.7 (3.1-4.5)	2.4 (1.8-3.2)	0.8 (0.6-1.2)	1.2 (0.9-1.7)	0.8 (0.6-1.2)	1.2 (0.9-1.6)	2.2 (1.7-2.7)	2.1 (1.7-2.7)
25	3.9 (3.3-4.8)	2.6 (2.0-3.5)	0.9 (0.6-1.3)	1.3 (1.0-1.8)	0.9 (0.6-1.3)	1.3 (0.9-1.7)	2.3 (1.9-2.9)	2.3 (1.8-2.9)
30	4.2 (3.5-5.0)	2.8 (2.1-3.7)	0.9 (0.6-1.3)	1.4 (1.0-1.9)	0.9 (0.7-1.3)	1.3 (1.0-1.8)	2.5 (2.0-3.1)	2.5 (1.9-3.1)
35	4.4 (3.6-5.3)	2.9 (2.2-3.9)	1.0 (0.7-1.4)	1.4 (1.1-1.9)	1.0 (0.7-1.4)	1.4 (1.0-1.9)	2.6 (2.1-3.2)	2.6 (2.0-3.3)
40	4.5 (3.8-5.5)	3.0 (2.3-4.0)	1.0 (0.7-1.4)	1.5 (1.1-2.0)	1.0 (0.7-1.4)	1.4 (1.0-1.9)	2.7 (2.2-3.4)	2.7 (2.1-3.5)
50	4.8 (4.0-5.8)	3.3 (2.4-4.3)	1.0 (0.7-1.5)	1.5 (1.1-2.1)	1.1 (0.7-1.5)	1.5 (1.1-2.0)	3.0 (2.4-3.6)	2.9 (2.3-3.7)
60	5.1 (4.2-6.2)	3.5 (2.6-4.6)	1.1 (0.7-1.6)	1.6 (1.2-2.2)	1.1 (0.8-1.6)	1.5 (1.1-2.1)	3.2 (2.5-3.9)	3.1 (2.4-4.0)
70	5.3 (4.4-6.5)	3.6 (2.7-4.8)	1.1 (0.8-1.6)	1.6 (1.2-2.2)	1.1 (0.8-1.6)	1.6 (1.2-2.2)	3.3 (2.7-4.1)	3.3 (2.6-4.2)

FS (25-) 27% to 40 (-47)%.
EPSS ≤ 6 mm.
Guidelines for approximate normal canine M-mode measurements based on allometric scaling to body weight (kg) to the ⅓ power ($BW^{⅓}$). Values may not be accurate for dogs that are extremely obese or thin, old or young, or athletic. Upper end of $LVID_D$ prediction interval also may encompass mild LV dilation.
AO, Aortic root; *BW,* body weight; *EPSS,* mitral E-point septal separation; *FS,* fractional shortening; IVS_D, interventricular septal thickness in diastole; IVS_S, interventricular septal thickness in systole; *LA,* left atrium; $LVID_D$, left ventricular diameter in diastole; $LVID_S$, left ventricular diameter in systole; LVW_D, left ventricular free wall thickness in diastole; LVW_S, left ventricular free wall thickness in systole.
*M-mode average measurement values and 95% prediction intervals for normal dogs.
†Note that M-mode LA measurement does not reflect maximum LA diameter (see text, p. 26). LA size should be assessed from appropriate 2-D images (see p. 21).
(From Cornell CC et al.: Allometric scaling of M-mode cardiac measurements in normal adult dogs, *J Vet Intern Med* 18:311, 2004.)

long-axis view, optimized for greatest LV size, often is better for assessing LV volume than the left apical view.

Diastolic measurements are made at the onset of the QRS complex of a simultaneously recorded ECG. Systolic measurements of the LV are made from the point of peak downward motion of the septum to the leading edge of the LV free-wall endocardium at the same instant. The septum and LV wall normally move toward each other in systole, although their peak movement may not coincide if electrical activation is not simultaneous. Paradoxic septal motion, in which the septum seems to move away from the LV wall and toward the transducer in systole, occurs in some cases of RV volume and/or pressure overload. This abnormal septal motion also can be visualized on 2-D images; it precludes accurate assessment of LV function using fractional shortening (FS; also called % delta D).

TABLE 2.2

Echocardiographic Measurement Guidelines for Cats*

$LVID_D$ (mm)	$LVID_S$ (mm)	LVW_D (mm)	LVW_S (mm)	IVS_D (mm)	IVS_S (mm)	LA† (mm)	AO (mm)
12-18	5-10	≤5.5	≤9	≤5.5	≤9	7-14	8-11

FS 35%-65%.
EPSS ≤ 4 mm.
AO, Aortic root; *EPSS,* mitral E-point septal separation; *FS,* fractional shortening; IVS_D, interventricular septum at end diastole; IVS_S, interventricular septum at end systole; *LA,* left atrium (systole); $LVID_D$, left ventricular internal diameter at end diastole; $LVID_S$, left ventricular internal diameter at end systole; LVW_D, left ventricular wall at end diastole; LVW_S, left ventricular wall at end systole.
*These values are based on the author's experience and compilation of published studies. Measurements can be higher in large cats. Ketamine increases heart rate and decreases $LVID_d$. See Suggested Readings for additional references.
†Orientation of M-mode cursor across the LA is variable among animals; maximum LA dimension is best assessed by two-dimensional imaging.

The FS commonly is used to estimate LV systolic function in dogs and cats. FS is the percent change in LV dimension from diastole to systole ([LVIDd − LVIDs]/LVIDd × 100). Most normal dogs have an FS between (25%-) 27% and 40 (-47)%; FS in most cats is between 35% and 65%, although there is some variability. It is important to remember that this index, like others taken during the cardiac ejection phase, has the important limitation of being dependent on ventricular loading conditions. For example, reduced LV afterload (as occurs with mitral insufficiency, ventricular septal defect, or peripheral vasodilation) facilitates blood flow out of the LV during systole, and therefore produces a smaller end-systolic dimension and greater FS. This "enhancement" of FS occurs even though intrinsic myocardial contractility is not increased. The exaggerated FS common in patients with severe mitral regurgitation creates the appearance of increased contractility in those with normal myocardial function and can mask deteriorating contractile function. Regional wall motion abnormalities and arrhythmias also can affect the FS.

The use of the calculated end-systolic volume index (ESVI) has been suggested as a more accurate way to assess myocardial contractility in the presence of mitral regurgitation in dogs. This index (ESV/m^2 body surface area) compares ventricular size after ejection with body size rather than with the dilated end-diastolic ventricular size. LV volumes should be estimated from 2-D rather than M-mode images. Extrapolation from human studies to dogs suggests an ESVI less than 30 mL/m^2 is normal, 30 to 60 mL/m^2 indicates mild LV systolic dysfunction, 60 to 90 mL/m^2 represents moderate LV dysfunction, and greater than 90 mL/m^2 indicates severe LV dysfunction. Other methods also can be used to assess LV function.

Mitral valve motion is evaluated with M-mode also. The anterior (septal) leaflet is most prominent; its motion has an "M" configuration. The posterior (parietal) leaflet is smaller; its motion mirrors the anterior leaflet, appearing as a "W." Tricuspid valve motion is similar. The mitral valve motion pattern is identified by letters (Fig. 2.10C). Point E occurs at maximal opening of the valve during the rapid ventricular filling phase. The valve drifts into a more closed position (point F) at the end of rapid ventricular filling. Atrial contraction causes the valve to open again (point A). At rapid heart rates, the E and A points often merge. The mitral valve closes (point C) at the onset of ventricular contraction. In normal animals, the mitral E point is close to the interventricular septum. Increased E point-to-septal separation usually is associated with reduced myocardial contractility, although aortic insufficiency also can cause this. In animals with dynamic LV outflow obstruction, hemodynamic forces during ejection pull the anterior mitral leaflet toward the septum, causing so-called *systolic anterior motion* (SAM). With SAM, some of the normally straight mitral echoes (between points C and D) bend toward the septum during systole (see Fig. 8.5, p. 164). Diastolic flutter of the anterior mitral leaflet sometimes can be seen when an aortic insufficiency jet causes the leaflet to vibrate (Figs. 2.11 and 2.12).

The diameter of the aortic root and sometimes its motion are measured with M-mode. The parallel walls of the aortic root shift rightward (upward on the screen) in systole. During diastole, one or two aortic valve cusps may be visualized as a straight line parallel to and centered between the aortic wall echoes. At the onset of ejection, the cusps separate toward the walls of the aortic root and then quickly come together again at the end of ejection. The shape of these echoes (two cusps) has been described as a train of boxcars or little rectangular boxes attached together by a string. Aortic diameter is measured at the level of the valve annulus in end diastole. The amplitude of posterior-to-anterior motion of the aortic root is often decreased in animals with poor cardiac output. The LA dimension (caudal to the aortic root) is measured at maximal systolic excursion. In normal cats and dogs, the (M-mode) ratio of LA to aortic root diameters is about 1 : 1. However, LA size is underestimated with this M-mode view because (especially in dogs) the M-mode cursor usually transects the LA close to the left auricle, not at its maximal dimension. In cats, the M-mode beam is more likely to cross the body of the LA, but its orientation can be inconsistent. Echo beam placement may be difficult in some animals, and the pulmonary artery can be inadvertently imaged instead. Therefore LA size assessment is best done from 2-D images.

Systolic time intervals (STIs) have been used sporadically to estimate cardiac function, but they also are influenced by cardiac filling and afterload. These intervals can be calculated if the opening and closing of the aortic valve are clearly seen on M-mode and a simultaneous ECG is recorded for timing. The common STIs are: LV ejection time (duration of time the aortic valve is open), preejection period (time from the onset of the QRS to aortic valve opening), and total electromechanical systole (LV ejection time plus preejection period). STIs also can be derived using Doppler echocardiography.

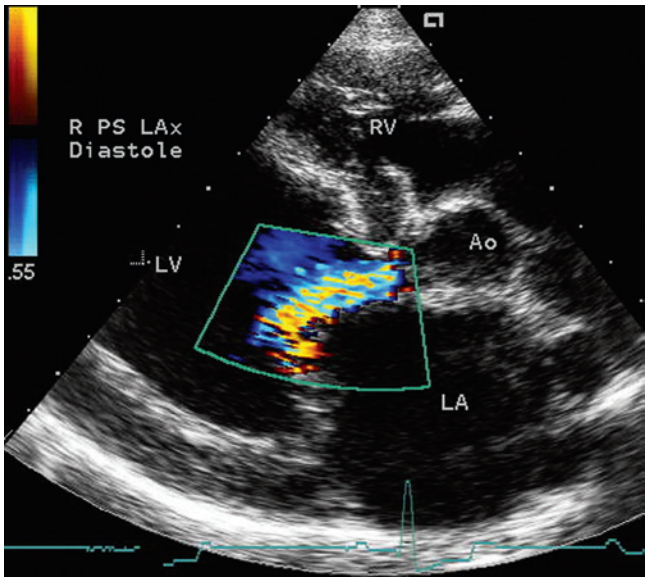


FIG 2.11
Color flow Doppler image of an aortic regurgitation jet angled toward and along the anterior leaflet of the mitral valve in a 2-year-old Rottweiler with aortic valve endocarditis. The regurgitant jet causes the mitral leaflet to flutter in diastole as seen in Fig. 2.12. Imaged from the right parasternal long-axis position. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

CONTRAST ECHOCARDIOGRAPHY

This technique, often called a "bubble study," uses rapid injection of a substance containing "microbubbles" either into a peripheral vein or selectively into the heart. These microbubbles generate tiny pinpoint echoes that temporarily "opacify" the blood pool being imaged (Fig. 2.13). The microbubbles appear as bright sparkles moving with the blood flow. Agitated sterile saline solution, a mixture of saline and the patient's blood, and commercial echo-contrast agents can be used as echo-contrast material. After injection into a peripheral vein, bubbles appear in the right heart chambers. Bubbles seen in the left heart or aorta indicate a right-to-left shunt. Saline microbubbles do not pass through the pulmonary capillaries (although some commercially available echo-contrast agents do), so agitated saline-contrast injection via selective left-sided heart catheterization is required to visualize intracardiac left-to-right shunts or mitral regurgitation. Doppler echocardiography has largely replaced echo-contrast studies, but they are still a useful tool in some cases.

DOPPLER ECHOCARDIOGRAPHY

Blood flow direction and velocity are imaged with Doppler echocardiography. Several types of Doppler echocardiography are used clinically, including pulsed wave (PW),

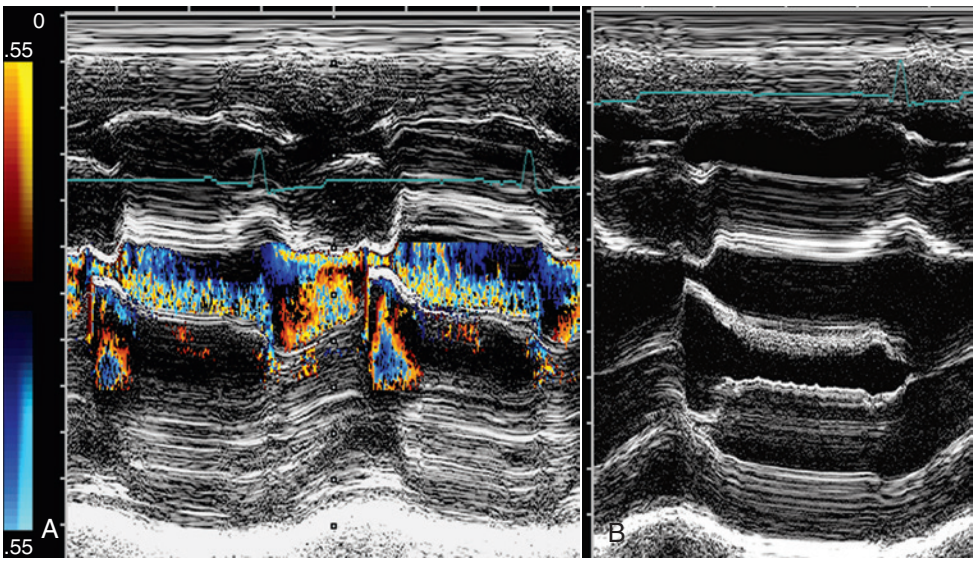


FIG 2.12
Color M-mode **(A)** and standard M-mode **(B)** images of the mitral valve from the dog in Fig. 2.11. The disturbed flow from aortic regurgitation is represented by the colors along the anterior leaflet in the left ventricular outflow region. Fine oscillations (fluttering) of the anterior mitral leaflet are seen in **B;** the leaflet appears wide and "fuzzy" compared with the thin, discrete posterior leaflet.

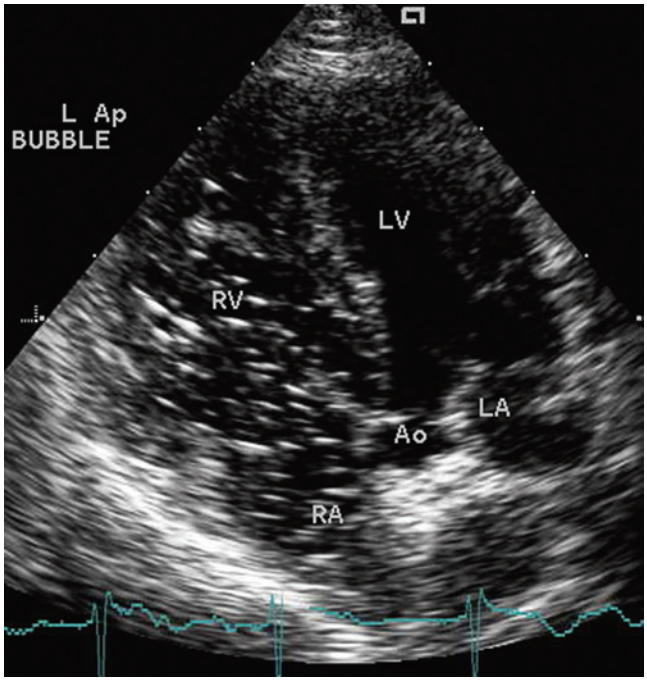


FIG 2.13
Echo "bubble" study in a dog with pulmonary hypertension. Bright speckles fill the right atrial and right ventricular chambers after an injection of agitated saline into a peripheral vein. Because there was no intracardiac shunt in this dog, no "bubbles" are seen in the left heart chambers, despite abnormally high right heart pressures. View from left apical position; *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

continuous wave (CW), and color flow (CF) mapping. Important clinical applications relate to identification of abnormal flow direction or turbulence and increased flow velocity. This allows detection and quantification of valvular insufficiency, obstructive lesions, and cardiac shunts. Cardiac output and other indicators of systolic function, as well as Doppler-derived indices of diastolic function, can be assessed. Adequate Doppler examinations are technically demanding and require a good understanding of hemodynamic principles and cardiac anatomy.

The Doppler modality is based on detection of frequency shifts between the emitted ultrasound energy and echoes reflected from moving blood cells (the Doppler shift*). Echoes returning from cells moving away from the transducer are of lower frequency, and those from cells moving toward the transducer are of higher frequency than the emitted signal. The higher the velocity of the cells, the greater the frequency shift. Optimal blood flow profiles and calculation of maximal blood flow velocity are possible when the ultrasound beam is aligned parallel to the flow. This contrasts with the perpendicular beam orientation needed for optimal M-mode and 2-D imaging. Calculated blood flow velocity diminishes as the angle of incidence between the Doppler ultrasound beam and direction of blood flow diverges from 0 degrees. This is because the calculated flow velocity is inversely related to the cosine of this angle (cosine 0 degrees = 1). As long as the angle between the ultrasound beam and path of blood flow is less than 20 degrees, maximal flow velocity can be estimated with reasonable accuracy. As the angle of incidence increases, the calculated velocity decreases. At an angle of 90 degrees, the calculated velocity is 0 (cosine 90 degrees = 0); therefore no flow signal is recorded when the ultrasound beam is perpendicular to blood flow. Flow signals usually are displayed with time on the x axis and velocity (scaled in m/sec or cm/sec) on the y axis. A zero baseline demarcates flow direction away from (below baseline) or toward (above baseline) the transducer. Higher velocities are displayed farther from baseline. Other flow characteristics (such as turbulence) also affect the Doppler spectral display.

Pulsed Wave Doppler

PW Doppler uses short bursts of ultrasound to analyze echoes returned from a specified area (designated the sample volume) along the Doppler cursor line. The advantage of PW Doppler is that blood flow velocity, direction, and spectral characteristics can be calculated from a specific location within the heart or blood vessel. The main disadvantage is that the maximum measurable velocity is limited. The pulse repetition frequency (time required to send, receive, and process returning echoes), as well as the transmitted frequency and the distance of the sample volume from the transducer, determine the maximum measurable velocity (called the *Nyquist limit*). The Nyquist limit is defined as two times the pulse repetition frequency. Lower frequency transducers and closer sample volume placement increase the Nyquist limit. When blood flow velocity is higher than the Nyquist limit, *aliasing* or velocity ambiguity occurs. This is displayed as a band of velocity signals extending above and below ("wrapped around") the baseline, so neither velocity nor direction is measurable (Fig. 2.14). When blood cells in a sample volume are moving in the same direction and at the same velocity, the velocity spectrum displayed with PW Doppler is relatively thin (tight). Variation in flow velocity within the sample volume causes spectral broadening (widening).

Characteristic blood flow patterns are obtained from the different valve areas. Flow across both AV valves has a similar pattern; likewise, flow patterns across the semilunar valve areas are similar. Normal diastolic flow across the mitral valve (Fig. 2.15) and tricuspid valve consists of an initial higher velocity signal during the rapid ventricular filling phase (E wave), which is followed by a smaller velocity signal associated with atrial contraction (A wave). Breed, age, and body weight have little influence on normal Doppler measurements. Peak velocities normally are higher across the mitral (peak E usually ≤ 0.9-1.0 m/sec; peak A usually ≤ 0.6-0.7 m/sec) compared with the tricuspid valve (peak E usually ≤ 0.8-0.9 m/sec; peak A usually ≤ 0.5-0.6 m/sec). The

*$V = C(\pm\Delta f/2f_0\cos\theta)$
V, Calculated blood flow velocity (m/sec); *C,* speed of sound in soft tissue (1540 m/sec); *±Δf,* Doppler frequency shift; f_0, transmitted frequency; *θ,* intercept angle (between ultrasound beam and blood flow direction).

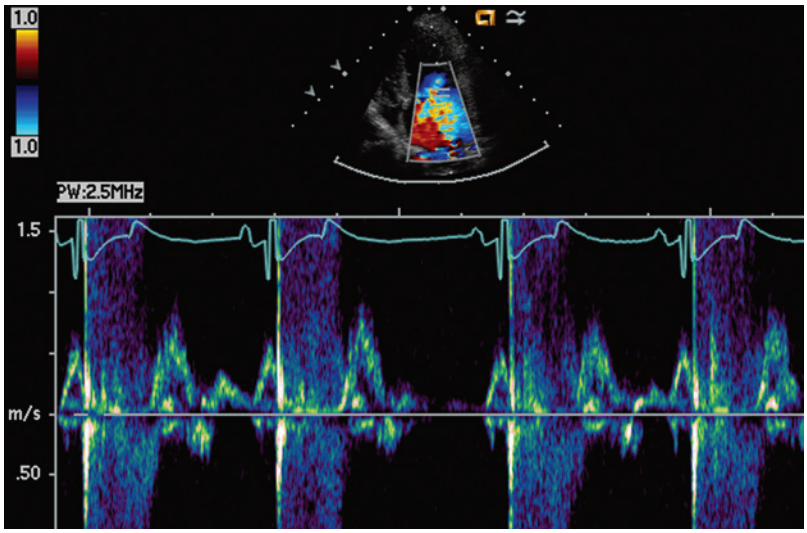


FIG 2.14
Mitral diastolic inflow and systolic regurgitant flow in a dog with degenerative mitral valve disease recorded with PW Doppler from left caudal parasternal position. The direction of mitral regurgitant flow is away from the transducer (below baseline). However, this direction cannot be discerned with PW because the flow velocity is too high, and the signal is *aliased* ("wrapped around the baseline").

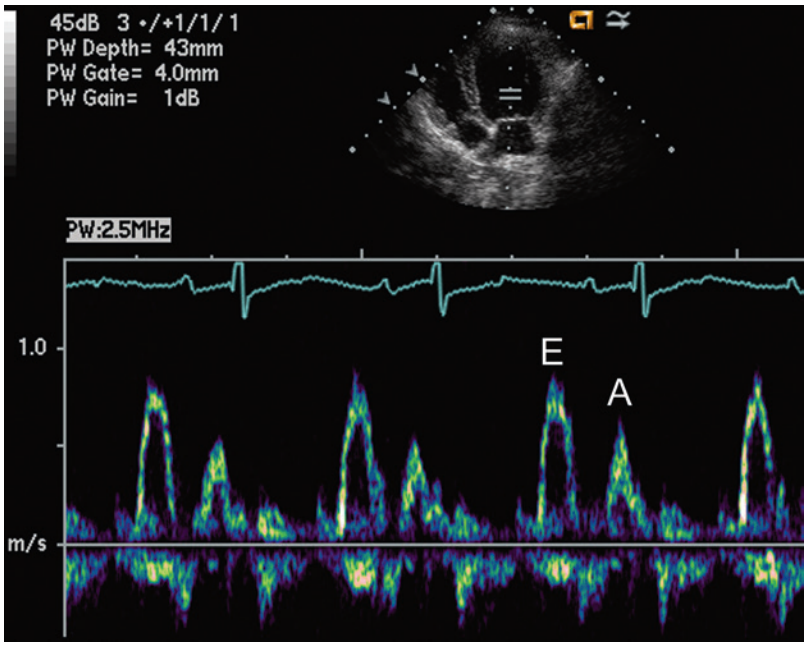


FIG 2.15
Normal mitral valve inflow recorded with PW Doppler from the left caudal (apical) parasternal position in a dog. The flow signal (above baseline) following the QRS-T of the ECG represents early diastolic flow into the ventricle *(E);* the second, smaller peak after the P wave represents inflow from atrial contraction *(A)*. Velocity scale in meters/second is on the left.

left apical four-chamber view usually provides optimal alignment for assessing mitral inflow velocities; the left cranial short-axis view is usually best for tricuspid inflow, although other imaging planes may provide adequate alignment in some cases. Multiple pulsed Doppler-derived and other indices have been used to assess diastolic function; however, no single index provides full insight to the complex process of ventricular filling. Some of these include the mitral valve inflow pattern (E/A ratio), tissue Doppler imaging of LV wall motion, isovolumic relaxation time (IVRT), mitral E:IVRT,

pulmonary venous flow patterns, and others (see Suggested Readings for more information).

Flow across the pulmonary and aortic valves (Fig. 2.16) accelerates rapidly during ejection with more gradual deceleration. Sample volume placement is at or just distal to the valve. Peak systolic pulmonary velocity is ≤ 1.4 to 1.5 m/sec in most normal dogs; the left cranial views usually provide better flow alignment. Peak aortic velocity is usually ≤ 1.6 to 1.7 m/sec, although some normal dogs (especially when unsedated) have peak aortic velocities slightly above 2 m/sec because of increased stroke volume, high sympathetic tone, or breed-related outflow tract structural characteristics. Ventricular outflow obstruction causes more rapid flow acceleration, increased peak velocity, and turbulence. In general, aortic velocities over 2.2 (-2.4) m/sec are consistent with outflow obstruction. Between 1.7 and approximately 2.2 m/sec lies a "gray zone" where mild LV outflow obstruction (e.g., some cases of subaortic stenosis) cannot be differentiated with certainty from normal but vigorous LV ejection. Maximal aortic/LV outflow velocities are obtained from the subcostal (subxiphoid) position in most dogs; however, in some dogs, the left apical view provides higher velocity recordings. The LV outflow region should be interrogated from both views and the greater maximal velocity value used.

Continuous Wave Doppler

CW Doppler employs continuous and simultaneous ultrasound transmission and reception along the line of interrogation. Theoretically, there is no maximum velocity limit with CW Doppler, so high-velocity flows can be measured (Fig. 2.17). The disadvantage of CW Doppler is that sampling of blood flow velocity and direction occurs all along the ultrasound beam, not in a specified area (so-called range ambiguity).

Pressure Gradient Estimation

In combination with M-mode and 2-D imaging, Doppler estimation of pressure gradients is used to assess the severity of congenital or acquired flow obstructions. In addition, the peak velocity of a valvular insufficiency jet can be used to estimate the pressure gradient across a regurgitant valve. The instantaneous pressure gradient across a stenotic or regurgitant valve is estimated using the maximum measured velocity of the flow jet. CF Doppler is useful to depict the flow jet's orientation and aid cursor alignment. Careful Doppler beam alignment is essential to record maximum velocity. CW Doppler is employed if aliasing occurs with PW Doppler. A modification of the Bernoulli equation is used to estimate pressure gradient (other factors in this relationship generally are of minimal clinical importance and are ignored):

$$\textbf{Pressure Gradient} = 4 \times (\textbf{maximum velocity})^2$$

Pulmonary artery systolic pressure can be estimated from maximal tricuspid regurgitation jet velocity (TRmax), if there is no RV outflow obstruction or pulmonic valve stenosis. The calculated systolic pressure gradient plus RA pressure (estimated as about 5 to 10 mm Hg, or the measured central venous pressure [CVP]) equals the peak RV systolic pressure, which approximates pulmonary artery systolic pressure. Pulmonary hypertension (PH) is associated with TRmax values over 2.8 m/sec. The severity of PH generally

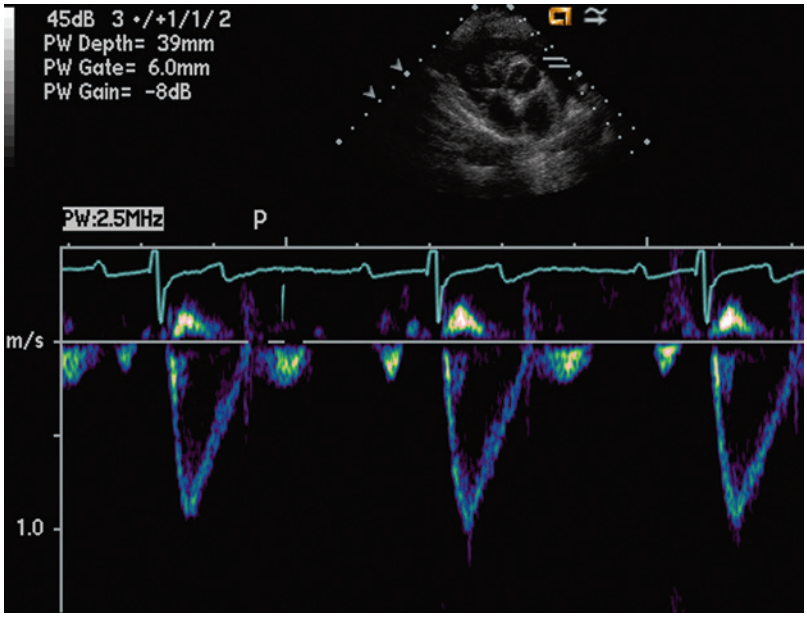


FIG 2.16
Normal pulmonary flow recorded with PW Doppler from the left cranial short-axis position in a dog. There is rapid blood flow acceleration (below baseline) into the pulmonary artery, with a peak velocity of about 1.0 m/sec. Velocity scale in meters per second is on the left.

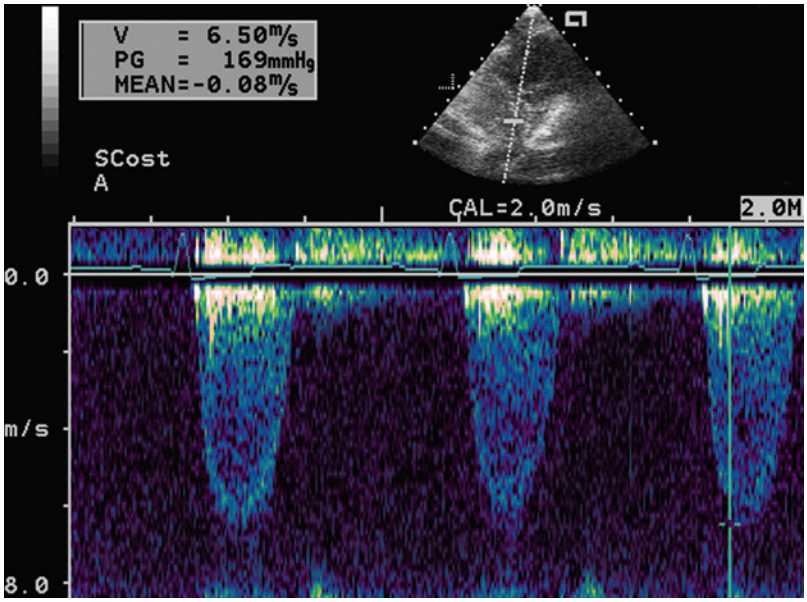


FIG 2.17
Continuous wave Doppler recording of high-velocity aortic outflow in a dog with severe subaortic stenosis, imaged from the subcostal position. Estimated systolic pressure gradient across the outflow region is 169 mm Hg, based on a peak velocity of 6.5 m/sec. Velocity scale in meters/second is on the left.

is categorized as mild (estimated systolic pulmonary artery pressure ≈35-50 mm Hg; TRmax 2.9-3.5 m/sec), moderate (≈51-75 mm Hg; TRmax 3.6-4.3 m/sec), or severe (>75 mm Hg; TRmax > 4.3 m/sec). Likewise, pulmonary diastolic pressure can be estimated from a pulmonary regurgitant (PR) jet velocity at end-diastole. The calculated end-diastolic pressure gradient between the pulmonary artery and the RV, plus the estimated RV diastolic pressure, represents pulmonary arterial diastolic pressure. The peak (early diastolic) PR provides an approximation of mean pulmonary artery pressure; peak PR velocities over 2.2 m/sec suggest PH.

Color Flow Mapping

CF mapping is a form of PW Doppler that combines the M-mode or 2-D modality with blood flow imaging. However, instead of one sample volume along one scan line, many sample volumes are analyzed along multiple scan lines. The mean frequency shifts obtained from multiple sample volumes are color coded for direction (in relation to the transducer) and velocity. Most systems code blood flow toward the transducer as red and blood flow away from the transducer as blue. Zero velocity is indicated by black, meaning either no flow or flow perpendicular to the angle of incidence. Differences in relative velocity of flow can be accentuated, and the presence of multiple velocities and directions of flow (turbulence) can be indicated by different display maps that use variations in brightness and color. Aliasing occurs often, even with normal blood flows, because of low Nyquist limits. Signal aliasing is displayed as a reversal of color (e.g., red shifting to blue; Fig. 2.18). Turbulence

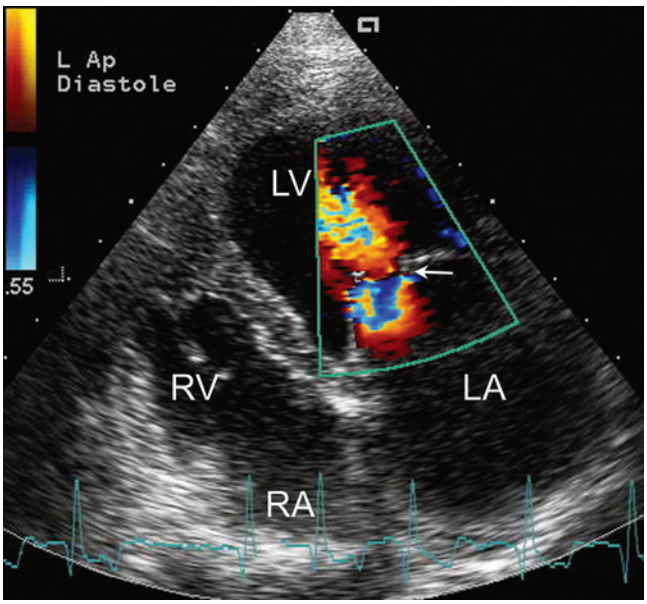


FIG 2.18
Example of color flow aliasing in a dog with mitral valve stenosis and atrial fibrillation. Diastolic flow toward the narrowed mitral orifice *(arrow)* accelerates beyond the Nyquist limit, causing red-coded flow (blood moving toward transducer) to alias to blue, then again to red, and once more to blue. Turbulent flow is seen within the left ventricle at the top of the two-dimensional image.

produces multiple velocities and directions of flow in an area resulting in a mixing of color; this display can be enhanced using a variance map, which adds shades of yellow or green to the red/blue display (Fig. 2.19).

The severity of valve regurgitation is estimated subjectively by the size and shape of the regurgitant jet during CF imaging. Although technical and hemodynamic factors confound the accuracy of such assessment, wide and long regurgitant jets generally are associated with more severe regurgitation than jets that are narrow at their point of origin. Other methods for quantifying valve regurgitation have been described as well. Maximum regurgitant jet velocity is not a good indicator of severity, especially with mitral regurgitation. Changes in chamber size (i.e., eccentric hypertrophy and remodeling) provide a better indication of severity with chronic regurgitation.

OTHER ECHOCARDIOGRAPHIC MODALITIES

Doppler Tissue Imaging and 2-D Speckle Tracking

Doppler tissue imaging (DTI) is a modality used to assess the motion of tissue, rather than blood cells, by altering the signal processing and filtering of returning echoes. Myocardial velocity patterns can be assessed with CF and PW spectral DTI techniques. Spectral DTI provides greater temporal resolution and quantifies velocity of myocardial motion at specific locations, such as the lateral or septal aspects of the mitral annulus (Fig. 2.20). Color DTI methods display mean myocardial velocities from different regions. Other techniques used to assess regional myocardial function and synchrony can be derived from DTI methods, including myocardial velocity gradients, myocardial strain, and strain rate.

Myocardial strain and strain rate indices can be helpful in assessing subclinical myocardial wall motion abnormalities and ventricular dyssynchrony. Strain is a measure of myocardial deformation or percent change from its original dimension. Strain rate describes the temporal rate of deformation. A significant limitation of Doppler-based techniques is their angle dependence, complicated by cardiac translational motion. A "speckle tracking" modality, based on 2-D echocardiography rather than DTI, is often used now as a potentially more accurate way to assess regional myocardial motion, strain, and strain rate. This modality relies on tracking the motion of gray scale "speckles" within the myocardium as they move throughout the cardiac cycle. More information can be found in the Suggested Readings.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) employs transducers mounted on a flexible, steerable endoscope tip to image cardiac structures through the esophageal wall. TEE can provide clearer images of some cardiac structures (especially those at or above the AV junction) compared with transthoracic echocardiography because chest wall and lung interference is avoided. This technique can be particularly useful for defining some congenital cardiac defects and identifying

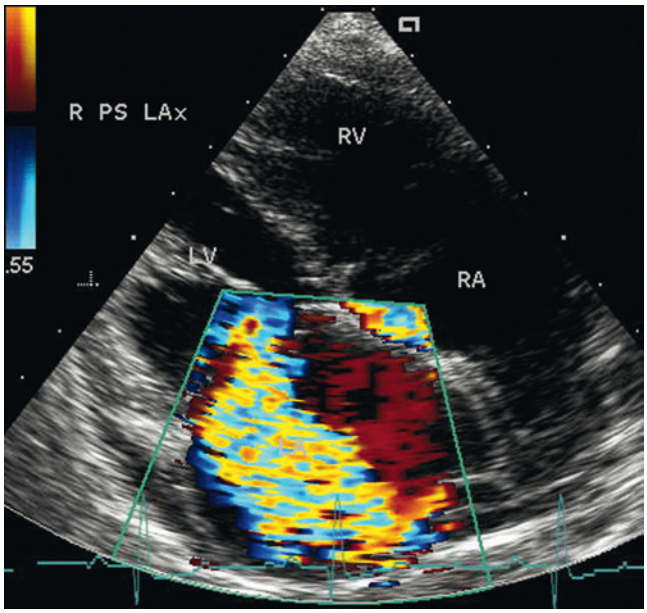


FIG 2.19
Systolic frame showing turbulent regurgitant flow into the enlarged LA of a dog with chronic mitral valve disease. The regurgitant jet curves around the dorsal aspect of the LA. Imaged from the right parasternal long-axis, four-chamber view. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

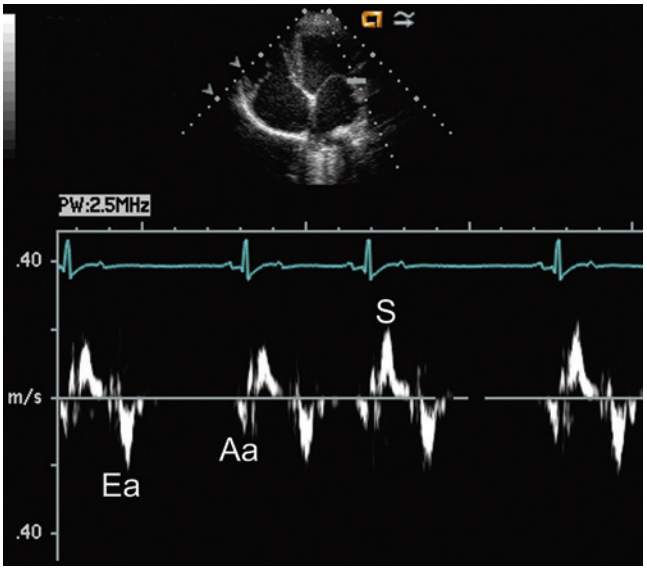


FIG 2.20
PW Doppler tissue image from a cat. The mitral annulus moves toward the left apex (and transducer) in systole *(S).* Early diastolic filling *(Ea)* shifts the annulus away from the apex as the LV expands. Additional motion occurs with late diastolic filling from atrial contraction *(Aa).*

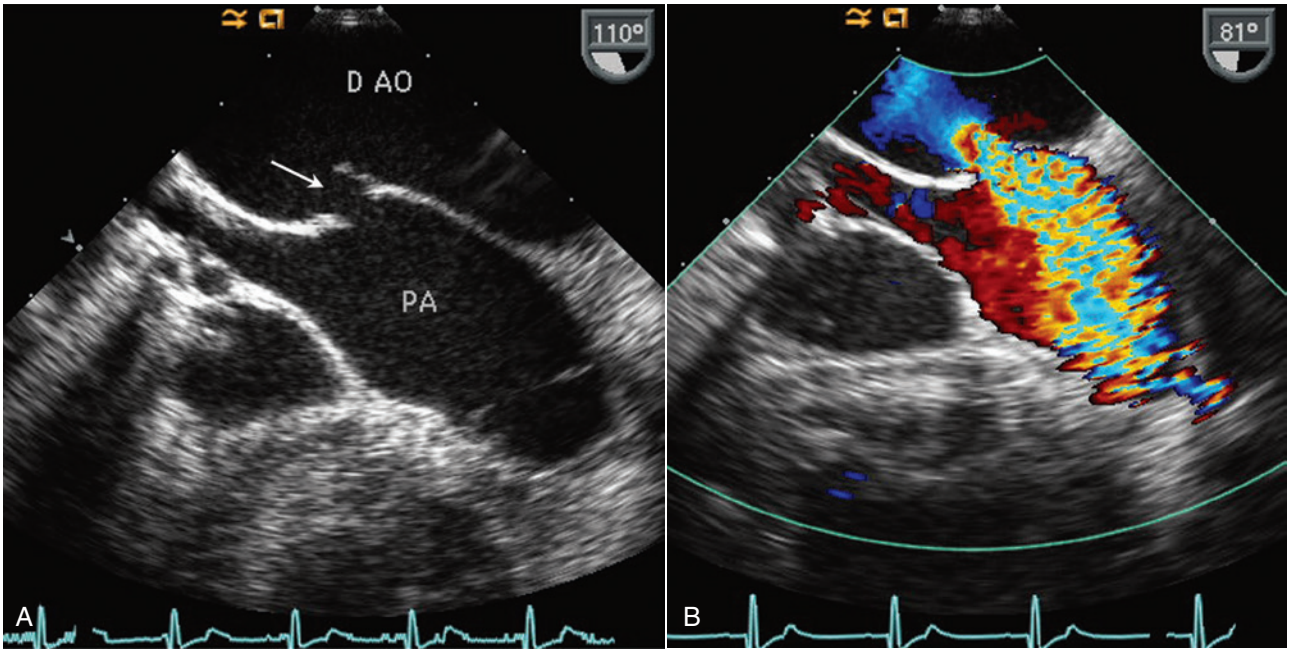


FIG 2.21
(A) Two-dimensional transesophageal echo (TEE) image at the heart base from a dog shows a patent ductus arteriosus *(arrow)* between the descending aorta *(D Ao)* and pulmonary artery *(PA)*. **(B)** Color flow Doppler image in diastole from the same orientation demonstrates flow acceleration toward the ductal opening in the D Ao and the turbulent ductal flow into the PA.

thrombi, tumors, or endocarditis lesions, as well as guiding cardiac interventional procedures (Fig. 2.21). The need for general anesthesia and the expense of the endoscopic transducers are the main disadvantages of TEE. Complications related to the endoscopy procedure are uncommon.

Three-Dimensional Echocardiography

The ability to generate and manipulate 3-D ultrasound images of the heart and other structures is becoming more widely available as a means to further evaluate cardiac structure and function. Anatomic and blood flow abnormalities can be viewed from any angle by rotating or bisecting the 3-D images. Three-dimensional capability is incorporated into some multimodality transthoracic and transesophageal transducers. Data acquisition for 3-D reconstruction of the entire heart generally requires several cardiac cycles.

LUNG ULTRASOUND

POC lung ultrasound (Vet BLUE protocol; Lisciandro, 2014) provides a means to detect pulmonary infiltrates and certain other abnormalities by the artifact or tissue interface patterns they cause. For patients presented in respiratory distress, a rapid lung ultrasound can help the clinician decide whether CHF or noncardiac disease is most likely. The exam can be done quickly with the patient in sternal or standing position and without shaving to minimize patient stress. Although not a replacement for thoracic radiographs, the technique can help direct acute therapy until the patient is stable enough for radiography. Lung ultrasound detects pulmonary edema, and other infiltrates, by the presence of artifacts known as "B" lines (also called lung rockets, comet tails, ring-down artifact). B lines are created because of the marked acoustic mismatch between small fluid-filled lung spaces and surrounding air. B lines appear as hyperechoic vertical artifacts stretching from the pleural-pulmonary interface to the furthest depth seen on the ultrasound image (Fig. 2.22); these B lines are narrowest at their origin and move with respiration. Cardiogenic pulmonary edema is strongly associated with the presence of three or more B lines in at least two of four standard positions on both sides of the chest; these occur most frequently in the middle lung zones. Pulmonary infiltrates other than cardiogenic edema can produce B lines too, although often not as extensively; such causes could include interstitial or alveolar infiltrates associated with acute respiratory distress syndrome, neoplasia, pneumonia, heartworm pneumonitis, pulmonary thromboembolism, noncardiogenic edema (as from electrocution or drowning), and pulmonary hemorrhage. An increased LA:Ao ratio, seen on concurrent focused echocardiogram, provides additional evidence for cardiac disease. The clinical history and initial physical exam findings also may suggest a cardiac versus noncardiac cause. The presence of pleural and pericardial effusions can be seen with ultrasound as well. See the Suggested Readings list for additional information about POC ultrasound.

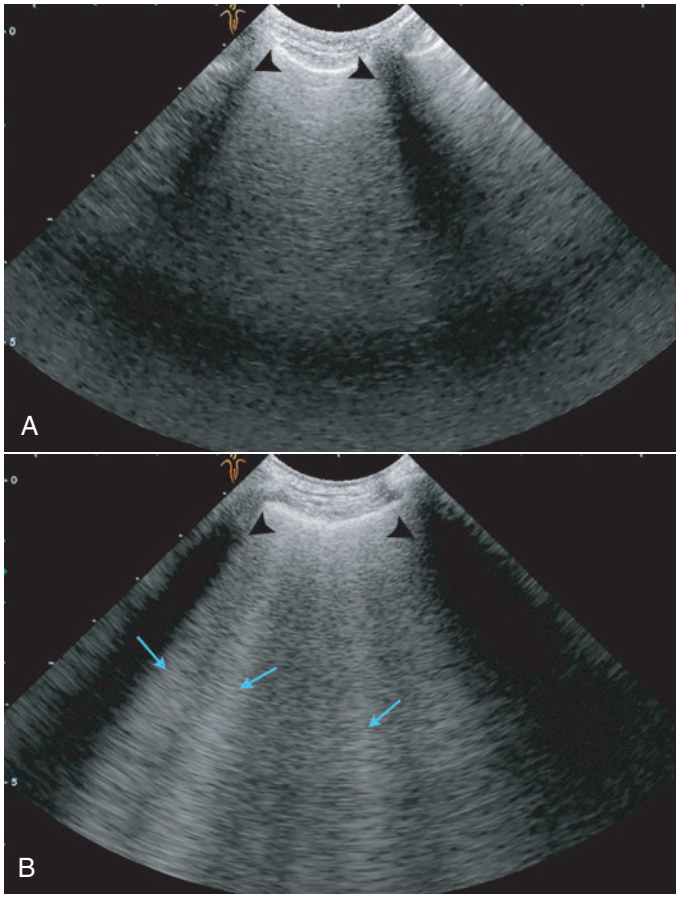


FIG 2.22
(A) Lung ultrasound image from a normal dog shows the typical appearance of well aerated lung, with its fine horizontal "A line" pattern, between two rib shadows (*arrowheads*). **(B)** Lung ultrasound image from a dog with pulmonary edema. Hyperechoic, vertical "B lines" (*small arrows*), which extend from the pleural-pulmonary interface (at top) to the bottom of the image, represent artifacts caused by the juxtaposition of intrapulmonary fluid/infiltrate and air-filled alveoli (creating a high acoustic impedance gradient).

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) graphically represents the electrical depolarization and repolarization of cardiac muscle. The ECG provides information on heart rate, rhythm, and intracardiac conduction; it may also suggest specific chamber enlargement, myocardial disease, ischemia, pericardial disease, certain electrolyte imbalances, and some drug toxicities. However, the ECG alone cannot be used to identify the presence of CHF, assess the strength (or even presence) of cardiac contractions, or predict whether the animal will survive an anesthetic or surgical procedure.

NORMAL ECG WAVEFORMS

The normal cardiac rhythm originates in the sinoatrial (SA) node. Specialized conduction pathways facilitate activation of the atria and ventricles (Fig. 2.23). The ECG waveforms, P-QRS-T, are generated as heart muscle is depolarized and then repolarized (Fig. 2.24 and Table 2.3). The QRS

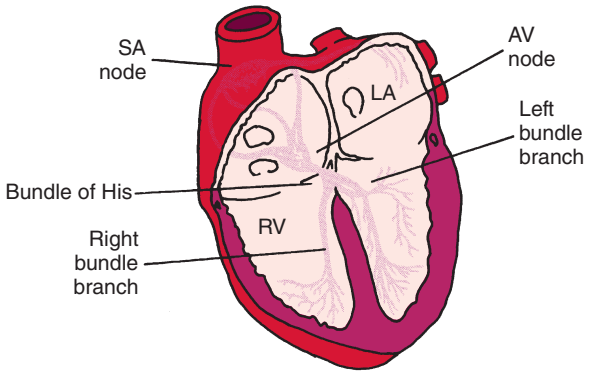


FIG 2.23
Schematic of cardiac conduction system. *AV,* Atrioventricular; *LA,* left atrium; *RV,* right ventricle; *SA,* sinoatrial. (Modified from Tilley LE: *Essentials of canine and feline electrocardiography,* ed 3, Philadelphia, 1992, Lea & Febiger.)

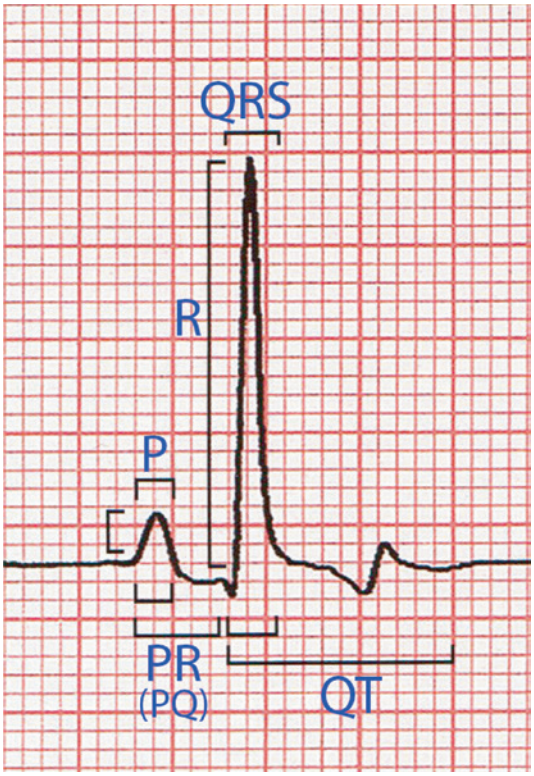


FIG 2.24
Normal canine P-QRS-T complex in lead II. Paper speed is 50 mm/sec (0.02 sec per each small box); calibration is standard (1 cm = 1 mV, 0.1 mV per each small box). Time intervals (seconds) are measured from left to right; waveform amplitudes (millivolts) are measured as positive (upward) or negative (downward) motion from baseline.

TABLE 2.3
Normal Cardiac Waveforms

WAVEFORM	EVENT
P	Depolarization (activation) of atrial muscle; normally is positive in leads II and aV_F
PR interval	Time from onset of atrial muscle activation, through conduction over the AV node, bundle of His, and Purkinje fibers; also called *PQ interval*
QRS complex	Depolarization of ventricular muscle; by definition, Q is the first negative deflection (if present), R the first positive deflection, and S is the negative deflection after the R wave
J point	End of the QRS complex (and ventricular muscle activation); junction of QRS and ST segment
ST segment	Represents the period between ventricular depolarization and repolarization (correlates with phase 2 of the action potential)
T wave	Ventricular muscle repolarization
QT interval	Total time of ventricular depolarization and repolarization

AV, Atrioventricular.

complex, as a representation of ventricular muscle electrical activation, does not necessarily have individual Q, R, and S wave components (or variations thereof). The configuration of the QRS complex depends on the lead being recorded, as well as the animal's intraventricular conduction characteristics.

LEAD SYSTEMS

Various leads are used to evaluate the cardiac activation process. The orientation of a lead with respect to the heart is called the *lead axis.* Each lead has direction and polarity. If the myocardial depolarization or repolarization wave travels parallel to the lead axis, a relatively large deflection will be recorded in that lead. As the angle between the lead axis and the orientation of the activation wave increases toward 90 degrees, the ECG deflection for that lead becomes smaller; it becomes isoelectric when the activation wave is perpendicular to the lead axis. Each lead has a positive and a negative pole or direction. A positive deflection will be recorded in a lead if the cardiac activation wave travels toward the positive pole (electrode) of that lead. If the wave of depolarization travels away from the positive pole, a negative deflection will be recorded in that ECG lead. Both bipolar and unipolar ECG leads are used clinically. A bipolar lead records electrical potential differences between two electrodes on the body surface; the lead axis is oriented between these two points. Unipolar leads have a recording (positive) electrode on the body surface. The negative pole of unipolar leads is formed by "Wilson's central terminal" (V), which is an average of all other electrodes and is analogous to zero.

The standard limb lead system records cardiac electrical activity in the frontal plane (as depicted by a DV/VD radiograph). In this plane, left-to-right and cranial-to-caudal currents are recorded. Fig. 2.25 depicts the six standard frontal leads (hexaxial lead system) overlying the cardiac ventricles. Unipolar limb leads are "augmented" (aVF, etc.) because their voltage is so low. Unipolar chest (precordial) leads "view" the heart from the transverse plane (Fig. 2.26). Box 2.2 lists common ECG lead systems.

APPROACH TO ECG INTERPRETATION

Routine ECG recording usually is done with the animal placed in right lateral recumbency on a nonconducting surface. The proximal limbs are parallel to each other and perpendicular to the torso. Other body positions may change the various waveform amplitudes and affect the calculated mean electrical axis (MEA). However, if only heart rate and rhythm are desired, any recording position can be used.

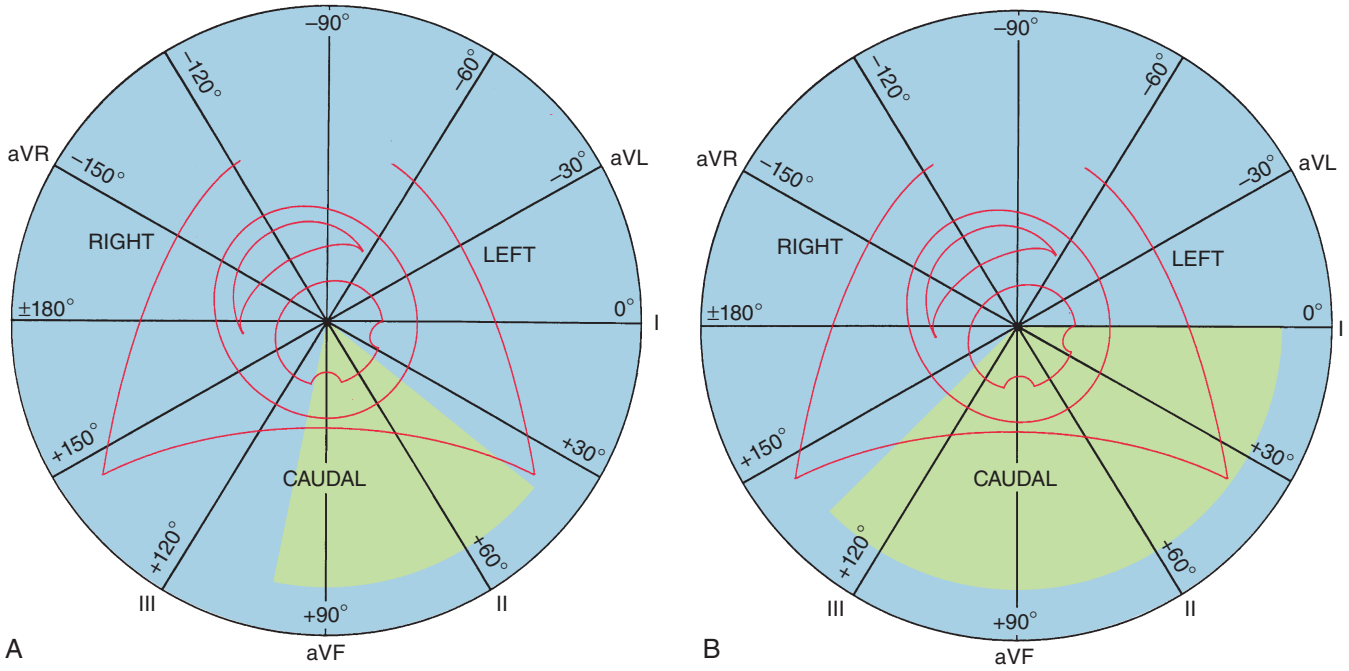


FIG 2.25
Frontal lead system: diagrams of six frontal leads over schematic of left and right ventricles within the thorax. Circular field is used for determining direction and magnitude of cardiac electrical activation. Each lead is labeled at its positive pole. Shaded area represents normal range for mean electrical axis. **(A)** Dog. **(B)** Cat.

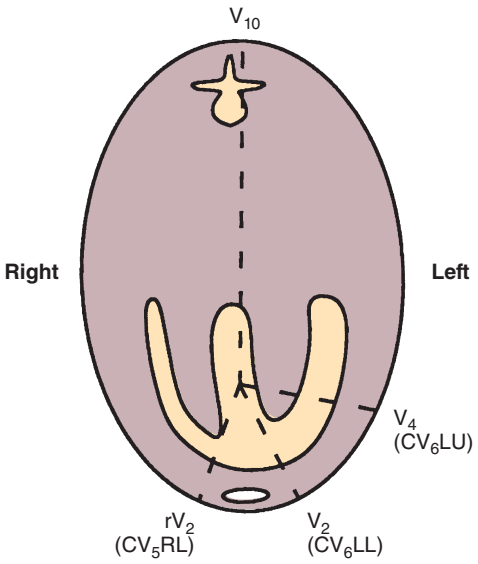


FIG 2.26
Commonly used chest leads seen from cross-sectional view. CV_5RL is located at right edge of the sternum in fifth intercostal space (ICS), CV_6LL is near sternum at sixth ICS, CV_6LU is at costochondral junction at sixth ICS, and V_{10} is located near seventh dorsal spinous process.

BOX 2.2

Small Animal Electrocardiographic Lead Systems

Standard Bipolar Limb Leads

I	RA (–) compared with LA (+)
II	RA (–) compared with LL (+)
III	LA (–) compared with LL (+)

Augmented Unipolar Limb Leads

aV_R	RA (+) compared with average of LA and LL (–)
aV_L	LA (+) compared with average of RA and LL (–)
aV_F	LL (+) compared with average of RA and LA (–)

Unipolar Chest Leads

V_1, rV_2 (CV_5RL)	Fifth right ICS near sternum
V_2 (CV_6LL)	Sixth left ICS near sternum
V_3	Sixth left ICS, equidistant between V_2 and V_4
V_4 (CV_6LU)	Sixth left ICS near costochondral junction
V_5 and V_6	Spaced as for V_3 to V_4, continuing dorsally in sixth left ICS
V_{10}	Over dorsal spinous process of seventh thoracic vertebra

Orthogonal Leads

X	Lead I (right to left) in the frontal plane
Y	Lead aV_F (cranial to caudal) in the midsagittal plane
Z	Lead V_{10} (ventral to dorsal) in the transverse plane

ICS, Intercostal space; *LA,* left arm (forelimb); *LL,* left leg (hindlimb); *RA,* right arm (forelimb).

Front limb electrodes are placed at the elbows or slightly below, not touching the chest wall or each other. Rear limb electrodes are placed at the stifles or hocks. With alligator clip or button/plate electrodes, copious ECG paste or (less ideally) alcohol is used to ensure good contact. Communication between two electrodes via a bridge of paste or alcohol or by physical contact should be avoided. The animal is gently restrained in position to minimize movement artifacts. A relaxed and quiet patient produces a better quality tracing. Holding the mouth shut to discourage panting or placing a hand on the chest of a trembling animal may be helpful.

A good ECG recording produces minimal artifact from patient movement, no electrical interference, and a clean baseline. The ECG complexes should be centered and totally contained within the background gridwork so that neither the top nor bottom of the QRS complex is clipped off. If the complexes are too large to fit entirely within the grid, the calibration should be adjusted (e.g., from standard [1 cm = 1 mV] to ½ standard [0.5 cm = 1 mV]). The calibration used during the recording must be known to accurately measure waveform amplitude. A calibration square wave (1 mV amplitude) can be inscribed manually during recording if this is not done automatically. The paper or digital recording speed and lead(s) used also must be evident for interpretation.

A consistent approach to ECG interpretation is recommended. First the recording speed, lead(s) used, and calibration are identified. Then the heart rate, heart rhythm, and MEA are determined. Finally, individual waveforms are measured. The heart rate is the number of complexes (or beats) per minute. Unless otherwise specified, this means QRS complexes (rather than P waves) are counted to provide the heart (ventricular) rate. Heart rate can be calculated by counting the number of complexes in 3 or 6 seconds and then multiplying by 20 or 10, respectively. If the heart rhythm is regular, 3000 divided by the number of small boxes (at paper/trace speed 50 mm/sec) between successive RR intervals equals the instantaneous heart rate. Because variations in heart rate are so common (in dogs especially), determining an average heart rate over several seconds is usually more accurate and practical than calculating an instantaneous heart rate.

Heart rhythm is assessed by scanning the entire ECG recording for irregularities and identifying individual waveforms. The presence and pattern of P waves and QRS-T complexes are determined. The relationship between the P waves and QRS-Ts is then evaluated. Calipers are often useful for evaluating the regularity and interrelationships of the waveforms. Estimation of MEA is described on p. 45.

Individual waveforms and intervals are, by convention, measured using lead II. Complex amplitude is recorded in millivolts and duration in seconds (or msec). Only one thickness of the inscribed pen/trace line should be included for each measurement. At 25 mm/sec recording speed, each small (1 mm) box on the ECG gridwork is 0.04 second in duration (from left to right). At 50 mm/sec recording speed, each small box equals 0.02 second. A deflection from baseline (up or down) of 10 small boxes (1 cm) equals 1 mV at standard calibration (0.1 mV per small box). ECG reference ranges for cats and dogs (Table 2.4) are representative of most normal animals, although complex measurements for some subpopulations can fall outside these ranges. For example, endurance-trained dogs can have ECG measurements that exceed the "normal" range, probably reflecting the training effects on heart size. Such changes in nontrained dogs suggest pathologic cardiac enlargement. Manual frequency filters, available on many ECG machines, can markedly attenuate the recorded voltages of some waveforms when activated, although baseline artifact is reduced. The effects of filtering on QRS amplitude may complicate the assessment for ECG chamber enlargement criteria.

SINUS RHYTHMS

The normal cardiac rhythm originates in the sinus node and produces the P-QRS-T waveforms previously described. The P waves are positive in caudal leads (II and aVF), and the PR (also called PQ) intervals are consistent. Regular sinus rhythm is characterized by less than 10% variation in the timing of the QRS to QRS (or R to R) intervals. Normally the QRS complexes are narrow and upright in leads II and aVF. However, an intraventricular conduction disturbance or ventricular enlargement pattern may cause them to be wide or abnormally shaped.

Sinus arrhythmia is characterized by cyclic slowing and speeding of the sinus rate. This usually is associated with respiration; the sinus rate tends to increase on inspiration and decrease with expiration as a result of fluctuations in vagal tone. There also may be a cyclic change in P-wave configuration ("wandering pacemaker") with the P waves becoming taller and spiked during inspiration and flatter in expiration. Sinus arrhythmia is a common and normal rhythm variation in dogs. It occurs in resting cats but rarely is seen in the clinical setting. Pronounced sinus arrhythmia can be associated with chronic pulmonary disease, especially in dogs.

"Brady-" and "tachy-" are modifying terms that describe abnormally slow or fast rhythms, respectively, without identifying intracardiac origin. Both sinus bradycardia and sinus tachycardia are rhythms that originate in the sinus node and are conducted normally; however, the heart rate of sinus bradycardia is slower than normal for the species, whereas that of sinus tachycardia is faster than normal. Some causes of sinus bradycardia and tachycardia are listed in Box 2.3.

Sinus arrest is the absence of sinus activity lasting at least twice as long as the animal's longest expected QRS to QRS interval. An escape complex usually interrupts the resulting pause if sinus activity does not resume soon enough. Long pauses can cause fainting or weakness. Sinus arrest cannot be differentiated with certainty from SA block on the surface ECG. Fig. 2.27 illustrates various sinus rhythms.

TABLE 2.4

Normal Electrocardiographic Reference Ranges for Dogs and Cats

DOGS	CATS
Heart Rate	
60-160 beats/min (adults) to 220 beats/min (puppies)	(120-)140-240 beats/min
Mean Electrical Axis (Frontal Plane)	
+40 to +100 degrees	0 to +160 degrees
Measurements (Lead II)	
P-wave duration (maximum)	
0.04 sec (0.05 sec, giant breeds)	0.035-0.04 sec
P-wave height (maximum)	
0.4 mV	0.2 mV
PR interval	
0.06-0.13 sec	0.05-0.09 sec
QRS complex duration (maximum)	
0.05 sec (small breeds) 0.06 sec (large breeds)	0.04 sec
R-wave height (maximum)	
2.5 mV (small breeds) 3 mV (large breeds)*	0.9 mV in any lead; QRS total in any lead <1.2 mV
ST segment deviation	
<0.2 mV depression <0.15 mV elevation	<0.1 mV deviation
T wave	
Usually < 25% of R wave height; can be positive, negative, or biphasic	Maximum 0.3 mV; can be positive (most common), negative, or biphasic
QT interval duration	
0.15-0.25 (to 0.27) sec; varies inversely with heart rate	0.12-0.18 (range 0.07-0.2) sec; varies inversely with heart rate
Chest Leads	
V_1; rV_2: positive T wave V_{2-3}: S wave 0.8 mV maximum; R wave 2.5 mV maximum* V_{4-6}: S wave 0.7 mV maximum; R wave 3 mV maximum* V_{10}: negative QRS; negative T wave	R wave 1.0 mV maximum in chest leads R/Q < 1.0; negative T wave

Each small box on the ECG paper grid is 0.02 second wide at 50 mm/sec paper speed, 0.04 second wide at 25 mm/sec, and 0.1 mV high at a calibration of 1 cm = 1 mV.
*May be greater in thin, deep-chested dogs younger than 2 years old.

ECTOPIC RHYTHMS

Impulses originating from outside the sinus node (known as *ectopic* impulses) are abnormal and create an arrhythmia (dysrhythmia). Ectopic impulses are described on the basis of their general site of origin (atrial, junctional, supraventricular, ventricular) and their timing (Fig. 2.28). *Timing* refers to whether the impulse occurs earlier than the next expected sinus impulse (and therefore is *premature*) or after a longer pause (considered late or *escape*). Escape complexes represent activation of a subsidiary pacemaker and function as a rescue mechanism for the heart. Premature ectopic impulses (complexes) occur singly or in multiples; groups of three or more constitute an episode of tachycardia. Episodes of tachycardia can consist of a brief run of ventricular premature complexes (VPCs; *paroxysmal* tachycardia) or can be quite prolonged (*sustained* tachycardia).

BOX 2.3

Causes of Sinus Bradycardia and Sinus Tachycardia

Sinus Bradycardia

Hypothermia
Hypothyroidism
Drugs (e.g., some tranquilizers, anesthetics, β-blockers, calcium entry blockers, digoxin)
Increased intracranial pressure
Brainstem lesions
Ocular pressure
Carotid sinus pressure
Other causes of high vagal tone (e.g., airway obstruction)
Sinus node disease
Severe metabolic disease (e.g., hyperkalemia, uremia)
Normal variation (athletic dog)
Cardiac arrest (before or after)

Sinus Tachycardia

Hyperthermia/fever
Hyperthyroidism
Anemia/hypoxia
Heart failure
Hypotension
Shock
Sepsis
Anxiety/fear
Excitement
Exercise
Pain
Drugs (e.g., anticholinergics, sympathomimetics)
Toxicities (e.g., chocolate, amphetamines, theophylline)
Electric shock
Other causes of high sympathetic tone

When a premature complex follows each normal sinus QRS, this creates a bigeminal pattern; the origin of the premature complexes determines whether the rhythm is described as atrial or ventricular *bigeminy*. Fig. 2.29 contains examples of ectopic supraventricular and ventricular complexes and rhythms.

Supraventricular Premature Complexes

Supraventricular premature complexes are impulses that originate above the atrioventricular (AV) node, either in the atria or the AV junctional area. Because they are conducted into and through the ventricles via the normal conduction pathway, their QRS configuration is normal (unless an intraventricular conduction disturbance also is present). Premature ectopic complexes arising within the atria (APCs, or PACs) usually are preceded by an abnormal P wave (of either positive, negative, or biphasic configuration) called a *P′ wave*. If an ectopic P′ wave occurs before the AV node has completely repolarized, the impulse may not be conducted into the ventricles (an example of physiologic AV block). In some cases, the premature impulse is conducted slowly (prolonged P′Q interval) or with a bundle branch block pattern. Although P′ waves usually do not precede junctional complexes, retrograde conduction into the atria sometimes causes a negative P′ wave to follow, be superimposed on, or even precede the associated QRS complex. If the specific origin of the ectopic complex(es) is unclear, the more general term *supraventricular premature complex* (or *supraventricular tachycardia*) is used. Clinically it often is more important to determine whether an arrhythmia originates from above the AV node (supraventricular) or below it (ventricular) rather than the more specific localization. Supraventricular premature complexes that also depolarize the sinus node reset the sinus rhythm and create a *noncompensatory pause* (i.e., the interval between the sinus complexes that precede and follow the premature complex is less than that of three consecutive sinus complexes).

Supraventricular Tachycardias

Tachycardias of supraventricular origin often involve a reentrant pathway using the AV node (either within the AV node or using an accessory pathway); a premature supraventricular or ventricular impulse can initiate reentrant supraventricular tachycardia (SVT). During episodes of reentrant SVT in animals with ventricular preexcitation (see p. 44), the PR interval usually normalizes (or becomes prolonged) and retrograde P′ waves may be evident. The QRS complexes are of normal configuration unless a simultaneous intraventricular conduction disturbance is present.

Atrial tachycardia is caused by rapid discharge of an abnormal atrial focus or by atrial reentry (repetitive activation caused by conduction of the electrical impulse around an abnormal circuit within the atria). In dogs, the atrial activation rate usually is between 260 and 380/minute. The P′ waves are often hidden in the QRS-T complexes. Atrial tachycardia can be paroxysmal or sustained. It generally is a regular rhythm unless the rate is too fast for the AV node to conduct every impulse, in which case physiologic AV block causes irregular ventricular activation. A consistent ratio of atrial impulses to ventricular activation (e.g., 2:1 or 3:1 AV conduction) preserves the regularity of this arrhythmia. Sometimes the impulses traverse the AV node but are delayed within the ventricular conduction system, causing a bundle branch block pattern on the ECG. Differentiation from ventricular tachycardia can be challenging in these cases.

Atrial Flutter

Atrial flutter is produced by rapid (usually > 400 impulses/min) waves of electrical activation regularly cycling through the atria. The ventricular response may be irregular or regular, depending on the pattern of AV conduction. The ECG baseline shows "saw tooth" flutter waves that represent the fast, recurrent atrial activation. Atrial flutter is not a stable rhythm; it often degenerates into atrial fibrillation (AF), or may convert back to sinus rhythm.

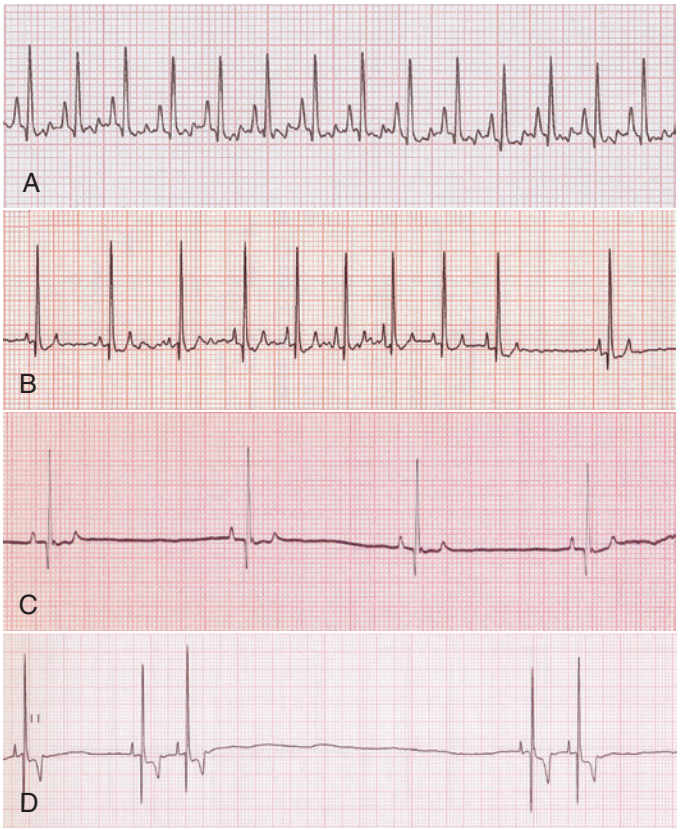


FIG 2.27
Sinus rhythms. **(A)** Sinus tachycardia in an older Shih Tzu; heart rate ~ 200 beats/min. **(B)** Sinus arrhythmia with wandering pacemaker in a dog. Note gradual variation in P-wave height associated with respiratory changes in heart rate; this variation is normal in the dog. Some baseline muscle tremor artifact is evident. **(C)** Sinus bradycardia (heart rate 40 beats/min) in a dog with brain disease. **(D)** Intermittent periods of sinus arrest in a 13-year-old Cocker Spaniel. All ECGs are lead II, 25 mm/sec, 1 cm = 1 mV.

Atrial Fibrillation

This common arrhythmia is characterized by rapid and chaotic electrical activation within the atria. There are no P waves on the ECG because there is no uniform atrial depolarization wave. Rather, the baseline usually shows small, irregular undulations (fibrillation waves). Lack of organized electrical activity also prevents effective atrial contraction. The AV node, being bombarded by these chaotic electrical impulses, conducts as many and as quickly as possible to the ventricles. Ultimately the (ventricular) heart rate is determined by AV conduction velocity and recovery time, which are influenced by prevailing autonomic tone. AF causes an irregular heart rhythm that is quite rapid when sympathetic tone is high (Fig. 2.30). The QRS complexes usually are normal in configuration because intraventricular conduction usually is normal. Minor variation in QRS complex amplitude is common, however, and intermittent or sustained bundle branch blocks can occur. AF tends to be a consequence of marked atrial enlargement in dogs and especially in cats; it often is preceded by intermittent atrial tachyarrhythmias and perhaps atrial flutter. AF sometimes occurs spontaneously in giant breed dogs without evidence of underlying heart disease; this is known as *lone AF*. The heart rate often is normal in dogs with lone AF.

Ventricular Premature Complexes

VPCs, or PVCs, originate below the AV node. Therefore ventricular muscle activation does not occur via the normal ventricular conduction pathway, and the QRS configuration of VPCs differs from the animal's normal sinus QRS complexes. Ventricular ectopic complexes usually are wider than sinus-origin complexes because of the slower intramuscular conduction. Because VPCs usually are not conducted backward through the AV node into the atria, the sinus rate continues undisturbed and the VPC is followed by a so-called *compensatory pause* in the sinus rhythm. When the configuration of multiple VPCs or ventricular tachycardia is consistent, the complexes are described as *uniform* or *monomorphic*. When VPCs in an individual animal have differing configurations, they are said to be *multiform* or *polymorphic*. Increased electrical instability may accompany multiform VPCs or ventricular tachycardia.

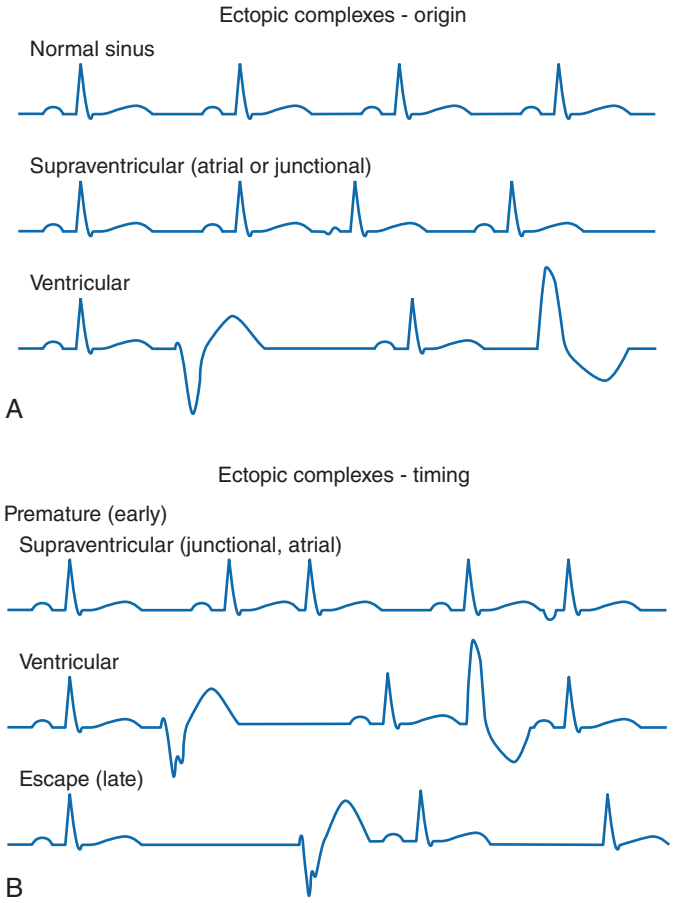


FIG 2.28
Diagrams illustrating the appearance of ectopic complexes. Abnormal impulses can originate **(A)** above the AV node (supraventricular) or from within the ventricles (ventricular). Supraventricular ectopic complexes have a normal-appearing QRS. An abnormal P wave usually precedes a complex originating in atrial tissue; no P wave (or a retrograde P wave in the ST segment—not shown) is common with an impulse originating from the AV junction. Ventricular-origin QRS complexes have a different configuration from the normal sinus QRS. The timing **(B)** of ectopic complexes refers to whether they appear before the next expected sinus complex (premature or early) or after a longer than expected pause (escape or late).

Ventricular Tachycardia

Ventricular tachycardia consists of a series of VPCs (usually at a rate > 100 beats/min). The QRS to QRS (RR) interval most often is regular, although some variation can occur. Nonconducted sinus P waves may be superimposed on or between the ventricular complexes, although they are unrelated to the VPCs because the AV node and/or ventricles are in the refractory period (physiologic AV dissociation). The term *capture beat* refers to the successful conduction of a sinus P wave into the ventricles uninterrupted by another VPC (i.e., the sinus node has "recaptured" the ventricles). If the normal ventricular activation sequence is interrupted by a VPC, a *fusion* complex can result. A fusion complex represents a melding of the normal QRS configuration and that of the VPC (see Fig. 2.29, *F*). Fusion complexes often are observed at the onset or end of a paroxysm (run) of ventricular tachycardia; they are preceded by a P wave and shortened PR interval. Identification of P waves (whether conducted or not) or fusion complexes helps in differentiating ventricular tachycardia from SVT with abnormal (aberrant) intraventricular conduction.

Polymorphic ventricular tachycardia is characterized by QRS complexes that vary in size, polarity, and often rate; sometimes the QRS configuration appears as if it were rotating around the isoelectric baseline. *Torsades de pointes* is a specific form of polymorphic ventricular tachycardia associated with Q-T interval prolongation.

Accelerated Idioventricular Rhythm

Also called *accelerated ventricular rhythm* or *idioventricular tachycardia,* an accelerated idioventricular rhythm originates within the ventricles and has a rate of about 60 to 100 beats/min in the dog (perhaps somewhat faster in the cat). Because the rate is slower than true ventricular tachycardia, it usually is a less serious rhythm disturbance. An accelerated ventricular rhythm can appear intermittently during sinus arrhythmia, as the sinus rate decreases; then the idioventricular rhythm usually is suppressed as the sinus rate increases. This rhythm is common in dogs recovering from motor vehicle trauma; it also occurs in many dogs with severe intra-abdominal or systemic disease. Often this rhythm disturbance has no deleterious effects, although it could progress to ventricular tachycardia, especially in clinically unstable patients.

Ventricular Fibrillation

Ventricular fibrillation (VF) is a lethal rhythm characterized by multiple reentrant circuits causing chaotic electrical activity within the ventricles. The ECG shows an irregularly undulating baseline with no recognizable waveforms (Fig. 2.31). The chaotic electrical activation causes only weak, uncoordinated mechanical activation, so there is no effective ventricular pumping function. Ventricular flutter, which appears as rapid sine-wave activity on the ECG, may precede fibrillation. "Course" VF has slightly larger ECG oscillations than "fine" VF and may precede it before death.

Escape Complexes

Ventricular asystole is the absence of ventricular electrical (and mechanical) activity. Escape complexes originate from automatic (*subsidiary pacemaker*) cells within the atria, the AV junction, or the ventricles (see Fig. 2.32, *B*) and constitute a protective mechanism. An escape complex occurs only after a pause in the dominant (usually sinus) rhythm. If the dominant rhythm does not resume, the escape focus continues to discharge at its own intrinsic rate, producing an *escape rhythm* (Fig. 2.32, *C*). Escape rhythms usually are regular. Ventricular escape rhythms (idioventricular rhythms) usually have an intrinsic rate of less than 40 to 50 beats/min in the dog and 100 beats/min in the cat, although

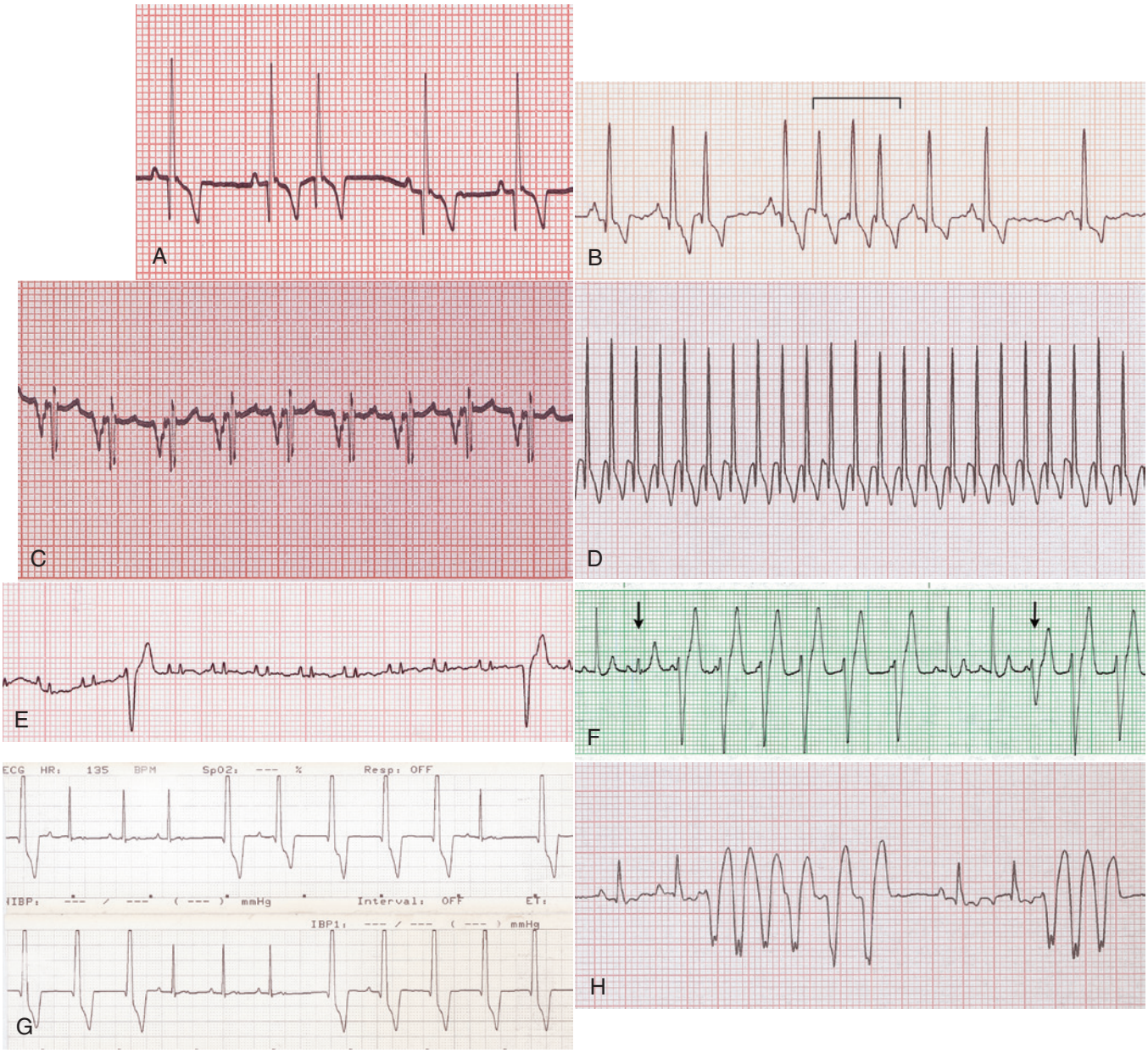


FIG 2.29
Ectopic complexes and rhythms. **(A)** Supraventricular premature complex in an old Doberman Pinscher. **(B)** Short paroxysm of supraventricular tachycardia *(bracket)* with 1 single premature complex in a mixed-breed dog with mitral regurgitation (lead II, 25 mm/sec). **(C)** Sustained atrial tachycardia in Irish Setter with mitral stenosis. Note negative, abnormal P waves. **(D)** Rapid supraventricular tachycardia in a Labrador Retriever puppy (heart rate ~360 beats/min). **(E)** Sinus rhythm with two isolated ventricular premature complexes in a cat with hypertrophic cardiomyopathy. **(F)** Intermittent paroxysms of ventricular tachycardia demonstrating fusion complexes *(arrows)* in a dog. **(G)** Accelerated idioventricular rhythm interspersed with a background of sinus arrhythmia in a dog. **(H)** Paroxysmal, rapid ventricular tachycardia in a dog with dilated cardiomyopathy. All ECGs are lead II, 25 mm/sec.

higher ventricular escape rates can occur. Junctional escape rhythms usually range from 40 to 60 beats/min in the dog, with a faster rate expected in the cat. It is important to differentiate escape from premature complexes. Escape activity should never be suppressed with antiarrhythmic drugs.

CONDUCTION DISTURBANCES

Abnormal impulse conduction within the atria can occur at several sites. SA block prevents impulse transmission from the SA node to adjacent atrial muscle. Although this cannot reliably be differentiated from sinus arrest on the ECG, with

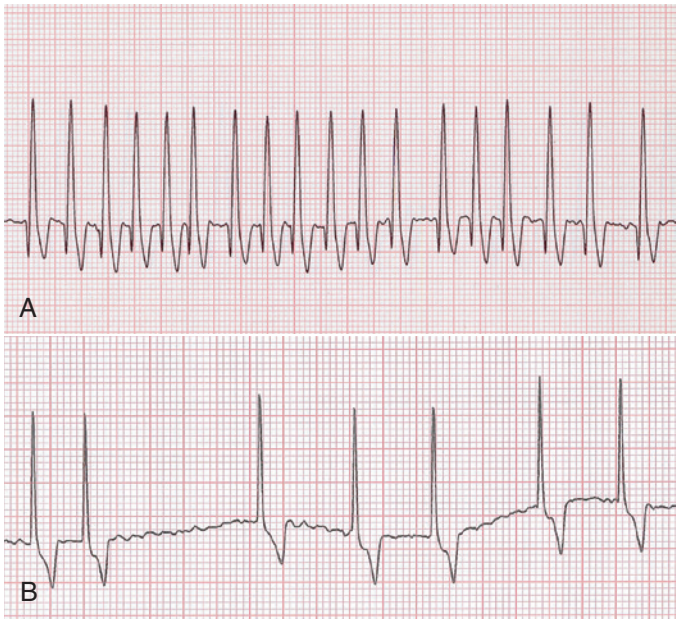


FIG 2.30
Atrial fibrillation. **(A)** Uncontrolled atrial fibrillation (heart rate 240 beats/min) in a Labrador Retriever with dilated cardiomyopathy (lead II, 25 mm/sec). **(B)** Well-controlled ventricular response rate after therapy in a different dog (heart rate ~100 beats/min). Note baseline fibrillation waves, lack of identifiable P waves, and irregular RR intervals. Lead II, 25 mm/sec.

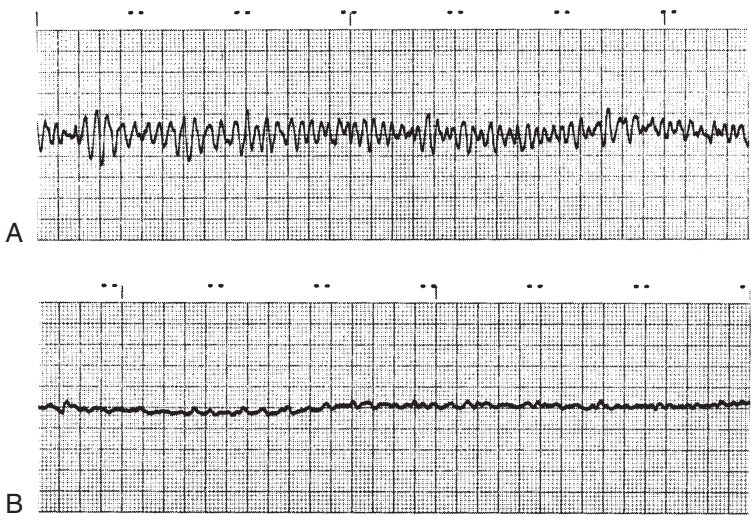


FIG 2.31
Ventricular fibrillation. Note chaotic baseline motion and absence of organized waveforms. **(A)** Coarse fibrillation; **(B)** fine fibrillation. Lead II, 25 mm/sec, dog.

SA block the interval between P waves is a multiple of the normal P–P interval. An (atrial, junctional, or ventricular) escape rhythm should take over the cardiac rhythm if there is prolonged sinus arrest or block. Atrial standstill occurs when diseased atrial muscle prevents normal electrical and mechanical function, regardless of sinus node activity; consequently, a junctional or ventricular escape rhythm results. P waves are not seen with atrial standstill. Because hyperkalemia interferes with normal atrial function, it can mimic atrial standstill.

Conduction Disturbances Within the Atrioventricular Node

Abnormalities of AV conduction can occur from excessive vagal tone; drugs (e.g., digoxin, xylazine, medetomidine, verapamil, anesthetic agents); and organic disease of the AV

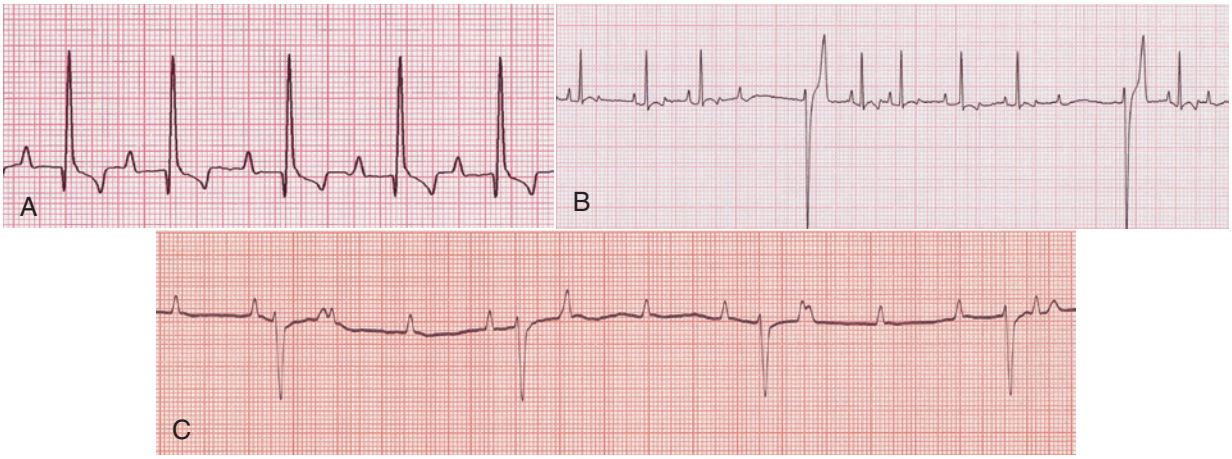


FIG 2.32
Atrioventricular (AV) conduction abnormalities. **(A)** First-degree AV block in an older Cocker Spaniel (lead II, 50 mm/sec). **(B)** Second-degree AV block (Wenckebach) with two ventricular escape complexes in an older West Highland White Terrier. The differentiation between escape and premature complexes is crucial (lead II, 25 mm/sec). **(C)** Complete (third-degree) heart block in a 19-year-old Lhasa Apso. There is underlying sinus rhythm, but no P waves are conducted; a slow ventricular escape rhythm has resulted (lead II, 25 mm/sec).

node and/or intraventricular conduction system. Three major types of AV conduction disturbance are described (Fig. 2.32). First-degree (1°) AV block, the mildest AV conduction disturbance, occurs when the atrial to ventricular conduction time is prolonged. All impulses are conducted with 1° AV block, but the PR interval is longer than normal. Second-degree (2°) AV block is characterized by intermittent AV conduction; some P waves are not followed by a QRS complex. When many P waves are not conducted, the patient is described as having high-grade 2° AV block. There are two subtypes of 2° AV block. Mobitz type I (Wenckebach) is characterized by progressive PR interval prolongation until conduction fails, resulting in a nonconducted P wave; it frequently is associated with high vagal tone or disorders of the AV node itself. Mobitz type II 2° AV block is characterized by uniform PR intervals preceding the blocked impulse; it is more likely to be associated with disease lower in the AV conduction system (e.g., bundle of His or major bundle branches). An alternative classification of 2° AV block based on QRS configuration has been described. Patients with type A 2° block have a normal, narrow QRS configuration; those with type B 2° block have a wide or abnormal QRS configuration, which suggests diffuse disease lower in the ventricular conduction system. Mobitz type I AV block usually is type A, whereas Mobitz type II frequently is type B. Escape complexes commonly appear during long pauses in ventricular activation. Third-degree (3°) or complete AV block means complete failure of AV conduction; no sinus (or supraventricular) impulses are conducted into the ventricles. Although a regular sinus rhythm or sinus arrhythmia often is evident, the P waves are completely dissociated from the QRS complexes, which result from a (usually) regular ventricular escape rhythm.

Intraventricular Conduction Disturbances

Abnormal (aberrant) ventricular conduction occurs in association with slowed or blocked impulse transmission within a major bundle branch or ventricular region. The right bundle branch, or the left anterior or posterior fascicles of the left bundle branch, can be affected singly or in combination. A block in all three major branches results in 3° (complete) heart block. Electrical activation of the myocardium served by the blocked pathway occurs relatively slowly, from myocyte to myocyte. Therefore the QRS complexes appear wide and abnormal, similar to a ventricular-origin QRS complex (Fig. 2.33). Right bundle branch block (RBBB) is sometimes identified in otherwise normal dogs and cats, although it can occur from disease or distention of the RV. Left bundle branch block (LBBB) usually is related to clinically relevant underlying LV disease. The left anterior fascicular block (LAFB) pattern is common with concentric LV hypertrophy and in cats with hypertrophic cardiomyopathy.

Ventricular Preexcitation

Early activation (preexcitation) of part of the ventricular myocardium can occur when there is an accessory conduction pathway that bypasses the normal, more slowly conducting AV nodal pathway. Several types of preexcitation and accessory pathways have been described. Most cause a shortened PR interval. Wolff-Parkinson-White (WPW) preexcitation also is characterized by early widening and slurring of the QRS by a so-called *delta* wave (Fig. 2.34). This pattern occurs because the accessory pathway (Kent bundle) lies outside the AV node (is extranodal) and allows early depolarization (represented by the delta wave) of part of the ventricle away from where normal ventricular activation begins. Other accessory pathways may connect the atria or

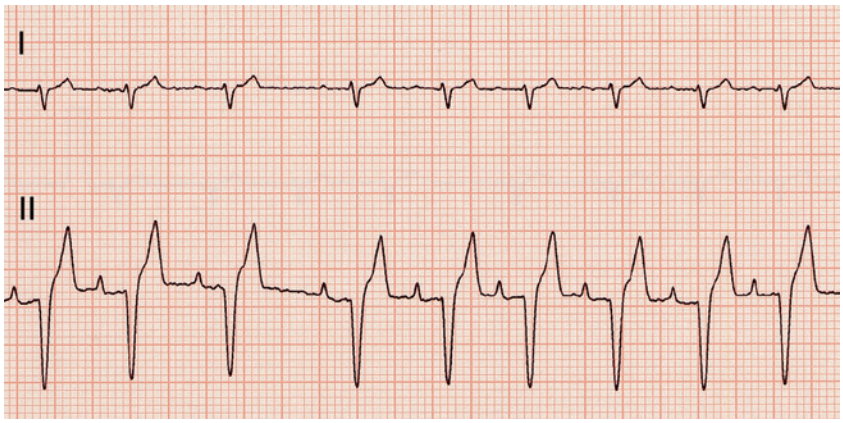


FIG 2.33
Electrocardiogram from a dog that developed right bundle branch block and first-degree AV block after doxorubicin therapy. Sinus arrhythmia, leads I and II, 25 mm/sec, 1 cm = 1 mV.

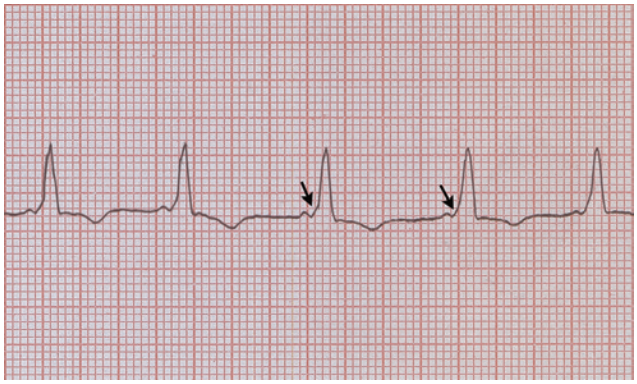


FIG 2.34
Ventricular preexcitation in a cat. Note slowed QRS upstroke (delta wave; *arrows*) immediately following each P wave. Lead II, 50 mm/sec, 1 cm = 1 mV.

dorsal areas of the AV node directly to the bundle of His. These cause a short PR interval without early QRS widening. Preexcitation can occur consistently, or be intermittent or concealed (not evident on ECG). The danger with preexcitation is that a reentrant SVT can occur using the accessory pathway and AV node (also called *AV reciprocating tachycardia*). In the most common pattern, the tachycardia impulses travel down into the ventricles via the AV node (antegrade or orthodromic conduction), then back up to the atria via the accessory pathway; however sometimes the direction is reversed. Rapid AV reciprocating tachycardia can cause weakness, syncope, CHF, and death. The presence of the WPW pattern on ECG in conjunction with AV reciprocating tachycardia that causes clinical signs is known as the *WPW syndrome*.

MEAN ELECTRICAL AXIS

The MEA describes the average direction of the ventricular depolarization process in the frontal plane. It represents the summation of the various instantaneous vectors that occur from beginning until completion of ventricular muscle depolarization. Major intraventricular conduction disturbances and/or ventricular enlargement can shift the average direction of ventricular activation and therefore the MEA. By convention, only the six frontal plane leads are used to determine MEA. Either of the following methods can be used:

1. Find the lead (I, II, III, aVR, aVL, or aVF) with the largest R wave (*Note:* the R wave, by definition, is a positive deflection). The positive electrode of this lead is the approximate orientation of the MEA.
2. Find the lead (I, II, III, aVR, aVL, or aVF) where the QRS complex is most isoelectric (i.e., the positive and negative QRS deflections are of about equal amplitude). Then identify the lead oriented perpendicular to this "isoelectric" lead on the hexaxial lead diagram (see Fig. 2.25). If the QRS complex in this perpendicular lead is mostly positive, the MEA is oriented toward the positive pole (electrode) of this lead. If the QRS in the perpendicular lead is mostly negative, the MEA is oriented toward that lead's negative pole. If all frontal plane leads appear isoelectric, the MEA is indeterminate. Fig. 2.25 shows the normal MEA range for dogs and cats.

CHAMBER ENLARGEMENT AND BUNDLE BRANCH BLOCK PATTERNS

Changes in the ECG waveforms can suggest enlargement or abnormal conduction within a particular cardiac chamber, although enlargement does not always produce these changes. A widened P wave is the classic pattern of LA enlargement (so-called *p mitrale*); sometimes the P wave is notched as well as wide. Tall, spiked P waves (so-called *p pulmonale*) suggest RA enlargement. With atrial enlargement, the usually obscure atrial repolarization (T_a) wave may be evident as a baseline shift in the opposite direction of the P wave.

A right-axis deviation and an S wave in lead I are strong criteria for RV enlargement (or RBBB). Other ECG changes usually can be found as well. Three or more of the criteria listed in Box 2.4 generally are present when RV enlargement exists. RV enlargement (dilation or hypertrophy) is likely to be pronounced if it is evident on the ECG because LV activation forces are normally so dominant. LV dilation and eccentric hypertrophy typically increase R-wave amplitude in the caudal leads (II and aVF) and sometimes widen the QRS. LV concentric hypertrophy inconsistently produces a left-axis deviation.

Conduction block in any of the major ventricular conduction pathways disturbs the normal activation process and alters QRS configuration. Electrical activation in regions of ventricular muscle served by the affected bundle branch occurs late and progresses slowly. This widens the QRS complex (especially the terminal portion of it) and shifts the QRS (and MEA) orientation toward the area of delayed activation. Box 2.4 and Fig. 2.35 summarize ECG patterns associated with ventricular enlargement or conduction delay. Box 2.5 lists common clinical associations.

BOX 2.4

Ventricular Chamber Enlargement and Conduction Abnormality Patterns

Normal

Normal mean electrical axis
No S wave in lead I
R wave taller in lead II than in lead I
Lead V_2 R wave larger than S wave

Right Ventricular Enlargement

Right-axis deviation
S wave present in lead I
S wave in V_{2-3} larger than R wave or > 0.8 mV
Q-S ("W" shape) in V_{10}
Positive T wave in lead V_{10}
Deep S wave in leads II, III, and aV_F

Right Bundle Branch Block (RBBB)

Same as right ventricular enlargement, with prolonged terminal (latter) portion of the QRS (wide, sloppy S wave)

Left Ventricular Dilation (Eccentric Hypertrophy)

Normal frontal axis
Taller than normal R wave in leads II, aV_F, V_{2-3}
Possibly widened QRS; slurring and displacement of ST segment and T-wave enlargement may also occur

Left Ventricular (Concentric) Hypertrophy

Left-axis deviation
R wave in lead I taller than R wave in leads II or aV_F
No S wave in lead I

Left Anterior Fascicular Block (LAFB)

Same as left ventricular hypertrophy, possibly with wider QRS

Left Bundle Branch Block (LBBB)

Normal frontal axis
Very wide and sloppy QRS; R waves may be taller than normal in leads II, aV_F, V_{2-3}
Small Q wave may be present in leads II, III, and aV_F (incomplete LBBB)

Other QRS Abnormalities

Small-voltage QRS complexes sometimes occur. Causes of reduced QRS amplitude include pleural or pericardial effusions, obesity, intrathoracic mass lesions, hypovolemia, and hypothyroidism. Small complexes occasionally are seen in dogs with dilated cardiomyopathy or without identifiable abnormalities.

Electrical alternans is an every-other-beat recurring alteration in QRS complex size or configuration. This most often is seen with large-volume pericardial effusions (see Chapter 9).

ST-T ABNORMALITIES

The ST segment extends from the end of the QRS complex (also called the *J-point*) to the onset of the T wave. In dogs

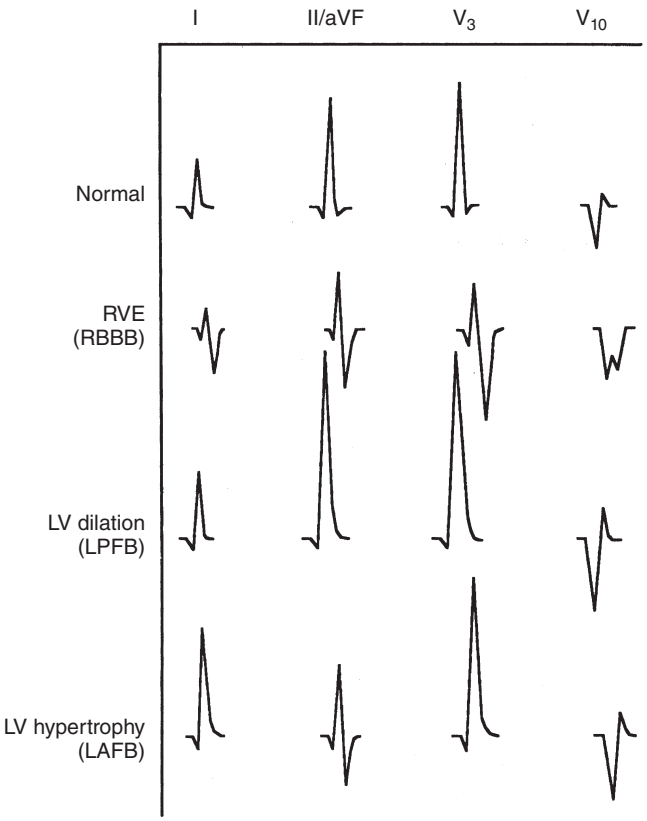


FIG 2.35
Schematic of common ventricular enlargement patterns and conduction abnormalities. Electrocardiogram leads are listed across top. *LAFB,* Left anterior fascicular block; *LPFB,* left posterior fascicular block; *LV,* left ventricular; *RBBB,* right bundle branch block; *RVE,* right ventricular enlargement.

BOX 2.5

Clinical Associations of Electrocardiographic Enlargement Patterns

Left Atrial Enlargement

Mitral insufficiency (acquired or congenital)
Cardiomyopathies
Patent ductus arteriosus
Subaortic stenosis
Ventricular septal defect
Mitral stenosis (rare)

Right Atrial Enlargement

Tricuspid insufficiency (acquired or congenital)
Chronic respiratory disease
Interatrial septal defect
Pulmonic stenosis

Left Ventricular Enlargement (Dilation)

Mitral insufficiency
Dilated cardiomyopathy
Aortic insufficiency
Patent ductus arteriosus
Ventricular septal defect
Subaortic stenosis

Left Ventricular Enlargement (Hypertrophy)

Hypertrophic cardiomyopathy
Subaortic stenosis

Right Ventricular Enlargement

Pulmonic stenosis
Tetralogy of Fallot
Tricuspid insufficiency (acquired or congenital)
Severe heartworm disease
Severe pulmonary hypertension (of other cause)

and cats this segment tends to slope into the T wave that follows without clear demarcation. Abnormal J-point and ST segment elevation (>0.15 mV in dogs or >0.1 mV in cats) or depression (>0.2 mV in dogs or >0.1 mV in cats) from baseline in leads I, II, or aVF often is clinically significant. Myocardial ischemia and other types of myocardial injuries are possible causes.

Atrial enlargement or tachycardia can cause pseudodepression of the ST segment because of prominent T_a waves. Other secondary causes of ST segment deviation include ventricular hypertrophy, slowed conduction, and some drugs (e.g., digoxin).

The T wave represents ventricular muscle repolarization; it may be positive, negative, or biphasic in normal cats and dogs. Changes in T wave size, shape, or polarity from previous recordings in a particular animal are probably clinically important. Abnormalities of the T wave can be primary (i.e., not related to the depolarization process) or secondary (i.e., related to abnormalities of ventricular depolarization). Secondary ST-T changes tend to be in the opposite direction of the main QRS deflection. Box 2.6 lists some causes of ST-T abnormalities.

QT Interval

The QT interval represents the total time of ventricular activation and repolarization. This interval varies inversely with average heart rate; for example, faster rates are associated with a shorter QT interval. Autonomic nervous tone, various drugs, and electrolyte disorders influence the duration of the QT interval (see Box 2.6). Inappropriate prolongation of the QT interval can facilitate development of serious reentrant arrhythmias when underlying nonuniformity in ventricular repolarization exists. Prediction equations for expected QT duration have been published for normal dogs and cats.

ELECTROCARDIOGRAPHIC MANIFESTATIONS OF DRUG TOXICITY AND ELECTROLYTE IMBALANCE

Antiarrhythmic agents, digoxin, anesthetic, and other drugs often alter heart rhythm and/or conduction either by their direct electrophysiologic effects or by affecting autonomic tone (Box 2.7).

Potassium has marked and complex influences on cardiac electrophysiology. Hypokalemia can increase spontaneous automaticity of cardiac cells, as well as nonuniformly slow repolarization and conduction; these effects predispose to both supraventricular and ventricular arrhythmias. Hypokalemia can cause progressive ST segment depression, reduced T wave amplitude, and QT interval prolongation. Severe hypokalemia also can increase QRS and P wave amplitudes and durations. In addition, hypokalemia exacerbates digoxin toxicity and reduces the effectiveness of class I antiarrhythmic agents (see Chapter 4). Hypernatremia and alkalosis worsen the effects of hypokalemia on the heart.

Moderate hyperkalemia actually has an antiarrhythmic effect by reducing automaticity and enhancing uniformity and speed of repolarization. However, rapid or severe increases in serum potassium concentration are arrhythmogenic, primarily because they slow conduction velocity and shorten the refractory period. A number of ECG changes may occur as serum potassium (K^+) concentration rises; however, these may be observed only inconsistently in clinical cases, perhaps because of additional concurrent metabolic abnormalities. Observations from experimental studies indicate an early change, as serum rises to and above 6 mEq/L, is a peaked ("tented") T wave as the QT interval shortens. However, the characteristic symmetric "tented" T wave may be evident in only some leads and may be of small amplitude. In addition, progressive slowing of intraventricular conduction leads to widening of the QRS complexes. Experimentally, conduction through the atria slows as serum K^+ nears 7 mEq/L, and P waves flatten. P waves disappear as atrial conduction fails at about 8 mEq/L. The sinus node is relatively resistant to the effects of hyperkalemia and continues to function, although the sinus rate may slow. Despite progressive atrial muscle unresponsiveness, specialized

BOX 2.6

Causes of ST Segment, T Wave, and QT Abnormalities

Depression of J Point/ST Segment

Myocardial ischemia
Myocardial infarction/injury (LV subendocardial)
Hyperkalemia or hypokalemia
Cardiac trauma
Secondary change (ventricular hypertrophy, conduction disturbance, VPCs)
Digitalis ("sagging" appearance)
Pseudodepression (prominent T_a wave)

Elevation of J Point/ST Segment

Pericarditis
Left ventricular epicardial injury
Myocardial infarction (transmural)
Myocardial hypoxia
Secondary change (ventricular hypertrophy, conduction disturbance, VPCs)
Digoxin toxicity

Prolongation of QT Interval

Hypocalcemia
Hypokalemia
Secondary to prolonged QRS
Hypothermia
Central nervous system abnormalities
Ethylene glycol poisoning
Quinidine toxicity

Shortening of QT Interval

Hypercalcemia
Hyperkalemia
Digitalis toxicity

Large T Waves

Myocardial hypoxia
Ventricular enlargement
Intraventricular conduction abnormalities
Hyperkalemia
Metabolic or respiratory diseases
Normal variation

Tented T Waves

Hyperkalemia

VPC, Ventricular premature complex.

fibers transmit sinus impulses to the ventricles, producing a *sinoventricular* rhythm. Hyperkalemia should be a differential diagnosis for patients with a wide-QRS complex rhythm without P waves, even if the heart rate is not slow. At extremely high serum K^+ concentrations (>10 mEq/L), an irregular ectopic ventricular rhythm, fibrillation, or asystole develops. Fig. 2.36 illustrates the electrocardiographic effects of severe hyperkalemia and the response to therapy in a dog with Addison disease. Hypocalcemia, hyponatremia, and acidosis accentuate the electrocardiographic changes caused by hyperkalemia, whereas hypercalcemia and hypernatremia tend to counteract them.

Marked ECG changes caused by other electrolyte disturbances are uncommon. Severe hypercalcemia or hypocalcemia could have noticeable effects (see Box 2.6), but this rarely is seen clinically. Severe hypomagnesemia can predispose to ventricular tachyarrhythmias and could cause U waves to appear on the ECG; in addition, it can exaggerate the effects of hypocalcemia as well as predispose to digoxin toxicity.

Heart Rate Variability

Phasic fluctuations in vagal and sympathetic tone during the respiratory cycle, as well as during slower periodic oscillations of arterial blood pressure, influence the variation in time between consecutive heartbeats. *Heart rate variability* (HRV) refers to the fluctuation of beat-to-beat time intervals around their mean value. HRV is influenced by baroreceptor function, the respiratory cycle, and sympathetic/parasympathetic balance. The degree of HRV decreases with severe myocardial dysfunction and heart failure, as well as other causes of increased sympathetic tone. The variation in instantaneous heart rate (R-to-R intervals) can be evaluated as a function of time (time-domain analysis) and in terms of the frequency and amplitude of its summed oscillatory components (frequency-domain or power spectral analysis). Frequency-domain analysis allows assessment of the balance between sympathetic and vagal modulation of the cardiovascular system. HRV assessment can provide an indicator of autonomic function, and possibly prognosis, although its clinical potential in veterinary patients has not been fully explored.

COMMON ARTIFACTS

Fig. 2.37 illustrates some common ECG artifacts. Electrical (60 Hz) interference can be minimized or eliminated by properly grounding the ECG machine. Turning off other electrical equipment or lights on the same circuit or having a different person restrain the animal may also help. Other artifacts sometimes are confused with arrhythmias; however, artifacts do not disturb the underlying cardiac rhythm. Conversely, ectopic complexes often disrupt the underlying rhythm; they also are followed by a T wave. Careful examination for these characteristics usually allows differentiation between intermittent artifacts and arrhythmias. When multiple leads can be recorded simultaneously, it is helpful to compare the cardiac rhythm and complex configurations in all leads available.

BOX 2.7

Electrocardiographic Changes Associated With Electrolyte Imbalance and Selected Drug Adverse Effects/Toxicity

Hyperkalemia (See Fig. 2.36)

Peaked (tented) T waves (can be large or small)
Short QT interval
Flat or absent P waves
Widened QRS
ST segment depression

Hypokalemia

Prolonged QT interval
ST segment depression
Small, biphasic T waves
Tachyarrhythmias

Hypercalcemia

Few effects
Short QT interval
Prolonged conduction
Tachyarrhythmias

Hypocalcemia

Prolonged QT interval
Tachyarrhythmias

Digoxin

PR prolongation
Second-degree (2°) or third-degree (3°) AV block
Sinus bradycardia or arrest
Accelerated junctional rhythm
Ventricular premature complexes
Ventricular tachycardia
Paroxysmal atrial tachycardia with block
Atrial fibrillation with slow ventricular rate

Lidocaine

AV block
Ventricular tachycardia
Sinus arrest

β-Blockers

Sinus bradycardia
Prolonged PR interval
AV block

Quinidine/Procainamide

Atropine-like effects
Prolonged QT interval
AV block
Ventricular tachyarrhythmias
Widened QRS complex
Sinus arrest

Medetomidine/Xylazine

Sinus bradycardia
Sinus arrest/sinoatrial block
AV block
Ventricular tachyarrhythmias (especially with halothane, epinephrine)

Barbiturates/Thiobarbiturates

Ventricular bigeminy

Halothane/Methoxyflurane

Sinus bradycardia
Ventricular arrhythmias (increased sensitivity to catecholamines, especially halothane)

AV, Atrioventricular.

AMBULATORY ELECTROCARDIOGRAPHY

Holter Monitoring

Continuous recording of cardiac electrical activity during normal daily activities (except swimming), strenuous exercise, and sleep is provided by Holter monitoring. This can be useful for detecting and quantifying intermittent cardiac arrhythmias and therefore helps identify cardiac causes of syncope and episodic weakness, if these occur during the monitoring period. Holter monitoring also is used to assess efficacy of antiarrhythmic drug therapy and to screen for arrhythmias associated with cardiomyopathy or other diseases. The Holter monitor is a small battery-powered digital (or analog) recorder worn by the patient, typically for 24 hours. Two or three ECG channels are recorded from modified chest leads using adhesive patch electrodes. During the recording period, the animal's activities are noted in a patient diary for later correlation with simultaneous ECG events. An event button on the Holter recorder can be activated to mark the time a syncopal or other episode is witnessed.

The recording is analyzed using computer algorithms that classify the recorded complexes, ideally with oversight and editing by a trained Holter technician experienced with veterinary recordings. This is important because a fully automated computer analysis can result in misclassification of some QRS complexes and artifacts from dog and cat recordings. A summary of the entire recording period and selected segments of the ECG are included in the Holter report. Evaluation of a full disclosure display of the entire recording also is helpful for comparison with the technician-selected ECG strips and the times of clinical events and patient activities noted in the patient diary (see Suggested Readings for more information). A Holter monitor, hook-up supplies, and analysis can be obtained from some commercial human Holter scanning services, as well as many veterinary teaching hospitals and cardiology referral centers.

Wide variation in heart rate can occur throughout the day in normal animals. In dogs, maximum heart rates of up to

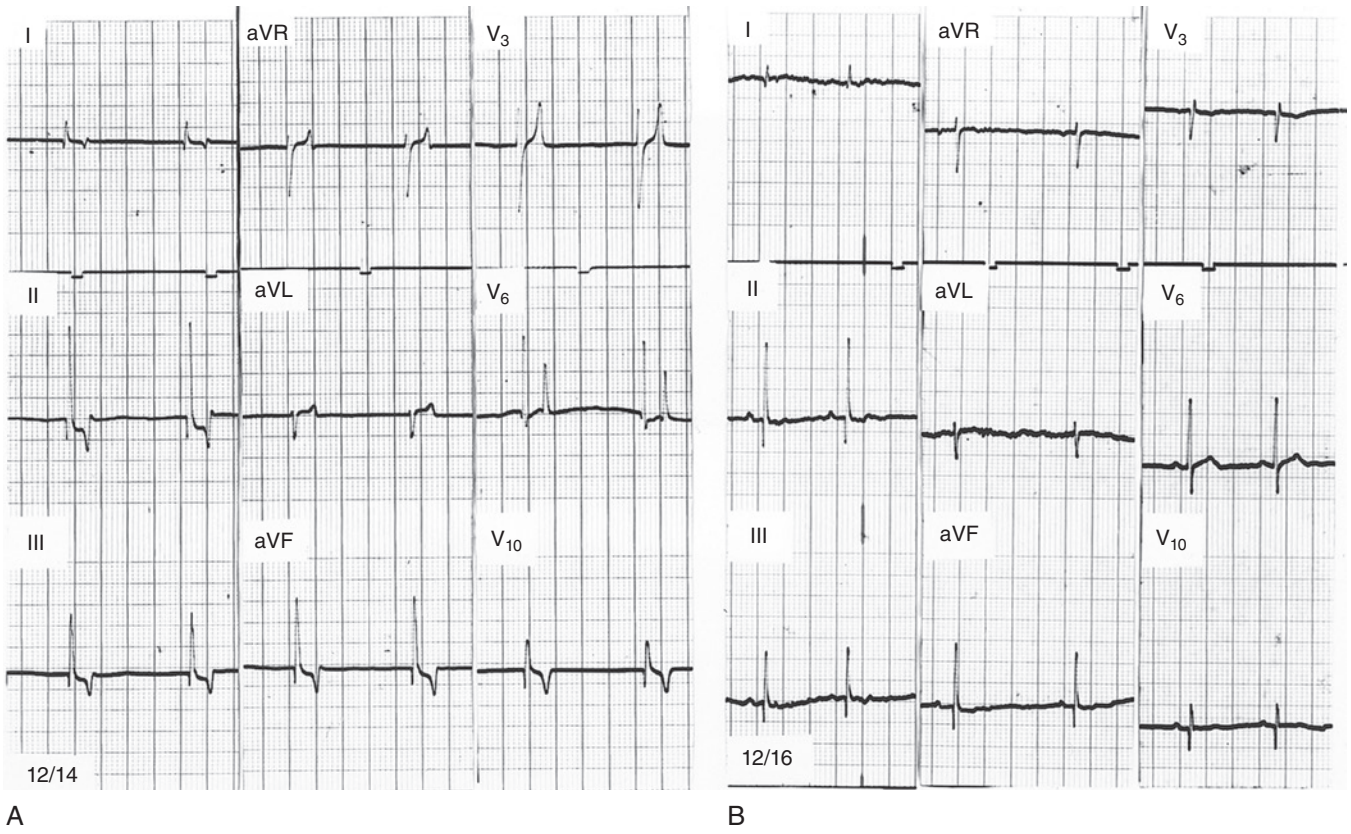


FIG 2.36
ECGs recorded in a female Poodle with hypoadrenocorticism at presentation **(A)** (K^+ = 10.2; Na^+ = 132 mEq/L), and 2 days later after treatment **(B)** (K^+ = 3.5; Na^+ = 144 mEq/L). Note absence of P waves, accentuated and tented T waves (especially in chest leads), shortened QT interval, and slightly widened QRS complexes in **A** compared with **B.** Leads as marked, 25 mm/sec, 1 cm = 1 mV.

300 beats/min have been recorded with excitement or activity. Episodes of bradycardia (<50 beats/min) are common, especially during quiet periods and sleep. Sinus arrhythmia, sinus pauses (sometimes for more than 5 seconds), and occasional 2° AV block appear to be common in dogs, especially at times when mean heart rate is lower. Heart rates in normal cats also vary widely over 24 hours, sometimes ranging from about 70 to 290 beats/min. Regular sinus rhythm predominates in normal cats, although sinus arrhythmia is evident at slower heart rates. Ventricular premature complexes occur only sporadically in normal dogs and cats; VPC prevalence appears to increase only slightly with age.

Intermittent Event Recording

Cardiac event recorders are small loop recorders. When activated, brief periods of a single modified chest lead ECG are stored within their microprocessor's memory. Event recorders are used most often to determine whether episodic weakness or syncope is caused by a cardiac arrhythmia. The event recorder typically is worn for periods of a week or longer. This is helpful in patients with intermittent weakness or collapse that may not recur often enough to be captured during a single 24-hour continuous ECG recording. However, because it cannot store prolonged, continuous ECG activity, the recorder must be manually activated when an episode is observed. The recorder then stores the ECG from a predetermined time frame (e.g., from 30-45 seconds before activation to 15-30 seconds after) for later retrieval and analysis.

Implantable (subcutaneous) ECG loop recorders also can be used in veterinary patients and allow intermittent ECG monitoring over a period of months. The ECG is recorded from two electrodes on the device's casing and held in a temporary memory buffer, similar to external event recorders, until manual or automatic activation triggers storage of a brief segment into more permanent memory. A compatible pacemaker programmer is used to set parameters for activation and recording, and to download the recorded ECG segments. Automatic activation is triggered by preset determinants for "bradycardia," "tachycardia," and "asystole."

Intermittent ECG acquisition using a handheld recording device (Kardia Mobile, AliveCor.com; Veterinary iPhone

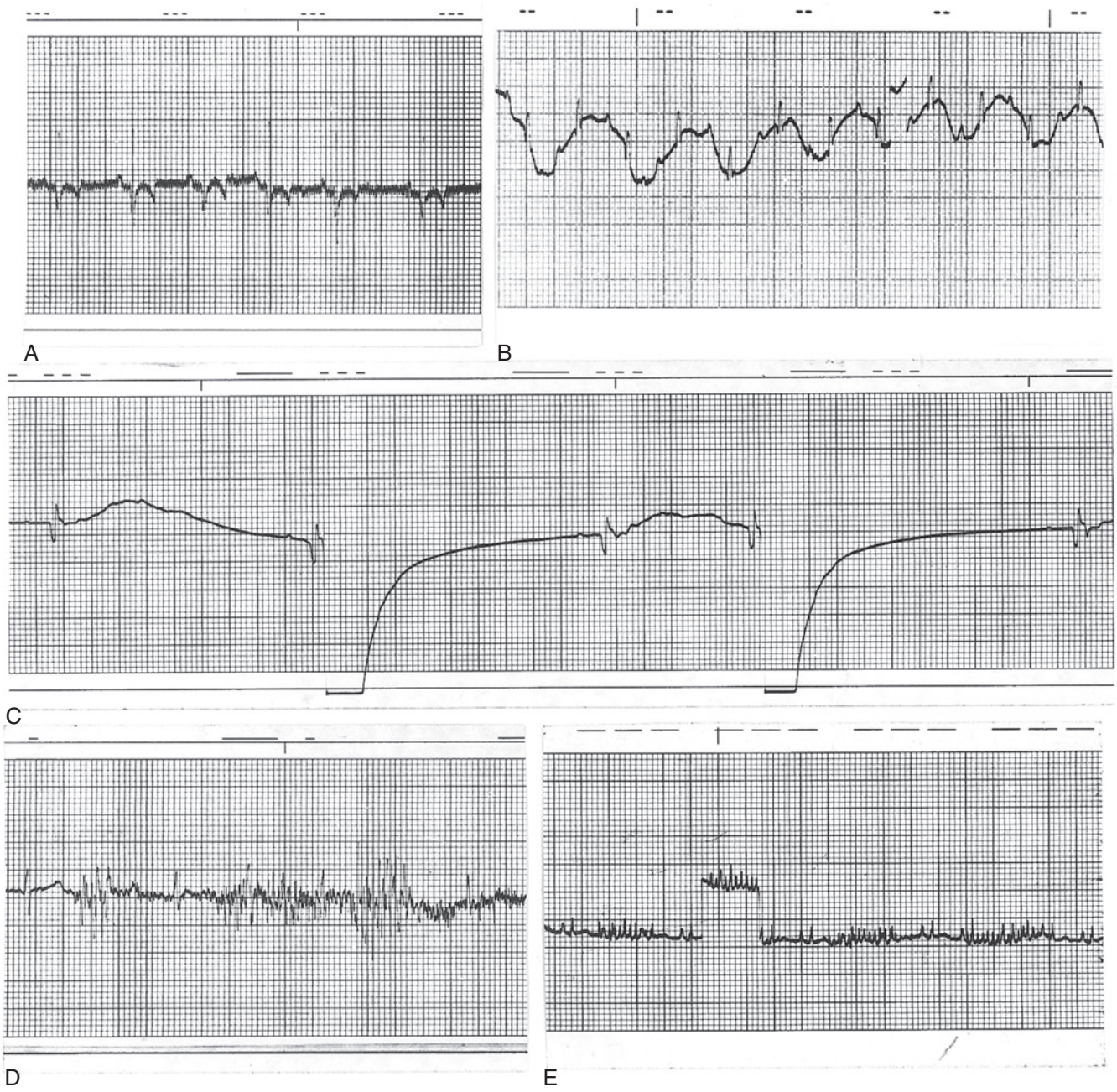


FIG 2.37
Common electrocardiogram artifacts. **(A)** 60 Hz electrical interference; lead III, 25 mm/sec, dog. **(B)** Baseline movement caused by panting; lead II, 25 mm/sec, dog. **(C)** Respiratory motion artifact; lead V_3, 50 mm/sec, dog. **(D)** Severe muscle tremor artifact; lead V_3, 50 mm/sec, cat. **(E)** Intermittent, rapid baseline spikes caused by purring in cat; a calibration mark is seen just left of the center of the strip. Lead aVF, 25 mm/sec.

ECG monitor, AliveCorVet.com) with smart phone interface is another means of assessing heart rate and rhythm that can be used anywhere. The patient is placed in right lateral recumbency, alcohol is applied to improve skin contact with electrodes on the back of the recorder, the device (with linked smart phone) is positioned on the chest wall over the heart, and the recording function is activated. After the ECG has been recorded, it is sent via email to the veterinarian for evaluation. This method can be useful for periodically assessing heart rhythm at home in cases with suspected arrhythmias and also for spot checks of heart rate control in animals with AF. Artifacts can hinder interpretation in some cases, especially in those patients that are not quiet and relaxed during recording.

OTHER TECHNIQUES

CENTRAL VENOUS PRESSURE MEASUREMENT

CVP is the fluid pressure within the RA and, by extension, the intrathoracic cranial vena cava. It is influenced by intravascular volume, venous compliance, and cardiac function. CVP measurement helps in differentiating high right heart-filling pressure (as from right heart failure or pericardial disease) from other causes of pleural or peritoneal effusion. However, it is important to note that pleural effusion itself can increase intrapleural pressure and raise CVP even in the absence of cardiac disease. Therefore CVP should be measured after thoracocentesis in patients with moderate- to large-volume pleural effusion. CVP sometimes is used to monitor critical patients receiving large intravenous fluid infusions. However, CVP is not an accurate reflection of left heart-filling pressure and thus is not a reliable way to monitor for cardiogenic pulmonary edema. The CVP in normal dogs and cats usually ranges from 0 to 8 (up to 10) cm H_2O. Fluctuations in CVP that parallel those of intrapleural pressure occur during respiration.

CVP is measured via a large-bore jugular catheter that extends into or close to the RA. The catheter is placed aseptically and connected by extension tubing and a three-way stopcock to a fluid administration set and container of crystalloid fluid. Free flow of fluid through this catheter system into the patient should be verified (stopcock side-port turned off). A water manometer is attached to the stopcock and positioned vertically with the stopcock (representing 0 cm H_2O) placed at the same horizontal level as the patient's RA. Usually the patient is placed in lateral or sternal recumbency for CVP measurement. The stopcock is turned off to the animal, allowing the manometer to fill with fluid; then the stopcock is turned off to the fluid reservoir so that the fluid column in the manometer equilibrates with the patient's CVP. Repeated measurements are more consistent when taken with the animal and manometer in the same position and during the expiratory phase of respiration. Small fluctuations in the manometer's fluid meniscus occur with the heartbeat, and slightly larger movement is associated with respiration. Marked change in the height of the fluid column associated with the heartbeat suggests either severe tricuspid insufficiency or that the catheter tip is within the RV.

ANGIOCARDIOGRAPHY

Nonselective angiocardiography can be used to define several acquired and congenital diseases, including cardiomyopathy and heartworm disease in cats, severe pulmonic or (sub) aortic stenosis, patent ductus arteriosus, and tetralogy of Fallot. Intracardiac septal defects and valvular regurgitation cannot reliably be identified. The quality of such studies is higher with a rapid injection of radiopaque contrast agent via a large-bore catheter and with smaller patient size. In most cases, echocardiography more safely provides similar or more information. However, evaluation of the pulmonary vasculature is better accomplished using nonselective angiocardiography.

Selective angiocardiography is performed by advancing cardiac catheters into specific areas of the heart or great vessels. Intracardiac and vascular pressure measurements, and blood sample acquisition for oxygen content assessment (oximetry), generally are done before making radiopaque contrast injections. Selective angiocardiography allows identification of abnormalities in anatomy and the path of blood flow. Doppler echocardiography often can provide comparable diagnostic information noninvasively. However, selective angiography is a necessary component of many cardiac interventional procedures.

CARDIAC CATHETERIZATION

Cardiac catheterization allows measurement of pressure, cardiac output, and blood oxygen concentrations from specific intracardiac locations. Specialized catheters are selectively placed into different areas of the heart and vasculature via the jugular vein, carotid artery, or femoral vessels. Congenital and acquired cardiac or vascular abnormalities can be identified with these procedures in combination with selective angiocardiography. The advantages of Doppler echocardiography often outweigh those of cardiac catheterization, especially in view of the good correlation between certain Doppler- and catheterization-derived measurements. However, cardiac catheterization is necessary for balloon valvuloplasty, ductal occlusion, and other interventional procedures.

Pulmonary capillary wedge pressure (PCWP) monitoring is done rarely to measure left heart-filling pressure in dogs with heart failure. A Swan-Ganz (end-hole, balloon-tipped) monitoring catheter is passed into the main pulmonary artery. When the balloon is inflated, the catheter tip becomes wedged in a smaller pulmonary artery, occluding flow in that vessel. The pressure measured at the catheter tip reflects pulmonary capillary pressure, which is essentially equivalent to LA pressure. This invasive technique allows differentiation of cardiogenic from noncardiogenic pulmonary edema and provides a means of monitoring cardiac output as well as the effectiveness of heart failure therapy. However, its use requires meticulous, aseptic catheter placement and continuous patient monitoring.

Endomyocardial Biopsy

Small samples of endocardium and adjacent myocardium can be obtained using a special bioptome passed into the RV via a jugular vein. Routine histopathology and other techniques to evaluate myocardial metabolic abnormalities can be performed on the samples. Endomyocardial biopsy sometimes is used for myocardial disease research but is rarely used in clinical veterinary practice.

Suggested Readings

Cardiac Biochemical Markers

Borgeat K, Connolly DJ, Luis Fuentes V. Cardiac biomarkers in cats. *J Vet Cardiol.* 2015;17:S74–S86.

Connolly DJ, et al. Assessment of the diagnostic accuracy of circulating cardiac troponin I concentration to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. *J Vet Cardiol*. 2009;11:71–78.

Ettinger SJ, et al. Evaluation of plasma N-terminal pro-B-type natriuretic peptide concentrations in dogs with and without cardiac disease. *J Am Vet Med Assoc*. 2012;240:171–180.

Falk T, et al. Cardiac troponin-I concentration, myocardial arteriosclerosis, and fibrosis in dogs with congestive heart failure because of myxomatous mitral valve disease. *J Vet Intern Med*. 2013;27:500–506.

Fox PR, et al. Multicenter evaluation of plasma N-terminal probrain natriuretic peptide (NT-pro BNP) as a biochemical screening test for asymptomatic (occult) cardiomyopathy in cats. *J Vet Intern Med*. 2011;25:1010–1016.

Langhorn RJ, Willesen JL. Cardiac troponins in dogs and cats. *J Vet Intern Med*. 2016;30:36–50.

Machen MC, et al. Multi-centered investigation of a point-of-care NT-proBNP ELISA assay to detect moderate to severe occult (pre-clinical) feline heart disease in cats referred for cardiac evaluation. *J Vet Cardiol*. 2014;16:245–255.

Oyama MA. Using cardiac biomarkers in veterinary practice. *Vet Clin Small Anim*. 2013;43:1261–1272.

Singh MK, et al. NT-proBNP measurement fails to reliably identify subclinical hypertrophic cardiomyopathy in Maine Coon cats. *J Feline Med Surg*. 2010;12:942–947.

Singletary GE, et al. Effect of NT-pro-BNP assay on accuracy and confidence of general practitioners in diagnosing heart failure or respiratory disease in cats with respiratory signs. *J Vet Intern Med*. 2012;26:542–546.

Singletary GE, et al. Prospective evaluation of NT-proBNP assay to detect occult dilated cardiomyopathy and predict survival in Doberman Pinschers. *J Vet Intern Med*. 2012;26:1330–1336.

Smith KF, Quinn RL, Rahilly LJ. Biomarkers for differentiation of causes of respiratory distress in dogs and cats: Part 1–Cardiac diseases and pulmonary hypertension. *J Vet Emerg Crit Care*. 2015;25:311–329.

Wells SM, Sleeper M. Cardiac troponins. *J Vet Emerg Crit Care*. 2008;18:235–245.

Wess G, et al. Utility of measuring plasma N-terminal pro-brain natriuretic peptide in detecting hypertrophic cardiomyopathy and differentiating grades of severity in cats. *Vet Clin Pathol*. 2011;40:237–244.

Radiography

Benigni L, Morgan N, Lamb CR. Radiographic appearance of cardiogenic pulmonary oedema in 23 cats. *J Small Anim Pract*. 2009;50:9–14.

Boddy KN, et al. Cardiac magnetic resonance in the differentiation of neoplastic and nonneoplastic pericardial effusion. *J Vet Intern Med*. 2011;25:1003–1009.

Buchanan JW, Bücheler J. Vertebral scale system to measure canine heart size in radiographs. *J Am Vet Med Assoc*. 1995;206:194–199.

Coulson A, Lewis ND. *An atlas of interpretive radiographic anatomy of the dog and cat*. Oxford: Blackwell Science; 2002.

De Rycke LM, et al. Computed tomography and cross-sectional anatomy of the thorax in clinically normal dogs. *Am J Vet Res*. 2005;66:512–524.

Diana A, et al. Radiographic features of cardiogenic pulmonary edema in dogs with mitral regurgitation: 61 cases (1998-2007). *J Am Vet Med Assoc*. 2009;235:1058–1063.

Drees R, et al. 64-multidetector computed tomographic angiography of the canine coronary arteries. *Vet Radiol Ultrasound*. 2011;52:507–515.

Ghadiri A, Avizeh R, Yadegari A. Radiographic measurement of vertebral heart size in healthy stray cats. *J Feline Med Surg*. 2008;10:61–65.

Gilbert SH, et al. The potential role of MRI in veterinary clinical cardiology. *Vet J*. 2010;183:124–134.

Guglielmini C, Diana A. Thoracic radiography in the cat: identification of cardiomegaly and congestive heart failure. *J Vet Cardiol*. 2015;17:S87–S101.

Lamb CR, et al. Use of breed-specific ranges for the vertebral heart scale as an aid to the radiographic diagnosis of cardiac disease in dogs. *Vet Rec*. 2001;148:707–711.

Lehmkuhl LB, et al. Radiographic evaluation of caudal vena cava size in dogs. *Vet Radiol Ultrasound*. 1997;38:94–100.

Litster AL, Buchanan JW. Vertebral scale system to measure heart size in radiographs of cats. *J Am Vet Med Assoc*. 2000;216:210–214.

Mai W, Weisse C, Sleeper MM. Cardiac magnetic resonance imaging in normal dogs and two dogs with heart base tumor. *Vet Radiol Ultrasound*. 2010;51:428–435.

Marin LM, et al. Vertebral heart size in retired racing Greyhounds. *Vet Radiol Ultrasound*. 2007;48:332–334.

Oui H, et al. Measurements of the pulmonary vasculature on thoracic radiographs in healthy dogs compared to dogs with mitral regurgitation. *Vet Radiol Ultrasound*. 2014;56:251–256.

Oura TJ, et al. A valentine-shaped cardiac silhouette in feline thoracic radiographs is primarily due to left atrial enlargement. *Vet Radiol Ultrasound*. 2015;56:245–250.

Sanchez X, et al. A new method of computing the vertebral heart scale by means of direct standardisation. *J Small Anim Pract*. 2012;53:641–645.

Schober KE, Wetli E, Drost WT. Radiographic and echocardiographic assessment of left atrial size in 100 cats with acute left-sided congestive heart failure. *Vet Radiol Ultrasound*. 2014;55:359–367.

Sleeper MM, Buchanan JW. Vertebral scale system to measure heart size in growing puppies. *J Am Vet Med Assoc*. 2001;219:57–59.

Sleeper MM, Roland R, Drobatz KJ. Use of the vertebral heart scale for differentiation of cardiac and noncardiac causes of respiratory distress in cats: 67 cases (2002-2003). *J Am Vet Med Assoc*. 2013;242:366–371.

Echocardiography

Bonagura JD, Luis-Fuentes V. Echocardiography. In: Mattoon JS, Nyland TG, eds. *Small animal diagnostic ultrasound*. 3rd ed. St. Louis: Elsevier-Saunders; 2015:217–331.

Campbell FE, Kittleson MD. The effect of hydration status on the echocardiographic measurements of normal cats. *J Vet Intern Med*. 2007;21:1008–1015.

Chetboul V. Advanced techniques in echocardiography in small animals. *Vet Clin North Am Small Anim Pract*. 2010;40:529–543.

Cornell CC, et al. Allometric scaling of M-mode cardiac measurements in normal adult dogs. *J Vet Intern Med*. 2004;18:311–321.

Culwell NM, et al. Comparison of echocardiographic indices of myocardial strain with invasive measurements of left ventricular systolic function in anesthetized healthy dogs. *Am J Vet Res*. 2011;72:650–660.

Goncalves AC, et al. Linear, logarithmic, and polynomial models of M-mode echocardiographic measurements in dogs. *Am J Vet Res*. 2002;63:994–999.

Linney CJ, et al. Left atrial size, atrial function and left ventricular diastolic function in cats with hypertrophic cardiomyopathy. *J Small Anim Pract*. 2014;55:198–206.

Lisciandro GR, et al. Frequency and number of ultrasound lung rockets (B-lines) using a regionally based lung ultrasound examination named vet BLUE (veterinary bedside lung ultrasound exam) in dogs with radiographically normal lung findings. *Vet Radiol Ultrasound*. 2014;55:315–322.

Ljungvall I, et al. Assessment of global and regional left ventricular volume and shape by real-time 3-dimensional echocardiography in dogs with myxomatous mitral valve disease. *J Vet Intern Med*. 2011;25:1036–1043.

Loyer C, Thomas WP. Biplane transesophageal echocardiography in the dog: technique, anatomy and imaging planes. *Vet Radiol Ultrasound*. 1995;36:212–226.

Rademacher N, et al. Transthoracic lung ultrasound in normal dogs and dogs with cardiogenic pulmonary edema: a pilot study. *Vet Radiol Ultrasound*. 2014;55:447–452.

Rishniw M, Erb HN. Evaluation of four 2-dimensional echocardiographic methods of assessing left atrial size in dogs. *J Vet Intern Med*. 2000;14:429–435.

Schober KE, Maerz I. Assessment of left atrial appendage flow velocity and its relation to spontaneous echocardiographic contrast in 89 cats with myocardial disease. *J Vet Intern Med*. 2006;20:120–130.

Schober KE, et al. Detection of congestive heart failure in dogs by Doppler echocardiography. *J Vet Intern Med*. 2010;24:1358–1368.

Serrano-Parreno B, et al. Evaluation of pulmonary hypertension and clinical status in dogs with heartworm by right pulmonary artery distensibility index and other echocardiographic parameters. *Parasit Vectors*. 2017;10:106.

Silva AC, et al. Longitudinal strain and strain rate by two-dimensional speckle tracking in non-sedated healthy cats. *Res Vet Sci*. 2013;95:1175–1180.

Simak J, et al. Color-coded longitudinal interventricular septal tissue velocity imaging, strain and strain rate in healthy Doberman Pinschers. *J Vet Cardiol*. 2011;13:1–11.

Smith DN, et al. Left ventricular function quantified by myocardial strain imaging in small-breed dogs with chronic mitral regurgitation. *J Vet Cardiol*. 2012;14:231–242.

Thomas WP, et al. Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. *J Vet Intern Med*. 1993;7:247–252.

Tidholm A, et al. Comparisons of 2- and 3-dimensional echocardiographic methods for estimation of left atrial size in dogs with and without myxomatous mitral valve disease. *J Vet Intern Med*. 2011;24:1320–1327.

Tidholm A, et al. Diagnostic value of selected echocardiographic variables to identify pulmonary hypertension in dogs with myxomatous mitral valve disease. *J Vet Intern Med*. 2015;29:1510–1517.

Tse YC, et al. Evaluation of a training course in focused echocardiography for noncardiology house officers. *J Vet Emerg Crit Care*. 2013;23:268–273.

Visser LC, et al. Diagnostic value of right pulmonary artery distensibility index in dogs with pulmonary hypertension: Comparison with Doppler echocardiographic estimates of pulmonary arterial pressure. *J Vet Intern Med*. 2016;30:543–552.

Volpicelli G, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med*. 2012;38:577–591.

Ward JL, et al. Accuracy of point-of-care lung ultrasonography for the diagnosis of cardiogenic pulmonary edema in dogs and cats with acute dyspnea. *J Am Vet Med Assoc*. 2017;250:666–675.

Wess G, Killich M, Hartmann K. Comparison of pulsed wave and color Doppler myocardial velocity imaging in healthy dogs. *J Vet Intern Med*. 2010;24:360–366.

Wess G, Sarkar R, Hartmann K. Assessment of left ventricular systolic function by strain imaging echocardiography in various stages of feline hypertrophic cardiomyopathy. *J Vet Intern Med*. 2010;24:1375–1382.

Electrocardiography

Bright JM, Cali JV. Clinical usefulness of cardiac event recording in dogs and cats examined because of syncope, episodic collapse, or intermittent weakness: 60 cases (1997-1999). *J Am Vet Med Assoc*. 2000;216:1110–1114.

Crosara S, et al. Holter monitoring in 36 dogs with myxomatous mitral valve disease. *Aust Vet J*. 2010;88:386–392.

Gelzer AR, Kraus MS, Rishniw M. Evaluation of in-hospital electrocardiography versus 24-hour Holter for rate control in dogs with atrial fibrillation. *J Small Anim Pract*. 2015;56:456–462.

MacKie BA, Stepien RL, Kellihan HB. Retrospective analysis of an implantable loop recorder for evaluation of syncope, collapse, or intermittent weakness in 23 dogs (2004-2008). *J Vet Cardiol*. 2010;12:25–33.

Motskula PF, et al. Prognostic value of 24-hour ambulatory ECG (Holter) monitoring in Boxer dogs. *J Vet Intern Med*. 2013;27:904–912.

Norman BC, Cote E, Barrett KA. Wide-complex tachycardia associated with severe hyperkalemia in three cats. *J Feline Med Surg*. 2006;8:372–378.

Perego M, Ramera L, Santilli RA. Isorhythmic atrioventricular dissociation in Labrador Retrievers. *J Vet Intern Med*. 2012;26:320–325.

Rishniw M, et al. Effect of body position on the 6-lead ECG of dogs. *J Vet Intern Med*. 2002;16:69–73.

Santilli RA, et al. Utility of 12-lead electrocardiogram for differentiating paroxysmal supraventricular tachycardias in dogs. *J Vet Intern Med*. 2008;22:915–923.

Santilli RA, et al. Evaluation of the diagnostic value of an implantable loop recorder in dogs with unexplained syncope. *J Am Vet Med Assoc*. 2010;236:78–82.

Santilli RA, et al. Orthodromic atrioventricular reciprocating tachycardia conducted with intraventricular conduction disturbance mimicking ventricular tachycardia in an English Bulldog. *J Vet Cardiol*. 2012;14:363–370.

Stern JA, Hinchcliff KW, Constable PD. Effect of body position on electrocardiographic recordings in dogs. *Aust Vet J*. 2013;91:281–286.

Stern JA, et al. Ambulatory electrocardiographic evaluation of clinically normal adult Boxers. *J Am Vet Med Assoc*. 2010;236:430–433.

Tag TL, Day TK. Electrocardiographic assessment of hyperkalemia in dogs and cats. *J Vet Emerg Crit Care*. 2008;18:61–67.

Ware WA, et al. Sudden death associated with QT interval prolongation and KCNQ1 gene mutation in a family of English springer spaniels. *J Vet Intern Med*. 2015;29:561–568.

Wess G, et al. Ability of a 5-minute electrocardiography (ECG) for predicting arrhythmias in Doberman Pinschers with cardiomyopathy in comparison with a 24-hour ambulatory ECG. *J Vet Intern Med*. 2010;24:367–371.

CHAPTER 3

Management of Heart Failure



OVERVIEW OF HEART FAILURE

Heart failure entails abnormalities of cardiac systolic or diastolic function, or both. These can occur without evidence of abnormal fluid accumulation (congestion), especially in the initial stages of disease. *Congestive heart failure* (CHF) is characterized by high cardiac filling pressure, which leads to venous congestion and tissue fluid accumulation. It is considered a clinical syndrome rather than a specific etiologic diagnosis. The pathophysiology of heart failure is complex. It involves structural and functional changes within the heart and vasculature, as well as other organs. The process of progressive cardiac remodeling inherent to heart failure can develop secondary to cardiac injury or stress from valvular disease, genetic mutations, acute inflammation, ischemia, increased systolic pressure load, and other causes.

CARDIAC RESPONSES

Cardiac remodeling refers to the changes in myocardial size, shape, and stiffness that occur in response to various mechanical, biochemical, and molecular signals induced by the underlying injury or stress. These changes include myocardial cell hypertrophy, cardiac cell drop-out or self-destruction (apoptosis), excessive interstitial matrix formation, fibrosis, and destruction of normal collagen binding between individual myocytes. The latter, resulting from effects of myocardial collagenases or matrix metalloproteinases, can lead to cardiac chamber dilation or distortion from myocyte slippage. Stimuli for remodeling include mechanical forces (for example, increased wall stress from volume or pressure overload) and the effects of various neurohormones (such as angiotensin II, norepinephrine, endothelin, and aldosterone) and proinflammatory cytokines (including tumor necrosis factor [TNF]-α), as well as other cytokines (such as osteopontin and cardiotrophin-1). Contributing biochemical abnormalities, related to cellular energy production, calcium fluxes, protein synthesis, and catecholamine metabolism, have been variably identified in different models of heart failure and in clinical patients. Myocyte hypertrophy and reactive fibrosis increase total cardiac mass by eccentric and, in some cases, concentric patterns of hypertrophy. Ventricular hypertrophy can increase chamber stiffness, impair relaxation, and increase filling pressures. These abnormalities of diastolic function also can have a negative effect on systolic function. Ventricular remodeling also can promote the development of arrhythmias. The initiating stimulus underlying chronic cardiac remodeling might occur years before clinical evidence of heart failure appears.

Acute increases in ventricular filling (preload) induce greater contraction force and blood ejection. This response, known as the *Frank-Starling mechanism,* allows beat-to-beat adjustments that balance the output of the two ventricles and increase overall cardiac output in response to acute increases in hemodynamic load. In the short term, the Frank-Starling effect helps normalize cardiac output under conditions of increased volume or pressure loading, but these conditions also increase ventricular wall stress and oxygen consumption.

Ventricular wall stress is directly related to ventricular pressure and internal dimensions, and inversely related to wall thickness (Laplace's law). Increased wall stress induces myocardial hypertrophy. The hypertrophy pattern that develops depends on underlying disease conditions. A ventricular systolic pressure load induces *concentric* hypertrophy; myocardial fibers and ventricular walls thicken as contractile units (sarcomeres) are added in parallel. With severe hypertrophy, capillary density and myocardial perfusion may become inadequate, especially in subendocardial areas. Chronic myocardial hypoxia and ischemia stimulate further fibrosis and dysfunction. Chronic volume loading increases diastolic wall stress and leads to *eccentric* hypertrophy; myocardial fiber elongation and chamber dilation occur as new sarcomeres are laid down in series. Reductions in the extracellular collagen matrix and intercellular support structure have been documented in dogs with chronic volume overload from mitral insufficiency. Compensatory hypertrophy lessens the importance of the Frank-Starling mechanism in stable, chronic heart failure. Although volume loads are better tolerated because myocardial oxygen demand is not as severe, both abnormal pressure and volume loading impair cardiac performance over time.

Eventually, decompensation and myocardial failure develop. In patients with primary myocardial diseases, initial cardiac pressure and volume loads are normal; however, intrinsic defects of the heart muscle lead to observed hypertrophy or secondary dilation.

Cardiac hypertrophy and other remodeling changes begin long before heart failure becomes manifest. Biochemical abnormalities involving cell energy production, calcium fluxes, and contractile protein function can contribute to this process. Eventually, ventricular function progressively deteriorates as contractility and relaxation become more deranged. Clinical heart failure can be considered a state of decompensated hypertrophy.

SYSTEMIC RESPONSES

Neurohormonal Mechanisms

Neurohormonal (NH) responses contribute to cardiac remodeling and also have more far-reaching effects. Over time, excessive activation of NH "compensatory" mechanisms leads to the clinical syndrome of CHF. Although these mechanisms support circulation in the face of acute hypotension and hypovolemia, their chronic activation accelerates the deterioration of cardiac function. Major NH changes in heart failure include increased sympathetic nervous tone, attenuated vagal tone, renin-angiotensin-aldosterone system activation, and increased release of vasopressin (antidiuretic hormone, ADH-) and endothelin. These NH systems work independently and also interact together to increase vascular volume (by enhancing sodium and water retention and thirst) as well as vascular tone (Fig. 3.1). The expanded vascular volume increases ventricular filling (preload), which then enhances cardiac output. However, this comes at the cost of increased venous and capillary pressure, which promotes interstitial fluid accumulation. Although increased lymphatic flow helps moderate the effects of rising venous pressure, continued volume retention eventually leads to edema and effusions. Prolonged systemic vasoconstriction increases the workload on the heart, can reduce forward cardiac output, and may exacerbate valvular regurgitation. The extent to which these mechanisms are activated varies with the severity and etiology of heart failure. In general, as failure worsens, NH activation increases. Increased production of endothelins and proinflammatory cytokines, as well as altered expression of vasodilatory and natriuretic factors, also contributes to the complex interplay among these NH mechanisms and their consequences.

The effects of sympathetic stimulation (such as increased contractility, heart rate, and venous return) can initially increase cardiac output. However, over time, these effects become detrimental by increasing afterload stress and myocardial oxygen requirements, contributing to cellular damage and myocardial fibrosis, and enhancing the potential for cardiac arrhythmias. Persistent sympathetic stimulation reduces cardiac sensitivity to catecholamines. Downregulation (reduced number) of myocardial β_1-receptors and other changes in cellular signaling can help protect the myocardium against the cardiotoxic and arrhythmogenic effects of catecholamines. β-blocking agents can reverse β_1-receptor downregulation but may worsen heart failure. Cardiac β_2- and α_1-receptors also are present but are not downregulated; these are thought to contribute to myocardial remodeling and arrhythmogenesis. Another cardiac receptor subtype (β_3-receptors) may promote further myocardial function deterioration through a negative inotropic effect.

Normal feedback regulation of sympathetic nervous and hormonal systems depends on arterial and atrial baroreceptor function. Baroreceptor responsiveness becomes attenuated in chronic heart failure, which contributes to sustained sympathetic and hormonal activation and reduced inhibitory vagal effects. Baroreceptor function can improve with reversal of heart failure, increased myocardial contractility, decreased cardiac loading conditions, or inhibition of angiotensin II and aldosterone (which directly attenuate baroreceptor sensitivity). Digoxin has a positive effect on baroreceptor sensitivity.

The renin-angiotensin system (RAAS) has far-reaching effects. Whether systemic renin-angiotensin-aldosterone activation always occurs before overt congestive failure is unclear and may depend on the underlying etiology. Renin release from the renal juxtaglomerular apparatus occurs secondary to low renal artery perfusion pressure, renal β-adrenergic receptor stimulation, and reduced Na^+ delivery to the macula densa of the distal renal tubule. Stringent dietary salt restriction and diuretic or vasodilator therapy can promote renin release. Renin facilitates conversion of the precursor peptide angiotensinogen to angiotensin I (an inactive form). Angiotensin-converting enzyme (ACE), found in the lung and elsewhere, converts angiotensin I to the active angiotensin II and is involved in the degradation of certain vasodilator kinins. There are also alternative pathways for angiotensin II generation.

Angiotensin II has several important effects, including potent vasoconstriction and stimulation of aldosterone release from the adrenal cortex. Additional effects of angiotensin II include increased thirst and salt appetite, facilitation of neuronal norepinephrine synthesis and release, blockade of neuronal norepinephrine reuptake, stimulation of vasopressin (ADH) release, and increased adrenal epinephrine secretion. Inhibition of ACE can reduce NH activation and promote vasodilation and diuresis. Local production of angiotensin II also occurs in the heart, vasculature, adrenal glands, and other tissues in dogs and cats. Local activity affects cardiovascular structure and function by enhancing sympathetic effects and promoting tissue remodeling that can include hypertrophy, inflammation, and fibrosis. Tissue chymase is thought to be more important in the conversion to active angiotensin II than ACE in the myocardium and extracellular matrix.

Aldosterone promotes sodium and chloride reabsorption, as well as potassium and hydrogen ion secretion in the renal collecting tubules; the concurrent water reabsorption augments vascular volume. Increased aldosterone concentration can promote hypokalemia, hypomagnesemia, and impaired baroreceptor function. It can potentiate the effects of

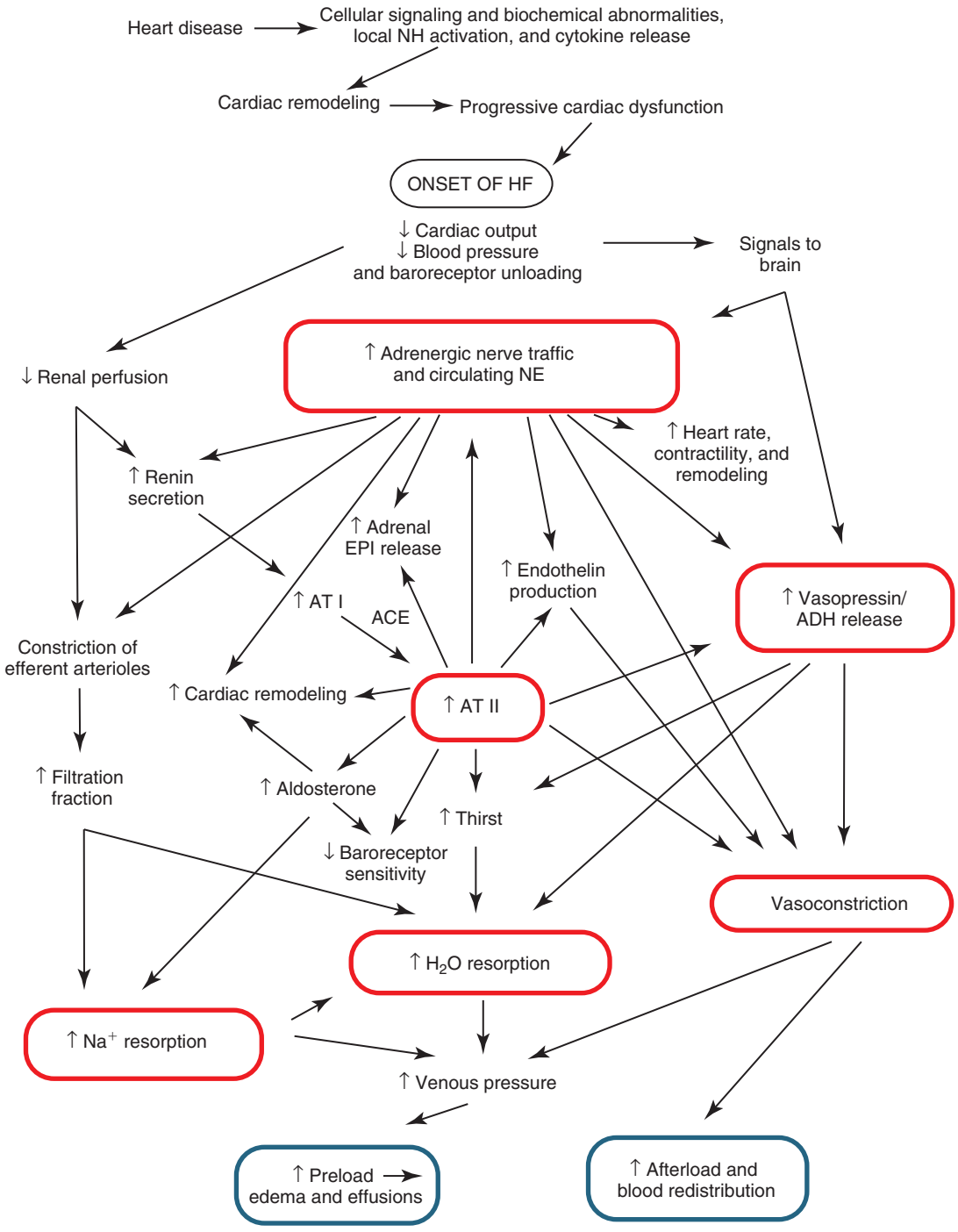


FIG 3.1
Important neurohormonal mechanisms leading to volume retention and increased afterload in congestive heart failure (CHF). *Note:* Additional mechanisms and interactions also contribute. Endogenous vasodilatory and natriuretic mechanisms also become activated during the evolution of CHF. *ACE,* Angiotensin-converting enzyme; *ADH,* antidiuretic hormone (vasopressin); *AT,* angiotensin; *EPI,* epinephrine; *HF,* heart failure; *NE,* norepinephrine.

catecholamines by blocking NE reuptake. Aldosterone receptors also are found in the heart and vasculature; aldosterone produced locally in the cardiovascular system mediates inflammation and fibrosis. Chronic exposure contributes to pathologic remodeling and myocardial fibrosis.

Arginine vasopressin (ADH) is released from the posterior pituitary gland. This hormone directly causes vasoconstriction and promotes free water reabsorption in the distal nephrons. Although increased plasma osmolality or reduced blood volume are the normal stimuli for ADH release,

reduced effective circulating volume and other nonosmotic stimuli (including sympathetic stimulation and angiotensin II) cause continued release of ADH in patients with heart failure. The continued release of ADH contributes to the dilutional hyponatremia sometimes found in patients with heart failure.

Increased circulating concentrations of other substances with a role in abnormal cardiovascular hypertrophy and/or fibrosis, including cytokines (e.g., TNF_{α}) and endothelins, also have been detected in animals with severe heart failure. Endothelin is a potent vasoconstrictor whose precursor peptide is produced by vascular endothelium. Endothelin production is stimulated by hypoxia and vascular mechanical factors and also by angiotensin II, ADH, norepinephrine, cytokines (including TNF_{α} and interleukin-I), and other factors.

Endogenous mechanisms that oppose the vasoconstrictor responses also are activated. These include natriuretic peptides, adrenomedullin, nitric oxide (NO), and vasodilator prostaglandins. Normally, a balance between vasodilator and vasoconstrictor effects maintains circulatory homeostasis, as well as renal solute excretion. As heart failure progresses, the influence of the vasoconstrictor mechanisms predominates despite increased activation of vasodilator mechanisms.

Natriuretic peptides are synthesized in the heart and play an important role in regulating blood volume and pressure. Atrial natriuretic peptide (ANP) is synthesized by atrial myocytes as a prohormone, which is then cleaved to the active peptide after its release. Mechanical stretch of the atrial wall stimulates ANP release. Brain natriuretic peptide (BNP) also is synthesized in the heart, mainly by the ventricles in response to myocardial dysfunction or ischemia. Natriuretic peptides promote diuresis, natriuresis, and peripheral vasodilation. They act to antagonize the effects of the RAAS, and also can alter vascular permeability and inhibit growth of smooth muscle cells. Natriuretic peptides are degraded by neutral endopeptidases. Circulating concentrations of ANP, BNP, and their precursor peptides (such as NT-proBNP) increase in patients with heart failure. This increase has been correlated with pulmonary capillary wedge pressure and severity of heart failure in both dogs and people. Adrenomedullin is another natriuretic and vasodilatory peptide produced in the adrenal medulla, heart, lung, and other tissues thought to play a role in heart failure.

NO, produced by the vascular endothelium in response to endothelial-nitric oxide synthetase (NOS), is a functional antagonist of endothelin and angiotensin II. This response is impaired in patients with heart failure. At the same time, myocardial inducible–NOS expression is enhanced; myocardial NO release has negative effects on myocyte function. Intrarenal vasodilator prostaglandins oppose the action of angiotensin II on the renal vasculature. The use of prostaglandin synthesis inhibitors in dogs or cats with severe heart failure could potentially reduce glomerular filtration (by increasing afferent arteriolar resistance) and enhance sodium retention.

Renal Effects

Renal efferent glomerular arteriolar constriction, mediated by sympathetic stimulation and angiotensin II, helps maintain glomerular filtration in the face of reduced cardiac output and renal blood flow. Higher oncotic and lower hydrostatic pressures develop in the peritubular capillaries, enhancing the reabsorption of tubular fluid and sodium. Angiotensin II–mediated aldosterone release further promotes sodium and water retention. Continued activation of these mechanisms leads to clinical edema and effusions.

Afferent arteriolar vasodilation mediated by endogenous prostaglandins and natriuretic peptides can partially offset the effects of efferent vasoconstriction, but progressive impairment of renal blood flow leads to renal insufficiency. Diuretics not only can magnify azotemia and electrolyte loss but also further reduce cardiac output and activate NH mechanisms.

Other Effects of Heart Failure

Reduced exercise capacity occurs in patients with heart failure. Although cardiac output may be fairly normal at rest, the ability to increase cardiac output in response to exercise is impaired. Inadequate forward output, poor diastolic filling, and pulmonary edema or pleural effusion can interfere with exercise ability. Furthermore, impaired peripheral vasodilation during exercise contributes to inadequate skeletal muscle perfusion and fatigue. Excessive peripheral sympathetic tone, angiotensin II (both circulating and locally produced), and vasopressin can contribute to impaired skeletal muscle vasodilatory capacity in patients with CHF. Increased vascular wall sodium content and interstitial fluid pressure stiffen and compress vessels. Other mechanisms can include impaired endothelium-dependent relaxation, increased endothelin concentration, and vascular wall changes induced by the growth factor effects of various NH vasoconstrictors. ACE inhibitor (ACEI) therapy, with or without spironolactone, may improve endothelial vasomotor function and exercise capacity. Pulmonary endothelial function is improved by ACEIs in dogs with CHF.

GENERAL CAUSES OF HEART FAILURE

The causes of heart failure are quite diverse. It can be useful to think of them in terms of underlying pathophysiology. In most cases of heart failure, the major initiating abnormality entails myocardial (systolic pump) failure, systolic pressure overload, volume overload, or reduced ventricular compliance (impaired filling). Nevertheless, several pathophysiologic abnormalities often coexist. Both systolic and diastolic function abnormalities are common in patients with advanced failure.

Myocardial failure is characterized by poor ventricular contractile function. It most commonly occurs from idiopathic dilated cardiomyopathy (DCM) but also from known causes of impaired myocardial contractility. Valvular insufficiency may or may not be present initially but usually develops as the affected ventricle dilates. Persistent tachyarrhythmias, some nutritional deficiencies, and other cardiac

insults also can lead to myocardial failure (see Chapters 7 and 8). Diseases that impose a volume or flow overload on the heart usually involve a primary "plumbing" problem (e.g., a leaky valve or abnormal systemic-to-pulmonary connection). Cardiac pump function often is maintained at a near-normal level for a prolonged time, although myocardial contractility does eventually deteriorate (see Chapters 5 and 6). Pressure overload results when the ventricle must generate higher-than-normal systolic pressure to eject blood. The concentric hypertrophy that develops as a compensatory mechanism increases ventricular wall thickness and stiffness, and can predispose to myocardial ischemia. Excessive pressure loads also eventually lead to declining myocardial contractility. Myocardial pressure overload is caused by ventricular outflow obstructions (congenital or acquired) and systemic or pulmonary hypertension (see Chapters 5, 10, and 11). Diseases that restrict ventricular filling impair diastolic function. These include hypertrophic and restrictive cardiomyopathies and pericardial diseases (see Chapters 8 and 9). Contractile ability usually is well maintained initially; however, elevated ventricular filling pressure leads to congestion behind the affected ventricle(s) and may diminish cardiac output. Other, less common causes of impaired filling include intracardiac mass lesions, congenital atrioventricular (AV) valve stenosis, and cor triatriatum. Table 3.1 lists common diseases according to their major initiating pathophysiology and typical clinical CHF manifestations.

TABLE 3.1

Common Causes of Congestive Heart Failure (CHF)

MAJOR PATHOPHYSIOLOGY	TYPICAL CHF MANIFESTATION*
Myocardial Failure	
Idiopathic dilated cardiomyopathy	Either L- or R-CHF
Infective myocarditis	Either L- or R-CHF
Drug toxicities (e.g., doxorubicin)	L-CHF
Myocardial ischemia/infarction (rare)	L-CHF
Volume-Flow Overload	
Mitral valve regurgitation (degenerative, congenital, infective)	L-CHF
Aortic regurgitation (infective endocarditis, congenital)	L-CHF
Ventricular septal defect	L-CHF
Patent ductus arteriosus	L-CHF
Tricuspid valve regurgitation (degenerative, congenital, infective)	R-CHF
Tricuspid endocarditis (rare)	R-CHF
Chronic anemia	Either L- or R-CHF
Thyrotoxicosis	Either L- or R-CHF
Pressure Overload	
(Sub)aortic stenosis	L-CHF
Systemic hypertension	L-CHF (rare)
Pulmonic stenosis	R-CHF
Heartworm disease	R-CHF
Pulmonary hypertension	R-CHF
Impaired Ventricular Filling	
Hypertrophic cardiomyopathy	L-(±R-) CHF
Restrictive cardiomyopathy	L-(±R-) CHF
Cardiac tamponade	R-CHF
Constrictive pericardial disease	R-CHF

**L-CHF*, Left-sided congestive heart failure signs (pulmonary edema as main congestive sign); *R-CHF*, right-sided congestive heart failure signs (pleural effusion and/or ascites as main congestive signs). Weakness and other low-output signs can occur with any of these diseases, especially those associated with arrhythmias.

APPROACH TO TREATING HEART FAILURE

Current perspectives on CHF management are based not only on mitigating the results of excessive NH activation (especially sodium and water retention) but also on modifying or blocking the activation process itself, with the aim of minimizing the progression of myocardial remodeling and dysfunction. Diuretics, dietary salt restriction, and some vasodilators help control signs of congestion. ACEIs, aldosterone, and sympathetic antagonists help modulate NH responses. Treatment strategies center on controlling edema and effusions, improving cardiac output, reducing cardiac workload, supporting myocardial function, and managing concurrent arrhythmias. The approach to these goals varies somewhat with different diseases, most notably those causing restriction to ventricular filling.

Classification of Severity

Guidelines for clinical staging of heart failure (based on the American Heart Association and American College of Cardiology [AHA/ACC] system) also are applied to veterinary patients (Table 3.2). These describe disease progression through four stages over time. This system emphasizes the importance of patient screening and early diagnosis. It is recommended as a guide in coordinating appropriate (and ideally, evidence-based) treatment to the severity of the clinical signs at each stage of disease. It also deemphasizes the term "congestive" in CHF because clinical signs of edema or effusions are not necessarily present all the time during the later stages (i.e., when CHF is "compensated" through appropriate medical therapy). Nevertheless, attention to the patient's fluid status is highly important.

The clinical severity of heart failure also is sometimes described according to the modified New York Heart Association (NYHA) classification scheme or the International

TABLE 3.2

Classification Systems for Heart Failure Severity

CLASSIFICATION	DEGREE OF SEVERITY
Modified AHA/ACC Heart Failure Staging System	
A	No apparent structural disease, yet considered "at risk" for developing heart disease (for example, breed-associated risk for DCM in Doberman Pinschers, and CMVD in Cavalier King Charles Spaniels)
B	Structural cardiac abnormality is evident (such as a murmur), but no clinical signs of heart failure have occurred
B1	Asymptomatic disease, with no/minimal radiographic or echo evidence of cardiac chamber enlargement/remodeling
B2	Asymptomatic disease, but cardiac chamber enlargement is evident
C	Structural cardiac abnormality evident, with clinical signs of heart failure either in the past (resolved with therapy) or currently present *Note:* Some clinicians subdivide stage C based on current signs of CHF into C1 – No current signs; C2 – mild congestive signs (low/medium grade); C3 – overt/severe CHF (high grade)
D	Persistent or end-stage heart failure signs, refractory to standard therapy (e.g., require ≥ 8-12 mg/kg/day of furosemide)
Modified NYHA Functional Classification	
I	Heart disease is present but no evidence of heart failure or exercise intolerance; cardiomegaly is minimal to absent
II	Heart disease present but clinical signs of failure only with strenuous exercise; radiographic cardiomegaly is usually present
III	Signs of heart failure with normal activity or mild exercise (e.g., cough, orthopnea); radiographic signs of cardiomegaly and pulmonary edema or pleural/abdominal effusion
IV	Severe clinical signs of heart failure at rest or with minimal activity; marked radiographic signs of CHF and cardiomegaly
International Small Animal Cardiac Health Council Functional Classification	
I	Asymptomatic patient
Ia	Signs of heart disease without cardiomegaly
Ib	Signs of heart disease and evidence of compensation (cardiomegaly)
II	Mild to moderate heart failure; clinical signs of failure evident at rest or with mild exercise and adversely affect quality of life
III	Advanced heart failure; clinical signs of CHF are immediately obvious
IIIa	Home care is possible
IIIb	Hospitalization recommended (cardiogenic shock, life-threatening edema, large pleural effusion, refractory ascites)

AHA/ACC, American Heart Association and American College of Cardiology; *CHF,* congestive heart failure.

Small Animal Cardiac Health Council (ISACHC) criteria. These systems group patients into functional categories on the basis of clinical observations rather than underlying cardiac disease or myocardial function. Such classification still can be helpful conceptually and for categorizing study patients, as well as complement the previously described staging system. Regardless of the clinical classification scheme, identification of the underlying etiology and contributing pathophysiologies, as well as the clinical severity, is important for individualized therapy.

PRECLINICAL CARDIAC DISEASE

Indications for cardiovascular medications in animals with preclinical (stage B) cardiac disease are not always clear-cut. Dogs and cats with systemic hypertension should receive appropriate antihypertensive therapy to help avoid target organ injury (see Chapter 11). For dogs with stage B2 chronic mitral valve disease, pimobendan has been shown to delay onset of CHF; pimobendan therapy is recommended for those dogs with clear evidence for cardiac enlargement that

have not yet developed signs of CHF (see Chapter 6). However, evidence is lacking regarding the use of pimobendan in dogs with early (stage B1) mitral valve disease, and it is not currently recommended at this stage. An ACEI generally is not advocated for dogs with preclinical mitral valve disease, unless it is used to reduce elevated blood pressure. However, some controversy remains, and although ACEIs do not appear to delay onset of CHF in most dogs with mitral valve disease, some dogs with advanced stage B2 disease might benefit from them. Doberman Pinschers, Irish Wolfhounds, and probably other dogs with occult DCM also benefit from the introduction of pimobendan and an ACEI before overt CHF develops (see Chapter 7). For cats with preclinical (stage B) hypertrophic cardiomyopathy (HCM), optimal strategy is not clear and consensus is lacking (see Chapter 8).

MANAGEMENT OF MILD OR EARLY CHF SIGNS

Mild pulmonary edema can produce subtle and variable clinical signs, including modest but persistent increases in resting respiratory rate (RRR; see later in this chapter), reduced exercise tolerance, excessive panting (in dogs), or occasional cough. Detecting mild changes in RRR is easier when owners know the animal's baseline rate and periodically have been monitoring the RRR. Thoracic radiographs are indicated when signs suggestive of decompensating CHF appear, especially if this is the first episode. When radiographic findings are consistent with mild cardiogenic pulmonary edema, initial therapy for CHF (furosemide, an ACEI, and pimobendan, if indicated), along with exercise restriction, often can be instituted on an outpatient basis. If the radiographs are nondiagnostic, but CHF is suspected, a furosemide trial (such as 2 mg/kg/day) with or without an ACEI can be given for a week or so, with RRR monitoring. If the clinical signs are caused by CHF, they usually resolve or substantially improve fairly quickly; in these cases additional CHF therapy, as indicated for the underlying disease, is added. An NT-proBNP test also can help in unclear cases, in that if the result is not elevated, the patient is unlikely to have CHF.

TREATMENT FOR ACUTE CONGESTIVE HEART FAILURE

GENERAL CONSIDERATIONS

Fulminant CHF is characterized by severe cardiogenic pulmonary edema, with or without pleural and/or abdominal effusions or poor cardiac output. It can occur in stage C or D patients. Therapy is aimed at rapidly clearing pulmonary edema, improving oxygenation, and optimizing cardiac output (Box 3.1). Thoracocentesis should be performed expediently if marked pleural effusion exists. Likewise, large-volume ascites should be drained, at least partially, to improve ventilation. Animals with severe CHF are greatly stressed. Physical activity must be maximally restricted to reduce total oxygen consumption; cage confinement is preferred. Environmental stresses such as excess heat and humidity or extreme cold should be avoided. When transported, the animal should be placed on a cart or carried. Unnecessary patient handling and use of oral medications should be avoided, when possible.

SUPPLEMENTAL OXYGEN

Oxygen administered by face mask or improvised hood, nasal catheter, endotracheal tube, or oxygen cage is beneficial as long as the method chosen does not increase the patient's distress. An oxygen cage with temperature and humidity controls is preferred; a setting of 65° F is recommended for normothermic animals. Oxygen flow of 6 to 10 L/min is usually adequate. Concentrations of 50% to 100% oxygen may be necessary initially, but this should be reduced within a few hours to 40% to avoid lung injury. When a nasal tube is used, humidified O_2 is delivered at a rate of 50 to 100 mL/kg/min. Extremely severe pulmonary edema with respiratory failure may respond to endotracheal or tracheotomy tube placement, airway suctioning, and mechanical ventilation. Positive end-expiratory pressure helps clear small airways and expands alveoli. Positive airway pressures can adversely affect hemodynamics, however, and extended use of high oxygen concentrations (>70%) can injure lung tissue (see Suggested Readings for more information). Continuous monitoring is essential for intubated animals.

DRUG THERAPY

Diuresis

Rapid diuresis can be achieved with intravenous (IV) furosemide; effects begin within 5 minutes, peak by 30 minutes, and last about 2 hours. This route also provides a mild venodilating effect. Some patients require aggressive initial doses or cumulative doses administered at frequent intervals (see Box 3.1). Furosemide can be given by constant rate infusion (CRI), which may provide greater diuresis than bolus injection. The veterinary formulation (50 mg/mL) can be diluted to 10 mg/mL for CRI using 5% dextrose in water (D_5W), lactated Ringer's solution (LRS), or sterile water. Dilution to 5 mg/mL in D_5W or sterile water also is described. The patient's respiratory rate, as well as other parameters (discussed in more detail later), guides the intensity of continued furosemide therapy. Once diuresis has begun and respiration improves, the dosage is reduced to prevent excessive volume contraction or electrolyte depletion.

Vasodilation

Vasodilator drugs can reduce pulmonary edema by increasing systemic venous capacitance, lowering pulmonary venous pressure, and reducing systemic arterial resistance. Although ACE inhibitors are a mainstay of chronic CHF management, more immediate afterload reduction usually is desirable for animals with acute pulmonary edema. The initial dose of an arteriolar vasodilator should be low, with subsequent titration upward as needed on the basis of blood pressure and clinical response. Arteriolar vasodilation is not

BOX 3.1

Acute Treatment of Decompensated Congestive Heart Failure

Minimize patient stress and excitement!
- Cage rest; transport on gurney (no activity allowed)
- Avoid excessive heat and humidity

Improve oxygenation:
- Ensure airway patency
- Give supplemental O_2 (avoid > 50% for > 24 hours)
- Postural support if needed (help maintain sternal recumbency, head elevation)
- If frothing evident, suction airways
- Intubate and mechanically ventilate if necessary
- Thoracocentesis, if moderate or severe pleural effusion suspected/documented

Diuresis
- Furosemide (dogs: 2-3[-5] mg/kg initial bolus, IV (or IM or SC), then 1-4 mg/kg q1-4h until respiratory rate decreases, then 1-4 mg/kg q6-12h; or use 0.6-1 mg/kg/h CRI over next 6 hours if inadequate response to boluses [see text]; cats: 1-2[-4] mg/kg initial bolus, IV (or IM or SC), then 1-2 mg/kg q1-4h until respiratory rate decreases, then 1-2 mg/kg q6-12h)
- (Provide access to water after diuresis is evident)

Support cardiac pump function (inodilator)
- Pimobendan (dogs: 0.2-0.3 mg/kg PO q12h, begin as soon as possible; cats: for CHF associated with advanced or end-stage cardiomyopathies or reduced contractility, dose as for dogs [controversial for first-onset CHF from HCM; not advised for HOCM])

Reduce anxiety:
- Butorphanol (dogs: 0.2-0.3 mg/kg IM [or IV, SC], can repeat in 30-60 min if needed; cats: 0.1-0.3 mg/kg IM [or IV, SC]); *or*
- Morphine (dogs: 0.025-0.1 mg/kg IV boluses q2-3 min to effect, or 0.1-0.5 mg/kg single IM or SC dose; do not use in cats); *or*
- Buprenorphine (cats: 0.005-0.02 mg/kg IV, IM, SC)

±Additional vasodilators:
- 2% Nitroglycerin ointment: dogs: 0.25-1.5 inch (0.6-3.8 cm) cutaneously q6h for 24-48 hours (can combine with hydralazine in dogs); cats: 0.25-0.5 inch (0.6-1.3 cm) cutaneously q6-8h for 24-48 hours; *or*
- Sodium nitroprusside (if able to monitor blood pressure closely): 0.5-1 µg/kg/min (initial) CRI in D_5W (for cats, dilute to 100-300 µg/mL). Titrate upward as needed; dogs: to 5(-15) µg/kg/min; cats: to 2(-5) µg/kg/min; until systolic blood pressure ~90-100 mm Hg (or mean of 70 mm Hg). Protect from light, and do not give for more than 24 hours; *or*
- Hydralazine (for further afterload reduction in dogs with MR, if not using nitroprusside); dogs: initial 0.5-1.0 mg/kg PO, repeat in 2-3 hours (until systolic arterial pressure is 90-110 mm Hg), then q12h; *or* cautious IV bolus at 0.05-0.1 mg/kg, repeat q1-2h if needed; *or*
- (Less useful as acute therapy [and avoid concurrent nitroprusside]: ACE inhibitor; *or* amlodipine [dogs: 0.05-0.1 mg/kg initially, to 0.3 mg/kg PO q12-24h]; see text)

±Additional inotropic support (if myocardial failure or persistent hypotension):
- Dobutamine* (1 µg/kg/minute initial CRI; titrate upward to effect q15-30 min, as needed; dogs: up to 20 µg/kg/min; cats: up to 10 µg/kg/min) for 24-48 hours then wean down. Alternatively, can use dopamine** (dogs: 1-10 µg/kg/min CRI; cats: 1-5 µg/kg/min CRI; start low, titrate to effect q15-30 min) for 24-48 hours then wean down; *and/or*
- Amrinone (1-3 mg/kg IV; 10-100 µg/kg/min CRI), or milrinone (50 µg/kg IV over 10 minutes initially; 0.375-0.75 µg/kg/min CRI [human dose])
- Digoxin (not generally used unless as adjunct for atrial fibrillation in dogs) PO (see Table 3.3); (digoxin loading dose [see text for indications]: PO—1 or 2 doses at twice calculated maintenance; dog IV [NOT advised unless other therapy not effective/available]: 0.0025 mg/kg slow IV bolus, repeat hourly over 4-hour period to effect (or total of 0.01 mg/kg)

±Reduce bronchoconstriction:
- Aminophylline (dogs: 4-8 mg/kg slow IV, IM, SC, or 6-10 mg/kg PO q6-8h; cats: 4-8 mg/kg IM, SC, PO q8-12h) or similar drug

Monitor and address abnormalities as possible:
- Respiratory rate, heart rate and rhythm, arterial pressure, O_2 saturation, body weight, urine output, hydration, attitude, appetite, serum biochemistry and blood gas analyses.

For acute CHF from diastolic dysfunction (e.g., cats with hypertrophic cardiomyopathy):
- General recommendations, O_2 therapy, furosemide, and sedation, as in the previous text.
- Thoracocentesis, if needed.
- ±Nitroglycerin
- If severe LV outflow obstruction or persistent and rapid sinus tachycardia, consider IV esmolol (200-500 µg/kg IV over 1 minute, followed by 25-200 µg/kg CRI) or diltiazem (0.15-0.25 mg/kg over 2-3 minutes IV)
- ±Pimobendan (see previous text)
- Monitor and manage abnormalities as possible (see previous text)
- ACE inhibitor (institute after appetite returns)

ACE, Angiotensin-converting enzyme; *CRI*, constant rate infusion; *D_5W*, 5% dextrose in water.
*Dilution of 250 mg dobutamine into 500 mL of D_5W or lactated Ringer's solution yields a solution of 500 µg/mL; CRI of 0.6 mL/kg/h provides 5 µg dobutamine/kg/min.
**Dilution of 40 mg dopamine into 500 mL of D_5W or lactated Ringer's solution provides a solution of 80 µg/mL; infusion at 0.75 mL/kg/h provides 1 µg dopamine/kg/min.

recommended for heart failure caused by diastolic dysfunction or ventricular outflow obstruction.

Sodium nitroprusside is a potent arteriolar and venous dilator with direct action on vascular smooth muscle; unfortunately, it has become prohibitively expensive in the United States. Nitroprusside is given by IV infusion because of its short duration of action. Blood pressure must be closely monitored when using this drug. The dose is titrated to maintain mean arterial pressure at about 80 mm Hg (at least > 70 mm Hg) or systolic blood pressure between 90 and 110 mm Hg. Nitroprusside CRI usually is continued for 12 to 24 hours. Dosage adjustments may be necessary because drug tolerance develops rapidly. Profound hypotension is the major adverse effect. Cyanide toxicity can result from excessive or prolonged use (e.g., longer than 48 hours). Nitroprusside should not be infused with other drugs and should be protected from light.

Hydralazine is an alternative to nitroprusside. It is a pure arteriolar dilator. Hydralazine is useful for refractory pulmonary edema caused by mitral regurgitation (MR) because it can reduce regurgitant flow and lower left atrial (LA) pressure. It should be used only cautiously in patients with DCM. An initial oral dose of 0.5 to 1 mg/kg (or 0.05 to 0.1 mg/kg IV or IM) can be repeated every 2 to 3 hours until the systolic blood pressure is between 90 and 110 mm Hg or clinical improvement is obvious. If blood pressure cannot be monitored, an initial PO dose of 1 mg/kg can be repeated in 2 to 4 hours if sufficient clinical improvement has not been observed. The addition of 2% nitroglycerin ointment may provide beneficial venodilating effects.

An ACEI or amlodipine, with or without nitroglycerin ointment, is an alternative to hydralazine/nitroglycerin. However, their onset of action is slower and effects are less pronounced, but this regimen can still be helpful. Usually an ACEI is introduced after the patient has been stabilized and appetite is returning. Amlodipine generally is reserved for dogs with refractory CHF caused by MR, or for patients with hypertension.

Nitroglycerin (and other orally or transcutaneously administered nitrates) acts mainly on venous smooth muscle to increase venous capacitance and reduce cardiac filling pressure. The major indication for nitroglycerin is acute cardiogenic pulmonary edema. Nitroglycerin ointment (2%) is applied to the skin, usually of the groin, axillary area, or ear pinna; however, the efficacy of this in heart failure is unclear. An application paper or glove is used to avoid contact with the skin of the person applying the drug.

Inotropic Support

The inodilator pimobendan is used for CHF caused by chronic MR and DCM, as well as a number of other causes of CHF. Its onset of action is fairly rapid, even with oral administration. The initial dose is usually given as soon as practicable, with subsequent doses continued as part of long-term HF management (see p. 69 and Table 3.3). The IV form of pimobendan is not yet available in the United States.

Other positive inotropic therapy might also be indicated for acute CHF caused by poor myocardial contractility or when there is persistent hypotension. Treatment for 1 to 3 days with an IV sympathomimetic (catecholamine) or phosphodiesterase (PDE) inhibitor drug can help support arterial pressure, forward cardiac output, and organ perfusion when myocardial failure or hypotension is severe.

Catecholamines enhance contractility via a cyclic adenosine monophosphate (cAMP)-mediated increase in intracellular Ca^{++}. They can provoke arrhythmias and increase pulmonary and systemic vascular resistance (potentially exacerbating edema formation). Their short half-life (<2 minutes) and extensive hepatic metabolism necessitate constant IV infusion. β-receptor downregulation and uncoupling limit their effectiveness within a few days of administration. Concurrent use of a β-blocker also blunts the effect of the catecholamines. Dobutamine (a synthetic analog of dopamine) has lesser effect on heart rate and afterload and is preferred over dopamine. Dobutamine stimulates β_1-receptors, with only weak action on β_2- and α-receptors. Lower doses (e.g., 3-7 μg/kg/min) have minimal effects on heart rate and blood pressure. The initial infusion rate should be low; this can be gradually increased over hours to achieve greater inotropic effect and maintain systolic arterial pressure between 90 and 120 mm Hg. Heart rate, rhythm, and blood pressure must be monitored closely. Although dobutamine is less arrhythmogenic than other catecholamines, higher infusion rates (e.g., 10-20 μg/kg/min) can precipitate supraventricular and ventricular arrhythmias. Adverse effects are more likely in cats; these include nausea and seizures at relatively low doses.

Dopamine at low doses (<2-5 μg/kg/min) also stimulates vasodilator dopaminergic receptors in some regional circulations. Low to moderate doses enhance contractility and cardiac output, but high doses (10-15 μg/kg/min) cause peripheral vasoconstriction and increase heart rate, O_2 consumption, and the risk of ventricular arrhythmias. An initial IV infusion of 1 μg/kg/min can be titrated upward to desired clinical effect. The infusion rate should be decreased if sinus tachycardia or other tachyarrhythmias develop.

Other acute IV inotropic therapy could include the bipyridine PDE inhibitors such as amrinone and milrinone increase intracellular Ca^{++} by inhibiting PDE III, an intracellular enzyme that degrades cAMP. However, they are unlikely to offer a substantive advantage over pimobendan. These drugs also cause vasodilation because increased cAMP promotes vascular smooth muscle relaxation. Hypotension, tachycardia, and gastrointestinal (GI) signs can occur when giving high doses. These drugs can exacerbate ventricular arrhythmias. The effects of amrinone are shortlived (<30 minutes) after IV injection in normal dogs, so CRI is required for sustained effect. Peak effects occur after 45 minutes of CRI in dogs. Amrinone is sometimes used as an initial slow IV bolus followed by CRI; half the original bolus dose can be repeated after 20 or 30 minutes. Milrinone has a much greater potency than amrinone, but there is scant information on the IV form in small animals. These agents could be

TABLE 3.3

Drugs for Managing Chronic Heart Failure

DRUG	DOGS	CATS
Diuretics		
Furosemide	1-3 (or more) mg/kg PO q8-24h (long term); use smallest effective dose. In refractory CHF, several intermittent 2 mg/kg SC doses/week, in place of PO doses, may be helpful (or use torsemide; see text [p. 66]). See Box 3.1 for acute CHF recommendations	1-2 (or more) mg/kg PO q8-24h; use smallest effective dose. See Box 3.1 for acute CHF recommendations
Torsemide	Dose at 1/12 to 1/8 of patient's total daily furosemide dose; administer in two divided doses	Same
Spironolactone	(0.5-)2 mg/kg PO q24h (or divided q12h)	0.5-1 mg/kg PO q24h (or divided q12h)
Chlorothiazide	10-40 mg/kg PO q12-48h (start qod with low dose)	10-40 mg/kg PO q12-48h (start qod with low dose)
Hydrochlorothiazide	0.5-4 mg/kg PO q12-48h (start qod with low dose)	0.5-2 mg/kg PO q12-48h (start qod with low dose)
ACE Inhibitors		
Enalapril	0.5 mg/kg PO q12-24h	0.25-0.5 mg/kg PO q(12-)24h
Benazepril	0.25-0.5 mg/kg PO q(12-)24h	0.25-0.5 mg/kg PO q(12-)24h
Captopril	0.5-2 mg/kg PO q8-12h	0.5-1.25 mg/kg PO q(8-)24h
Lisinopril	0.25-0.5 mg/kg PO q(12-)24h	0.25-0.5 mg/kg PO q24h
Ramipril	0.125-0.25 mg/kg PO q24h	0.125 mg/kg PO q24h
Imidapril	0.25 mg/kg PO q24h	—
Other Vasodilators		
Hydralazine	0.5-2 (to 3) mg/kg PO q12h (to 1 mg/kg initial). See Box 3.1 for acute CHF recommendations	2.5 (up to 10) mg/cat PO q12h
Amlodipine	0.05 (initial) to 0.3(-0.5) mg/kg PO q(12-)24h	0.3125-0.625(-1.25) mg/cat (or 0.1-0.5 mg/kg) PO q24(-12)h
Prazosin	0.05-0.2 mg/kg PO q8-12h	0.25-0.5 mg/cat PO q12-24h
Nitroglycerin 2% ointment	1/4-1½ inch cutaneously q4-6h for 24-48 hours	1/4-½ inch cutaneously q4-6h for 24-48 hours
Isosorbide dinitrate	0.5-2 mg/kg PO q(8-)12h	—
Isosorbide mononitrate	0.25-2 mg/kg PO q12h	—
Positive Inotropes		
Pimobendan	0.2-0.3 mg/kg PO q12h; for refractory (stage D) CHF, could be increased up to 0.4-0.5 mg/kg q8h	As for dog, or 1.25 mg/cat PO q12(-8)h
Digoxin	PO: 0.003-0.005 mg/kg PO q12h. Decrease by 10% for elixir. Maximum: 0.5 mg/day or 0.375 mg/day for Doberman Pinschers. (See Box 3.1 for loading doses)	0.007 mg/kg (or 1/4 of 0.125 mg tab) PO q48h

used concurrently with digoxin and a catecholamine but would seem redundant with pimobendan.

If arrhythmias develop during IV inotropic therapy, the infusion rate is reduced or the drug is discontinued. Catecholamine infusion is likely to increase the ventricular response rate in animals with atrial fibrillation (AF), by enhancing AV conduction. If dobutamine or dopamine is deemed necessary for such a case, diltiazem (IV or oral) is used to reduce the heart rate (see Table 4.2). Oral digoxin with an initial loading dose is an alternative. Digoxin is not recommended intravenously; the only, and rare, exception might be for a sustained supraventricular tachyarrhythmia when other acute antiarrhythmic therapy is unavailable or ineffective (see Chapter 4, p. 80). Acidosis and hypoxemia associated with severe pulmonary edema can increase myocardial sensitivity to digitalis-induced arrhythmias.

Other Acute Therapy

Mild sedation (see Box 3.1) can reduce anxiety. Because morphine can induce vomiting, butorphanol is a better choice in dogs. Morphine is contraindicated in dogs with neurogenic edema because it can raise intracranial pressure. Morphine should not be used in cats.

Some dogs with severe pulmonary edema and bronchoconstriction benefit from short-term bronchodilator therapy. Aminophylline, given slowly IV or IM, has mild diuretic and positive inotropic actions as well as a bronchodilating effect; it also decreases fatigue of respiratory muscles. Adverse effects include increased sympathomimetic activity and arrhythmias. The oral route can be used when respiration improves because GI absorption is rapid.

HEART FAILURE CAUSED BY DIASTOLIC DYSFUNCTION

When acute CHF is caused by hypertrophic or restrictive cardiomyopathy, thoracocentesis (if needed), diuretics, and oxygen therapy are given as outlined previously. Cutaneous nitroglycerin can also be used. For cats with a rapid tachyarrhythmia, persistent sinus tachycardia, or marked LV outflow obstruction, a β_1-blocker such as atenolol or IV esmolol can reduce the frequency of ectopic beats, control heart rate, and reduce the LV outflow pressure gradient. However, propranolol (or another nonselective β-blocker) should be avoided in patients with fulminant pulmonary edema because β_2-blockade could induce bronchoconstriction. Pimobendan can be helpful in cats with reduced myocardial contractility, restrictive or end-stage cardiomyopathy, and recurrent or progressive CHF from HCM. Whether pimobendan therapy should be started at first-onset CHF in cats with HCM is controversial; prospective clinical evidence is awaited to support or refute this use. In cats with hypertrophic obstructive cardiomyopathy (HOCM), there is concern regarding use of pimobendan (as well as other positive inotropic or vasodilator agents). Because increased contractility and arterial vasodilation can worsen dynamic LV outflow obstruction and potentially cause hypotension, pimobendan is theoretically contraindicated.

Arteriolar vasodilators can be detrimental in the presence of LV outflow obstruction, because afterload reduction provokes greater systolic obstruction (see Chapter 8). However, ACEIs at standard doses do not appear to worsen the LV outflow gradient. Addition of an ACEI is recommended as soon as the animal begins eating again.

MONITORING AND FOLLOW-UP

Repeated assessment is important for monitoring the effectiveness of therapy and for early detection of hypotension or severe azotemia caused by excessive diuresis. Mild azotemia is common. Hypokalemia and metabolic alkalosis also can occur after aggressive diuresis. Maintaining serum potassium concentration within the mid- to high-normal range is especially important for animals with arrhythmias. Serum biochemical testing every 24 to 48 hours is advised until the patient is drinking well and beginning to eat.

Arterial blood pressure should be monitored, usually by indirect means because gaining arterial access can increase patient stress. Indirect measures of organ perfusion such as capillary refill time, mucous membrane color, pulse oximetry, urine output, toe-web temperature, and mentation also are useful. Body weight should be monitored, especially with aggressive diuretic therapy.

Central venous pressure (CVP) does not adequately reflect left heart filling pressures. It should not be used to guide diuretic or fluid therapy in patients with cardiogenic pulmonary edema. Although pulmonary capillary wedge pressure can reliably guide therapy, placement and care of an indwelling pulmonary artery catheter require meticulous attention to asepsis and close monitoring.

Pulse oximetry is helpful for monitoring oxygen saturation (SpO_2). Supplemental O_2 should be given if SpO_2 is less than 90%; mechanical ventilation is indicated if SpO_2 is less than 80% despite O_2 therapy. Arterial sampling for blood gas analysis is more accurate but is stressful for the patient. Resolution of radiographic evidence for pulmonary edema usually lags behind clinical improvement by a day or two.

After respiratory signs begin to abate and diuresis is evident, drinking water is offered. Fluid administration (either subcutaneously or intravenously) generally is NOT advised for patients with CHF. In most cases, gradual rehydration by free choice water intake is preferred even after aggressive diuresis. However, cautious fluid therapy may be necessary for heart failure patients with advanced renal dysfunction, marked hypokalemia, hypotension, persistent anorexia, digoxin toxicity, or other serious systemic disease. Some animals require relatively high cardiac filling pressure to maintain cardiac output, especially those with myocardial failure or markedly reduced ventricular compliance (as from HCM or pericardial disease). Diuresis and vasodilation in such cases can cause inadequate cardiac output and hypotension. For most patients with decompensated CHF that need a drug by CRI, the smallest fluid volume possible should be used. Careful monitoring and continued diuretic use are important to prevent recurrent pulmonary edema. When additional fluid therapy is necessary, D_5W or a reduced

sodium fluid (such as 0.45% NaCl with 2.5% dextrose) with added KCl is administered at a conservative rate (for example, 15 to 30 mL/kg/day IV). Alternatively, 0.45% NaCl with 2.5% dextrose or LRS can be administered subcutaneously.

Potassium supplementation at a maintenance rate is provided by 0.05 to 0.1 mEq/kg/h (or more conservatively, 0.5-2 mEq/kg/day). For animals with hypokalemia, higher rates are used: 0.15 to 0.2 mEq/kg/h for mild K^+ deficiency; 0.25 to 0.3 mEq/kg/h for moderate deficiency; and 0.4 to 0.5 mEq/kg/h for severe deficiency. Serum K^+ concentration measurement in 4 to 6 hours is advised when supplementing for moderate to severe deficiency. Hyponatremia and worsened fluid retention can develop after administering low-sodium IV solutions in some patients. These require a more balanced crystalloid solution. Other supportive therapies for CHF and any underlying disease(s) depend on individual patient needs. Parenteral fluid administration is discontinued as the animal is able to resume oral food and water intake.

MANAGEMENT OF CHRONIC HEART FAILURE

GENERAL CONSIDERATIONS

A general approach to chronic heart failure therapy is presented in this section. Additional information is found in the chapters describing different diseases. Long-term heart failure management in dogs with chronic mitral valve disease or DCM generally involves a combination of furosemide, pimobendan, an ACEI (usually enalapril or benazepril), and the addition of spironolactone. A diet moderately reduced in salt also is recommended for most heart failure patients. Therapy is tailored to the individual animal's needs by adjusting dosages, adding or substituting drugs, and modifying lifestyle or diet. Pleural effusion and large-volume ascites that accumulate despite medical therapy should be drained to facilitate respiration. Likewise, pericardial effusion that compromises cardiac filling must be drained (see Chapter 9). As heart disease progresses, more aggressive therapy usually is necessary.

Exercise restriction helps reduce cardiac workload regardless of heart failure etiology. For animals with active CHF, no exercise should be allowed until all signs of congestion have been well controlled. Strenuous exercise can provoke dyspnea and potentially serious cardiac arrhythmias even in animals with compensated CHF. However, regular mild to moderate activity (as tolerated) is thought to be beneficial for patients with no clinical signs of congestion (i.e., compensated heart failure). Chronic heart failure is associated with skeletal muscle changes that lead to fatigue and dyspnea. Physical training is known to improve cardiopulmonary function and quality of life in human patients with chronic heart failure. This is partly mediated by improvement in vascular endothelial function and restoration of flow-dependent vasodilation. Although it is difficult to know how much exercise is best, regular (not sporadic) mild to moderate activity is encouraged, as long as excessive respiratory effort or fatigue is not induced. Bursts of strenuous activity should be avoided.

DIURETICS

Diuretic therapy remains fundamental for the long-term management of CHF because of its ability to decrease cardiogenic pulmonary edema and effusions (see Table 3.3). Furosemide (and other loop diuretics) interferes with ion transport in the loop of Henle and has the potent ability to promote both salt and water loss. Diuretics of other classes, such as potassium-sparing agents and thiazides, are sometimes combined with furosemide for more intense diuresis in patients with advanced heart failure. Given to excess, diuretics promote excessive volume contraction and activate the renin-angiotensin-aldosterone cascade. Diuretics also can exacerbate preexisting dehydration or azotemia. Therefore the indication for their use in such animals should be clearly established, and the lowest effective dose should be used.

Furosemide

Furosemide is the loop diuretic used most widely for cats and dogs with heart failure (also see p. 61). It acts on the ascending limb of the loop of Henle to inhibit active Cl^-, K^+, and Na^+ cotransport, thereby promoting excretion of these electrolytes and H^+; Ca^{++} and Mg^{++} are also lost in the urine. Loop diuretics also can increase systemic venous capacitance, possibly by mediating renal prostaglandin release. In addition, furosemide may promote salt loss by increasing total renal blood flow and preferentially enhancing renal cortical flow. The loop diuretics are well absorbed when given orally. After oral administration, diuresis occurs within 1 hour, peaks between 1 and 2 hours, and may last for 6 hours. Furosemide is highly protein bound; about 80% is actively secreted unchanged in the proximal renal tubules, with the remainder excreted as glucuronide.

Although aggressive furosemide treatment is indicated for acute, fulminant pulmonary edema, the smallest effective doses should be used for chronic heart failure therapy. The dosage will vary depending on the clinical situation. Respiratory pattern, hydration, body weight, exercise tolerance, renal function, and serum electrolyte concentrations are used to monitor response to therapy. Furosemide (or other diuretic) alone is not recommended as the sole treatment for chronic heart failure because it can exacerbate NH activation and reduce renal function.

Adverse effects usually are related to excessive fluid and/or electrolyte losses. Lower doses are used in cats because they are more sensitive to the drug than dogs. Although hypokalemia is the most common electrolyte disturbance, it is unusual in dogs that are not anorexic. Excessive diuresis can result in hyponatremic, hypochloremic alkalosis.

Other Loop Diuretics

Other more potent loop diuretics are sometimes used instead of furosemide. Torsemide (dosed initially at one

tenth of the patient's prior furosemide dose) has been useful in dogs with refractory CHF and diuretic resistance. It produces greater Na^+ excretion, has a longer half-life, and also has some anti-aldosterone effect. Adverse effects are similar to those of furosemide but potentially more intense.

Spironolactone

Spironolactone is probably more useful for its anti-aldosterone effects in cardiac and other tissues than for its diuretic effect, although it may be a helpful adjunct in patients with chronic refractory heart failure. Spironolactone is a competitive antagonist of aldosterone. In the kidney, it promotes Na^+ loss and K^+ retention in the distal renal tubule and can reduce the renal potassium wasting of furosemide and other diuretics, especially when circulating aldosterone concentration is high. However, it has negligible diuretic effect in normal dogs.

Despite initial decline in aldosterone release with ACEI therapy, aldosterone levels can increase with time (so-called aldosterone escape). This may involve reduced hepatic clearance, increased release stimulated by K^+ elevation or Na^+ depletion, and local tissue aldosterone production. Spironolactone's anti-aldosterone effect is thought to mitigate aldosterone-induced cardiovascular remodeling and baroreceptor dysfunction. The drug has improved survival in people with moderate to severe CHF. This might relate to a reduction in susceptibility to ventricular tachyarrhythmias from lessened myocardial fibrosis and inflammatory cytokine expression. In dogs with DCM and chronic MR, spironolactone (at 2 mg/kg/day PO) was associated with improved morbidity and mortality, although not all reports note a survival benefit.

Spironolactone's onset of action is slow; peak effect occurs within 2 to 3 days. Administration with food increases its bioavailability. Because it is a potassium-sparing diuretic, it must be used cautiously in patients receiving an ACEI or potassium supplement, and it is absolutely contraindicated in hyperkalemic patients. Adverse effects usually relate to excess K^+ retention and GI disturbances. Spironolactone may decrease digoxin clearance. Ulcerative facial dermatitis has occurred in cats, especially at higher doses.

Eplerenone is another aldosterone antagonist with more selective action. In experimental heart failure, eplerenone significantly reduced ventricular remodeling and fibrosis. Clinical experience in dogs and cats is lacking, however, and it is unclear whether this drug is more advantageous than spironolactone.

Thiazide Diuretics

Thiazide diuretics decrease Na^+ and Cl^- absorption and increase Ca^{++} absorption in the distal convoluted tubules. Mild to moderate diuresis with excretion of Na^+, Cl^-, K^+, and Mg^{++} results, and alkalosis can occur. The thiazides decrease renal blood flow and should not be used in azotemic animals. Adverse effects are uncommon when used alone (not advised for CHF) in the absence of azotemia. However, marked hypokalemia or other electrolyte disturbance, severe azotemia, and dehydration can occur when used in combination with other diuretics, with excessive use, or in anorectic patients. Thiazides can cause hyperglycemia in diabetic or prediabetic animals by inhibiting conversion of proinsulin to insulin. Chlorothiazide's effects begin within 1 hour, peak at 4 hours, and last 6 to 12 hours. Hydrochlorothiazide produces diuresis within 2 hours, with peak effect at 4 hours, and duration of about 12 hours. Dosing every other day or even less frequently (instead of q12-24h) may be necessary to avoid serious azotemia and electrolyte abnormalities when used in the management of chronic refractory heart failure.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACEIs are indicated for most causes of chronic heart failure (see Table 3.3). Their use has led to clinical improvement and lowered mortality rates in people with heart failure. Similar benefits seem to occur in dogs with stages C and D heart failure from myocardial failure or volume overload. Cats with diastolic dysfunction are also thought to benefit from ACEIs. Although ACEI therapy does not delay CHF onset in most dogs with preclinical (stage B) chronic MR, it remains an integral part of standard therapy once CHF develops (stage C).

ACEIs moderate excess NH responses in several ways; therefore they have considerable advantages over hydralazine and other arteriolar dilators. ACEIs have only modest diuretic and vasodilatory effects; their main benefits arise from opposing the effects of NH activation and abnormal cardiovascular remodeling changes. By blocking the formation of angiotensin II, ACEIs allow arteriolar and venous vasodilation. The secondary inhibition of aldosterone release helps reduce Na^+ and water retention and therefore edema/effusions, as well as the adverse effects of aldosterone directly on the heart. ACEIs reduce ventricular arrhythmias and the rate of sudden death in people (and probably animals) with heart failure, likely because angiotensin II–induced facilitation of norepinephrine and epinephrine release is inhibited. Their vasodilating effects may be enhanced by vasodilator kinins normally degraded by ACE. A local vasodilating effect may occur through inhibition of ACE found within vascular walls, even in the absence of high circulating renin concentrations. Local ACE inhibition may be beneficial by modulating vascular smooth muscle and myocardial remodeling. However, it is unclear whether ACE inhibitors prevent ventricular remodeling and dilation in dogs with spontaneous heart disease. ACE inhibitors have been variably effective in treating dogs with hypertension.

Most ACEIs (except captopril and lisinopril) are prodrugs that are converted to their active form in the liver; therefore severe liver dysfunction can interfere with this conversion. Adverse effects of ACEIs include vomiting/diarrhea, deterioration of renal function, hypotension, and

hyperkalemia (especially when used with a potassium-sparing diuretic or potassium supplement). Angiotensin II is important in mediating renal efferent arteriolar constriction, which maintains glomerular filtration when renal blood flow decreases. As long as cardiac output and renal perfusion improve with therapy, renal function is usually maintained. Poor glomerular filtration is more likely to result with overdiuresis, excess vasodilation, or severe myocardial dysfunction. Measurement of serum creatinine and electrolytes is recommended within 1 week of initiating therapy and periodically thereafter. Azotemia is first addressed by decreasing the diuretic dosage. If necessary, the ACEI dosage is decreased or discontinued. Hypotension can usually be avoided by starting with low initial doses. Other adverse effects reported in people include rash, pruritus, impairment of taste, proteinuria, cough, and neutropenia. The mechanism of ACEI-induced cough in people is unclear but may involve inhibition of endogenous bradykinin degradation or may be associated with increased NO generation. NO has an inflammatory effect on bronchial epithelial cells.

Enalapril

Enalapril is about 20% to 40% bioavailable; administration with food does not reduce its bioavailability. It is hydrolyzed in the liver to enalaprilat, its most active form. Peak ACE-inhibiting activity occurs within 4 to 6 hours in dogs. Duration of action is 12 to 14 hours, and effects are minimal by 24 hours at the recommended once-daily dose. Enalapril often is given once daily initially but usually is increased to every 12 hours in dogs being treated for CHF. In cats, maximal activity occurs within 2 to 4 hours after an oral dose of either 0.25 or 0.5 mg/kg; some ACE inhibition (50% of control) persists for 2 to 3 days. Enalapril and its active metabolite are excreted in the urine. Renal failure and severe CHF prolong its half-life, so reduced doses or use of benazepril instead are recommended in such patients. Severe liver dysfunction will interfere with the conversion of the prodrug to the active enalaprilat. Injectable enalaprilat is also available, but sparse veterinary data exist on its use; this form is not well absorbed orally.

Benazepril

Benazepril is metabolized to its active form, benazeprilat. Only about 40% is absorbed when administered orally, but feeding does not affect absorption. After oral administration, peak ACE inhibition occurs within 2 hours in dogs and cats; its effect can last more than 24 hours. In cats doses of 0.25 to 0.5 mg/kg result in 100% inhibition of ACE, which is maintained at greater than 90% for 24 hours and tapers off to about 80% by 36 hours. Benazepril has an initial half-life of 2.4 hours and terminal half-life of about 29 hours in cats. Repeated doses produce moderate increases in drug plasma concentration. Benazepril is a preferred ACEI for animals with renal disease. This drug is eliminated equally in urine and bile in dogs. In cats about 85% of the drug is excreted in the feces and only 15% in urine. The drug is generally well tolerated. It may also slow renal function deterioration in cats with kidney disease.

Other Angiotensin-Converting Enzyme Inhibitors

Other ACEIs used in animals with heart failure have included ramipril, imidapril, lisinopril, and captopril. Ramipril is rapidly absorbed and converted to ramiprilat, although bioavailability is fairly low (similar to benazepril). Ramipril produces good ACE inhibition within 1-2 hours; with high affinity for ACE, its ACEI effect can last ~24 hours despite rapid clearance of free ramiprilat. Ramipril's pharmacokinetic properties are not significantly altered by moderate renal dysfunction. Imidapril also is comparable to enalapril and benazepril in efficacy. It appears to have a longer half-life, about 18-20 hours, in dogs. Elimination of both ramipril and imidapril is about 40% through the kidney and 60% by the liver. Captopril, the first ACEI used clinically, contains a sulfhydryl group, in contrast to enalapril and others. Although disulfide metabolites can act as free radical scavengers, the clinical significance of this for animals in heart failure is unclear. Captopril is rarely used as it requires more frequent dosing. Hemodynamic effects peak in 1 to 2 hours after oral administration and last less than 4 hours in dogs. Captopril is excreted in the urine. Lisinopril is a lysine analog of enalaprilat with direct ACE-inhibiting effects. Its bioavailability is between 25% and 50%, and absorption is not affected by feeding. The time to peak effect is 6 to 8 hours. The duration of ACE inhibition appears long, but more specific information in animals is lacking. Once-daily administration has been tried with apparent effectiveness.

Angiotensin Receptor Blockers

The angiotensin receptor blockers (ARBs) are drugs that directly block type I angiotensin II receptors rather than reduce the production of angiotensin II. The ARB agents sometimes are called "sartans" (valsartan, losartan, telmisartan, etc.). In experimental models of myocardial ischemia and heart failure, ARB treatment has reduced ventricular remodeling, fibrosis, and dysfunction, as does ACEI. Some experimental evidence suggests the combination of an ARB with an ACEI might reduce ventricular remodeling to a greater degree than with either agent alone. However, their combined use is not advocated in people with heart failure. Clinical experience with ARB use in dogs and cats with CHF is slim, although some studies are underway. Whether, or in what situations, an ARB instead of an ACEI (or possibly both together) would be most effective in the setting of CHF in dogs and cats is not clear.

A new combination drug for heart failure in people (Entresto, Novartis) incorporates the ARB valsartan with sacubitril, an inhibitor of neprilysin (the enzyme that degrades natriuretic peptides). In people with CHF and reduced myocardial contractility, this combination drug has reduced mortality and hospitalization, compared with enalapril. Clinical experience with this agent in dogs (and cats) with CHF is limited so far.

POSITIVE INOTROPIC AGENTS

Pimobendan

Pimobendan (Vetmedin) is called an *inodilator* because it increases contractility while also causing systemic and pulmonary vasodilation (see Table 3.3). Pimobendan has a calcium-sensitizing effect on the contractile proteins by increasing the affinity of the regulatory protein troponin C for Ca^{++}. This promotes increased contractility without an increase in free cellular Ca^{++} and therefore myocardial O_2 requirement. As a benzimidazole-derivative phosphodiesterase III inhibitor, pimobendan also slows cAMP breakdown and enhances adrenergic effects on Ca^{++} fluxes and myocardial contractility. The drug potentially has other beneficial effects by modulating NH and proinflammatory cytokine activation. It also has some antithrombotic properties but only at high doses. Peak plasma concentrations occur within an hour of oral dosing. Bioavailability is about 60% in dogs, but this decreases in the presence of food, so administration at least an hour before feeding sometimes is recommended. Pimobendan is highly proteinbound. Elimination is mainly via hepatic metabolism and biliary excretion. There is an active metabolite with phosphodiesterase III inhibitory effect that contributes to the drug's systemic and pulmonary vasodilatory effects. Concurrent Ca^{++} or β-blocker therapy may diminish the drug's positive inotropic effect. Adverse effects are uncommon but can include anorexia, vomiting, or diarrhea.

Pimobendan has been shown to improve clinical status and survival in dogs with CHF from DCM or chronic MR when added to standard therapy. Pimobendan is associated with longer survival times when compared with ACEI in dogs with CHF, although the combination of pimobendan with an ACEI usually is employed clinically. Pimobendan does not appear to increase the frequency of ventricular arrhythmias and sudden death in dogs with CHF. Pimobendan also is now recommended therapy for dogs with advanced preclinical chronic mitral valve disease (stage B2) because it can delay the onset of CHF, as shown in a large prospective multinational study (Epic trial). Likewise, pimobendan was shown to delay CHF onset and improve survival in Doberman Pinschers and Irish Wolfhounds with occult DCM. It presumably benefits other animals with progressive myocardial function deterioration as well. There is disagreement regarding pimobendan's use in cats with first-onset CHF caused by HCM, and it may be contraindicated for HOCM, as previously noted (p. 65). However, pimobendan is a recommended component of CHF therapy for cats with dilated, restrictive, and other end-stage cardiomyopathies.

Digoxin

As an oral positive inotropic drug, digoxin has been eclipsed by pimobendan. However, digoxin still is used in some cases of advanced DCM and end-stage MR as an adjunct to, and combined with, pimobendan to support myocardial function. Digoxin's ability to sensitize baroreceptors and thereby modulate NH activation probably is its most important attribute in patients with heart failure. Digoxin has only a modest positive inotropic effect and a narrow therapeutic window, so it must be dosed and monitored carefully. Digoxin is used most often for heart rate control in dogs with AF; it is moderately effective for slowing AV conduction. Digoxin also can suppress some other supraventricular arrhythmias (see Chapter 4). Digoxin generally is contraindicated when sinus or AV node disease is present. Other potential contraindications include azotemia, ventricular tachyarrhythmias (because it can exacerbate such arrhythmias), and concurrent use of a drug that can potentiate digoxin's effects. Digoxin usually is contraindicated in patients with HCM, especially those with ventricular outflow obstruction. It is almost never used in cats now. Digoxin is not helpful in patients with pericardial disease. Because of its potential toxicity, low doses are used and serum concentrations should be monitored. Serum concentrations in the low to mid therapeutic range are desired (see p. 70).

Digoxin increases contractility by competitively binding and inhibiting the Na^+, K^+-ATPase pump at the myocardial cell membrane. Intracellular Na^+ accumulation then promotes Ca^{++} entry via the sodium-calcium exchange. However, digoxin's inotropic effect may be minimal in diseased myocardial cells in which systolic Ca^{++} release and diastolic reuptake are impaired, and it can predispose to cellular Ca^{++} overload, delayed afterdepolarizations, and electrical instability.

The antiarrhythmic effects of digoxin are mediated primarily by increased parasympathetic tone to the sinus and AV nodes and atria. Some direct effects further prolong conduction time and refractory period of the AV node. Sinus rate slowing, reduced ventricular response rate to AF and atrial flutter, and suppression of atrial premature depolarizations are resulting effects. Although some ventricular arrhythmias might be suppressed (probably via enhanced vagal tone), digoxin has potential arrhythmogenic effects, especially in patients with heart failure.

Oral maintenance doses are used to initiate digoxin therapy. When a more rapid increase in serum concentration is important, the drug can be given at twice the oral maintenance dose for 1 to 2 doses. However, loading doses can result in toxic concentrations. IV digoxin loading is not recommended. Alternate IV drug therapy for supraventricular tachycardia usually is more effective (see Chapter 4), and other positive inotropic drugs (see p. 63 and Box 3.1) are safer and more effective than digoxin for immediate support of myocardial contractility.

Digoxin is well absorbed orally and undergoes minimal hepatic metabolism; absorption is approximately 60% for the tablet form and 75% for the elixir. Kaolin-pectin compounds, antacids, the presence of food, and malabsorption syndromes decrease bioavailability. About 27% of the drug in serum is proteinbound. The serum half-life in dogs ranges from less than 23 to more than 39 hours; therapeutic serum concentrations are achieved within 2 to 4.5 days with every 12-hour dosing. In cats, the reported serum half-life ranges widely from about 25 to more than 78 hours; chronic oral administration increases the drug's half-life. The alcohol-based

elixir produces approximately 50% higher serum concentrations than the tablet form of digoxin. For the rare feline case where digoxin might be helpful, dosing every 48 hours produces effective serum concentrations, with steady state achieved in about 10 days. Digoxin elimination is primarily by glomerular filtration and renal secretion in dogs, although approximately 15% is metabolized by the liver. Renal and hepatic elimination appear equally important in cats.

Serum digoxin concentration (and risk of toxicity) increases with renal failure because of reduced clearance and volume of distribution. However, there is no consistent correlation between the degree of azotemia and the serum digoxin concentration in dogs. Lower doses and close monitoring of serum digoxin concentration are recommended in animals with renal disease.

Digoxin dose and serum concentration are only weakly correlated in dogs with heart failure. Because much of the drug is bound to skeletal muscle, animals with reduced muscle mass or cachexia as well as those with compromised renal function easily can become toxic at usual calculated doses. Digoxin has poor lipid solubility. Initial dosing should be based on the patient's estimated lean body weight, especially in obese animals. Management of digoxin toxicity is outlined later. Conservative dosing and monitoring of serum digoxin concentrations are important to prevent toxicity.

Serum concentration measurement is recommended at 7 days (or 10 days for cats) after beginning digoxin therapy. Digoxin serum concentration also should be measured after a dosage change, or whenever potential signs of toxicity occur. Samples should be drawn 8 (to 10) hours post-dose. The target serum concentration range is 0.8 to 1.5 ng/mL. If the serum concentration is less than 0.8 ng/mL, the digoxin dose could be increased by 25% to 30%, and the serum concentration remeasured the following week. If serum concentrations cannot be measured and toxicity is suspected, the drug should be discontinued. If necessary, the drug can be reinstituted at half of the original dose after a couple days.

Digoxin Toxicity

Azotemia and hypokalemia both predispose to digoxin toxicity. Therefore it is important to monitor renal function and serum electrolyte concentrations during digoxin therapy. Hypokalemia predisposes the patient to myocardial toxicity by allowing increased digoxin binding to membrane Na^+, K^+-ATPase; conversely, hyperkalemia displaces digitalis from those binding sites. Hypercalcemia and hypernatremia potentiate both the inotropic and the toxic effects of the drug. Hyperthyroidism can potentiate the myocardial effects of the drug. Hypoxia sensitizes the myocardium to the toxic effects of digoxin. Certain drugs can affect serum digoxin concentrations when administered concurrently, including amiodarone, quinidine, and verapamil. Diltiazem, prazosin, spironolactone, and triamterene possibly increase serum digoxin concentration. Drugs affecting hepatic microsomal enzymes may also have effects on digoxin metabolism.

Digoxin toxicity causes GI, myocardial, and sometimes central nervous system (CNS) signs. GI toxicity can develop before signs of myocardial toxicity. Signs include anorexia, depression, vomiting, borborygmi, and diarrhea. Some of these GI signs result from the direct effects of digoxin on chemoreceptors in the area postrema of the medulla. CNS signs include depression and disorientation.

Myocardial toxicity can cause ventricular or supraventricular tachyarrhythmias, sinus arrest, Mobitz type I second-degree AV block, and junctional rhythms. Myocardial toxicity can occur before any other signs and can lead to collapse and death, especially in animals with myocardial failure. Therefore PR interval prolongation on the electrocardiogram (ECG) or signs of GI toxicity should not be used to guide progressive dosing of digoxin. Digoxin can stimulate spontaneous automaticity of myocardial cells by inducing and potentiating late afterdepolarizations; cellular stretch, calcium overloading, and hypokalemia enhance this effect. Toxic concentrations enhance automaticity by increasing sympathetic tone to the heart, whereas the parasympathetic effects of slowed conduction and altered refractory period facilitate development of reentrant arrhythmias. In patients taking digoxin, toxicity should be suspected when ventricular arrhythmias or tachyarrhythmias with impaired conduction appear.

Therapy for digoxin toxicity depends on its manifestations. GI signs usually respond to drug withdrawal and correction of fluid or electrolyte abnormalities. AV conduction disturbances resolve after drug withdrawal, although anticholinergic therapy may be necessary. Lidocaine is used to treat digoxin-induced ventricular tachyarrhythmias because it can suppress arrhythmias caused by re-entry and late afterdepolarizations, with little effect on sinus rate and AV conduction. A β-blocker might help control ventricular tachyarrhythmias not responsive to lidocaine alone, but this is not used if AV conduction block is present. Phenytoin (diphenylhydantoin) is a rarely used alternative antiarrhythmic agent for dogs with digoxin-induced ventricular tachyarrhythmias if lidocaine is ineffective (see Chapter 4, p. 82).

If the serum potassium concentration is less than 4 mEq/L, IV potassium supplementation is helpful (see p. 83). Magnesium supplementation also can help in suppressing arrhythmias; $MgSO_4$ has been used at 25 to 40 mg/kg via slow IV bolus, followed by infusion of the same dose over 12 to 24 hours. Fluid therapy to correct dehydration and maximize renal function should be used only with caution and at conservative volumes in patients with heart failure. Quinidine should not be used because it increases digoxin serum concentration. Oral administration of the steroid-binding resin cholestyramine is useful only soon after accidental digoxin overdose because this drug undergoes minimal enterohepatic circulation. A preparation of digoxin-specific antigen-binding fragments (digoxin-immune Fab) derived from ovine antidigoxin antibodies occasionally has been used for digoxin overdose; the Fab fragment–digoxin complex inactivates digoxin's effects and is subsequently excreted by the kidney.

OTHER VASODILATORS

Vasodilators can affect arterioles, venous capacitance vessels, or both ("balanced" vasodilators). Arteriolar dilators relax arteriolar smooth muscle and thereby decrease systemic vascular resistance and LV afterload. In patients with MR, arteriolar dilators decrease the systolic pressure gradient across the mitral valve, reduce regurgitant flow, and enhance forward flow into the aorta. Reduced regurgitant flow can diminish LA pressure, pulmonary congestion, and possibly LA size. Arteriolar vasodilators are used in advanced heart failure from MR and sometimes DCM, as an adjunct to ACEI and other therapy, to provide additional afterload reduction.

Arteriolar (or mixed) vasodilator therapy is initiated using low doses to avoid hypotension and reflex tachycardia. Reduction in concurrent diuretic dosage may be advisable. Monitoring for signs of hypotension is especially important. Ideally, arterial blood pressure is measured multiple times over several hours after starting therapy or dosage increase. Dosage titration to a mean arterial pressure between 70 to 80 mm Hg has been suggested as a therapeutic goal; however, systolic pressures of less than 90 to 100 mm Hg should be avoided. A venous pO_2 of greater than 30 mm Hg (from a free-flowing jugular vein), as a means to indicate reduced tissue oxygen extraction, also can help guide dosage titration. Clinical signs of drug-induced hypotension include weakness, lethargy, tachycardia, and poor peripheral perfusion. The vasodilator dose can be titrated upward, if necessary, while monitoring for hypotension with each increase in dose.

Venodilators relax systemic veins, increase venous capacitance, decrease cardiac filling pressures (preload), and reduce pulmonary congestion. They are most often used in the setting of acute CHF.

Hydralazine

Hydralazine directly relaxes arteriolar smooth muscle when the vascular endothelium is intact, but it has little effect on the venous system. The drug reduces arterial blood pressure, improves pulmonary edema, and increases jugular venous oxygen tension (presumably from increased cardiac output) in dogs with MR and heart failure. The most common indication for hydralazine is acute, severe CHF from MR when nitroprusside use is impractical. Hydralazine can cause marked reflex tachycardia. The dosage should be reduced if this occurs. Hydralazine can contribute to the enhanced NH response in patients with heart failure, which makes it less desirable than ACEIs for chronic use.

Hydralazine has a faster onset of action than amlodipine. Its effect peaks within 3 hours and lasts up to 12 hours. Administration of hydralazine with food decreases bioavailability by more than 60%. There also is extensive first-pass hepatic metabolism of this drug. However, increased doses saturate this mechanism and increase bioavailability in dogs. General precautions for initiating and titrating therapy are outlined in the preceding section.

Hypotension is the most common adverse effect of hydralazine therapy. GI upset also can occur, which may require drug discontinuation. High dosages have been associated with a lupus-like syndrome in people, although this has not been reported in animals.

Amlodipine

This dihydropyridine L-type Ca^{++} channel blocker causes peripheral vasodilation as its major action. Amlodipine has little effect on AV conduction. Besides being used to treat hypertension in cats, and sometimes in dogs (see Chapter 11), it is an adjunctive therapy for advanced stage C (and stage D) heart failure. In dogs that cannot tolerate ACEIs, amlodipine could be used in combination with a nitrate.

Amlodipine's oral bioavailability is good. It has a long duration of action (at least 24 hours in dogs). Plasma concentration peaks in 3 to 8 hours; half-life is about 30 hours. Plasma concentrations increase with long-term therapy. Maximal effect develops over 4 to 7 days after therapy is begun in dogs. The drug is metabolized in the liver. Elimination is through the urine and feces. Because of the delay in achieving maximum effect, low initial doses and weekly blood pressure monitoring during up-titration are recommended. An initial dose of 0.05 to 0.1 mg/kg PO q24(-12)h is suggested when used for additional afterload reduction in dogs receiving other heart failure therapy. Chronic administration of amlodipine (for ≥ 5 months) has been associated with development of gingival hyperplasia in a small number of dogs being treated for chronic degenerative valve disease; the hyperplasia appears to resolve after amlodipine discontinuation.

Prazosin

Prazosin selectively blocks α_1-receptors in both arterial and venous walls. It rarely is used for chronic CHF management because drug tolerance develops over time, and the capsule dose size is inconvenient in small animals. Controlled clinical studies in dogs are lacking. Hypotension, especially after the initial dose, is the most common adverse effect. Tachycardia is less likely to occur than with hydralazine because presynaptic α_2-receptors, important in the feedback control of norepinephrine release, are not blocked.

Nitrates

Nitrates act as venodilators (although IV nitroprusside has mixed vasodilator effects; see p. 63). They are metabolized in vascular smooth muscle to produce NO, which indirectly mediates vasodilation. Nitroglycerin ointment or isosorbide dinitrate has been used occasionally in the management of chronic CHF, either combined with standard therapy for refractory CHF or with hydralazine or amlodipine in animals that cannot tolerate ACEIs. Nitrates affect blood redistribution in people, but there are few studies involving dogs, especially using the oral route for CHF management. There is extensive first-pass hepatic metabolism, and the efficacy of oral nitrates is questionable. Nitroglycerin ointment (2%) is applied cutaneously (see p. 63). Self-adhesive,

sustained-release preparations may be useful, but they have not been systematically evaluated in small animals. Transdermal patches (0.2 mg/h [5 mg/24 h] nitroglycerin transdermal system), applied for 12 hours per day, have been used with anecdotal success in large dogs. Large doses, frequent application, or long-acting formulations are most likely to be associated with drug tolerance. Whether intermittent treatment (with drug-free intervals) prevents nitrate tolerance from developing in dogs and cats is unknown. Isosorbide dinitrate and mononitrate are orally administered nitrates. Their efficacy in dogs is unknown. They occasionally have been used in refractory (stage D) heart failure or in combination with an arteriolar dilator for patients unable to tolerate an ACEI.

DIETARY CONSIDERATIONS

A good-quality diet with adequate calories and protein, as well as moderate salt restriction, is recommended for most patients with chronic heart failure. Progressive weight loss can be problematic, especially as heart failure advances, so diet palatability and calorie content are important. Protein restriction is not recommended unless there is concurrent renal disease. Heart failure can interfere with the kidney's ability to excrete sodium and water loads. Therefore moderate dietary salt restriction is recommended to help control fluid accumulation. However, very low salt intake can increase RAAS activation. It is unclear whether reduced-salt intake is necessary before overt CHF develops; however, at minimum, refraining from feeding the patient high-salt table scraps or treats is prudent. High-salt foods include processed meats, canned fish, cheese, canned vegetables and soups, breads, salty processed snack foods, as well as many dog treats.

A moderate degree of salt restriction entails a sodium intake of about 30 mg/kg/day (about 0.06% sodium for canned food or 210-240 mg/100 g of dry food). Although diets for senior animals or those with renal disease usually provide this level of salt, their protein restriction is a drawback for many cases. Supplementing with additional protein (such as hard-boiled eggs or cooked chicken) is a strategy. Other commercial diets that provide reduced-salt, adequate protein, and omega-3 fatty acid (FA) supplementation are available (including Royal Canin Veterinary Diet Canine Early Cardiac, Hill's Prescription Diet j/d, Purina Veterinary Diets JM Joint Mobility, or Purina's CV Cardiovascular Feline Formula); a good source for additional information and updates can be found at www.tufts.edu/vet/heartsmart. Prescription cardiac diets (such as Hill's Prescription Diet h/d) usually have greater sodium restriction (e.g., 13 mg sodium/kg/day, or about 90-100 mg sodium/100 g of dry food, or 0.025% sodium in a canned food), but also can have more protein restriction. Although possibly helpful in managing refractory CHF, an additional protein source may be needed. Severe sodium restriction (e.g., 7 mg/kg/day) can exacerbate NH activation and contribute to hyponatremia. Recipes for homemade low-salt diets are available but providing balanced vitamin and mineral content may be difficult.

Dietary changes are best instituted gradually and when the patient is not in acute CHF; for example, mix the new with the old diet in a 1:3 or 1:4 ratio for several days, then gradually increase the proportion of new diet over a week or so until the new diet alone is being fed. Drinking water in some areas can contain high sodium concentrations. This might become important for animals with end-stage CHF that is difficult to control. Nonsoftened water or (where water from the public water supply contains > 150 ppm of sodium) distilled water can be recommended to further decrease salt intake. Supplementation of specific nutrients is important in some cases (discussed later).

Inappetence is a common problem with advanced heart failure, even though energy needs are increased. Fatigue, increased respiratory effort, azotemia, adverse medication effects (including digoxin toxicity), and low diet palatability all can contribute to poor appetite. At the same time, poor splanchnic perfusion, bowel and pancreatic edema, and secondary intestinal lymphangiectasia may reduce nutrient absorption and promote protein loss in advanced CHF. Hypoalbuminemia and reduced immune function may develop. Such factors, as well as renal or hepatic dysfunction, also can alter the pharmacokinetics of certain drugs.

Strategies that can help improve appetite include warming the food to enhance its flavor, adding small amounts of more palatable human foods (e.g., nonsalted meats or gravy, low-sodium soup) or canned reduced-sodium cat food. Sprinkling on a salt substitute (KCl) or garlic powder, handfeeding, and providing small quantities of the diet several times a day also can help. In some cases, a drug with appetite-stimulating properties (such as mirtazapine or capromorelin, or cyproheptadine for cats) might help, although their effects in patients with CHF are not well reported.

Cardiac cachexia is the syndrome of progressive muscle wasting as well as fat loss associated with advanced chronic CHF. Increased energy requirements, metabolic abnormalities, and reduced food intake are contributing factors. Cardiac cachexia usually is identified only after CHF develops and becomes most evident in cases with more chronic, refractory heart failure. It is seen in dogs more often than cats, especially those with right-sided CHF signs and/or DCM. Muscle loss over the spine and gluteal region usually is noted first. Weakness and fatigue occur with loss of lean body mass; cardiac mass also can be affected. Cardiac cachexia is thought to be a predictor of poor survival. It also is associated with reduced immune function in people. The pathogenesis of cardiac cachexia involves multiple factors, especially proinflammatory cytokines, TNF_{α}, and interleukin-1. These substances suppress appetite and promote hypercatabolism. Dietary supplementation with fish oils, which are high in omega-3 fatty acids (eicosapentaenoic [EPA] and docosahexaenoic [DHA] acids) can reduce cytokine production, may improve endothelial function, and appear to have antiarrhythmic effects, among other benefits. Oral doses of 40 mg/kg/day EPA and 25 mg/kg/day DHA have been suggested. Over-the-counter fish oil capsules containing 180 mg EPA and 120 mg DHA in each 1-g capsule can be used at a

dose of 1 capsule per 10 lb of body weight per day. Several veterinary fish oil supplements also are available. Cod liver oil and flax seed oil are not recommended for omega-3 FA supplementation.

Grossly obese pets with heart disease may benefit from a weight-reducing diet. Obesity increases metabolic demands on the heart and expands blood volume. Mechanical interference with respiration promotes hypoventilation, which could contribute to cor pulmonale and complicate preexisting heart disease. However, animals in heart failure that are mildly overweight, or that gain or maintain their weight, could have a survival advantage.

Taurine

Taurine is an essential nutrient for cats. Prolonged deficiency causes myocardial failure and other abnormalities (see Chapter 8, p. 169). Most commercial and prescription cat foods are well supplemented with taurine, which has markedly reduced the prevalence of taurine-responsive DCM in cats. But taurine concentrations should be measured in cats diagnosed with DCM, because the diet of some cats may still be deficient. Taurine-deficient cats are given oral supplements of taurine (250-500 mg) twice daily.

Some dogs with DCM appear deficient in taurine and/or L-carnitine, most notably American Cocker Spaniels but also others (see Chapter 7, p. 151). Dogs fed protein-restricted or vegetarian diets can become taurine-deficient, and some develop evidence of DCM. Taurine supplementation for dogs less than 25 kg is 500 to 1000 mg every 8 hours; for dogs 25 to 40 kg the dose is 1 to 2 g every 8 to 12 hours. Although not all taurine-deficient American Cocker Spaniels need both taurine and L-carnitine, most appear to.

L-Carnitine

Although L-carnitine deficiency has been identified in Boxers and Doberman Pinschers with DCM, its prevalence is thought to be low, and the number of affected dogs responsive to L-carnitine supplementation even lower. Nevertheless, a trial period of supplementation (at a higher dosage) may be worthwhile. After at least 4 months, reevaluation by echocardiogram is done to assess LV functional improvement. Dogs treated with carnitine supplementation may give off a peculiar odor.

The minimum effective dose of L-carnitine is not known; it may vary with the type of deficiency, if present at all. Several dose ranges have been suggested, including 50 to 100 mg/kg PO every 8 to 12 hours for systemic deficiency or 200 mg/kg every 8 hours for myopathic deficiency. Others use 1 g of oral L-carnitine every 8 hours for dogs less than 25 kg and a dose of 2 g every 12 hours for dogs between 25 and 40 kg. One half teaspoonful of pure L-carnitine powder is the equivalent of 1 g. Both taurine and L-carnitine can be mixed with food for easier administration.

Other Supplements

The role of other dietary supplements is unclear. Oxidative stress and free-radical damage probably play a role in the pathogenesis of myocardial dysfunction. Increased circulating cytokines in heart failure can promote oxidative stress. Although vitamin C supplementation has a beneficial effect on endothelial function, the role of supplemental antioxidant vitamins in animals with CHF is unclear. Coenzyme Q-10 is an antioxidant and co-factor involved in cellular energy production. Whether it provides any measurable benefit is controversial; doses of 30(-90) mg PO q12h have been used in dogs with uncertain effect.

β-Blockers in Patients With Heart Failure

β-blockers must be used cautiously, especially in animals with myocardial failure, because of their negative inotropic effect. Their main role is in the management of certain arrhythmias, such as AF and sometimes ventricular tachyarrhythmias (see Chapter 4). Although in people with heart failure, chronic use of some β-blockers can improve cardiac function and reduce pathologic ventricular remodeling and mortality, a similar clinical benefit of chronic low-dose β-blocker therapy has not been proven in dogs or cats. Currently, β-blockers are not recommended as part of routine combination therapy for chronic heart failure, unless indicated for cardiac rhythm or rate control. Careful monitoring is important because CHF decompensation, bradycardia, and hypotension can occur, necessitating β-blocker dosage reduction or discontinuation.

CHRONIC DIASTOLIC DYSFUNCTION

Furosemide is continued orally in patients with CHF from HCM and other causes of diastolic dysfunction. Gradual reduction to the lowest dosage and frequency effective for controlling edema is the aim. An ACEI is thought to be beneficial in most cases and is instituted during the transition to chronic therapy, if not before. Antiplatelet therapy is recommended for cats (see Chapter 12). Some cats appear to benefit from pimobendan, especially those with advanced disease or reduced systolic function (see previous discussion). Spironolactone also can be useful as adjunct therapy, especially for cases with recurrent pleural effusion. Diltiazem or a β-blocker is not recommended routinely for most cats with CHF from HCM, because efficacy has not been established and their long-term effect is questionable. However, one or the other of these agents may be indicated for antiarrhythmic therapy (see Chapter 4). The use of ivabradine (a "funny" current [I_f] inhibitor) for heart rate control could prove helpful in the future by improving diastolic filling time; clinical experience is needed to guide specific recommendations.

REEVALUATION AND MONITORING

Client education is important for the long-term management of chronic heart failure. A good understanding of the patient's underlying disease, the signs of heart failure, and the purpose and potential adverse effects of each medication make compliance and early identification of complications more likely. Home monitoring of the patient's resting (ideally, sleeping) respiratory rate is hugely helpful for monitoring control of

pulmonary edema in animals with chronic heart failure. Even before the initial onset of CHF, when the patient still has stage B disease, the authors recommend that clients assess the RRR to become comfortable with the technique and to establish the animal's baseline RRR (see Box 3.2). RRRs for normal animals in the home environment usually are 30 breaths/min or less. A persistent increase (of ≥ 20%) above the patient's normal baseline RRR often is the earliest sign of decompensating heart failure. RRRs above 40 breaths/min typically accompany clinical pulmonary edema. This is because pulmonary edema increases lung stiffness; faster, more shallow respirations reduce the work of ventilating stiffer lungs. It is more difficult to monitor heart rate without disturbing the animal's rest or sleep. However, in cases where this can be done, a persistent increase in resting heart rate usually accompanies the heightened sympathetic tone of decompensating CHF.

In addition to home monitoring, periodic recheck examinations are important because complications often develop. The time frame for recheck visits may vary from a few days to every 4 months or so, depending on heart disease severity and patient stability. All medications and their dosage schedules should be reviewed at each visit. Ask the owner about the patient's RRR, diet, appetite level, activity and stamina, whether there are any problems with administering the medications or if refills are needed, and any other concerns.

A thorough physical examination (see Chapter 1) is important at each evaluation. Depending on the patient's status, additional clinical tests might include blood pressure measurement, thoracic radiographs, serum biochemistry analyses, resting or ambulatory ECG recording, an echocardiogram, or other tests. Measurement of serum electrolyte and creatinine or blood urea nitrogen (BUN) concentrations is usually done at each recheck visit. Electrolyte imbalance (especially hypokalemia or hyperkalemia, hypomagnesemia, and sometimes hyponatremia) can occur from the use of diuretics, ACEIs, and salt restriction. Poor appetite as well as loop diuretics can promote hypokalemia; however, potassium supplements should not be used without documenting hypokalemia, especially when an ACEI and spironolactone are prescribed. Serum magnesium concentration does not accurately reflect total body stores; however, supplementation may be especially beneficial in animals that develop ventricular arrhythmias while receiving furosemide and digoxin. Hyponatremia in patients with severe CHF results from an inability to excrete free water (dilutional hyponatremia) rather than from a total body sodium deficit. It can be difficult to correct and is considered a poor prognostic sign. In some cases, reducing the furosemide and/or other diuretic dose, cautiously adding/increasing an arteriolar vasodilator (to improve renal perfusion), or increasing inotropic support (with higher pimobendan dose or addition of another inotrope) might improve serum Na^+ concentration. However, vigilant monitoring is necessary to avoid worsened congestion, hypotension, and other potential adverse effects.

Many factors can exacerbate the signs of heart failure, including physical exertion, infection, anemia, exogenous fluid administration (excess volume or sodium load), high-salt diet or dietary indiscretion, erratic administration of medication, inappropriate medication dosage for the level of disease, development of cardiac arrhythmias, environmental stress (such as heat, humidity, cold, smoke), development or worsening of concurrent extracardiac disease, and progression of underlying heart disease (including ruptured chordae tendineae, secondary pulmonary hypertension and right heart failure, and LA tear). Repeated episodes of acute, decompensated congestive failure that sometimes require hospitalization and intensive diuresis are relatively common in patients with chronic progressive heart failure.



BOX 3.2

Owner Instructions for Monitoring Resting Respiratory Rate

While your pet is quietly sleeping (or almost sleeping) and without touching or disturbing him/her, count the number of breaths taken during a period of 15 seconds. (You can usually determine this by watching the chest move in and out.)

Multiply this number by 4 to obtain the breaths per minute.

Keep track of this number by recording it in a calendar or logbook, or with a respiratory rate monitoring phone app.

Most dogs and cats with normal lungs have an RRR of <30 breaths/min; some are <20/min.

Once you have determined your pet's normal baseline RRR, continue to monitor the RRR periodically.

If this number becomes persistently increased by more than 20% above his/her normal baseline (and especially if the RRR increases >40 breaths/min), this may be an early indicator of congestion (fluid) in the lungs and you should contact your veterinarian.

STRATEGIES FOR RECURRENT OR REFRACTORY CONGESTIVE HEART FAILURE

It is important to confirm that the standard stage C heart failure therapies are being appropriately administered to patients that develop recurrent, decompensated CHF. For dogs, especially those with chronic MR or DCM, this involves furosemide (at approximately 2 mg/kg q12 or 8 h), combined with pimobendan (at 0.2-0.3 mg/kg q12h) and an ACEI (usually enalapril or benazepril, at 0.5 mg/kg q12h); spironolactone (2 mg/kg q24h) usually is included here as well. Recurrent episodes of CHF often respond initially to an increased dose of furosemide and/or pimobendan (to q8h ±increased dosage, see following text). Renal function and electrolytes should be assessed; ultimately, increases in furosemide dosage are limited mainly by kidney function. If the ACEI has been dosed only once daily, it is increased to every 12 hours, unless this is not tolerated. If spironolactone is not already being administered, it should be added. Arrhythmias commonly develop in animals with advanced heart failure

and can precipitate congestive signs. It is important to characterize the type and severity of the arrhythmia to guide treatment. Effective antiarrhythmic therapy can help control CHF signs. For AF, therapy is adjusted to maintain a heart rate of <140 or 150 beats/min in the hospital, or between 80 and 110 beats/min at home, (for example, by a gradual increase in diltiazem dosage, and using serum digoxin concentration measurement to optimize digoxin dose; see Chapter 4 for additional information). Referral to a veterinary cardiologist, or internist with extensive experience managing CHF, is encouraged and appropriate for patients with advanced cardiac disease and CHF. Specialty consultation can help further characterize the patient's cardiac status and any complicating factors, optimize therapy, and provide support with ongoing patient care.

Refractory, stage D, heart failure is considered to be present when the patient requires over 8-12 mg/kg/day of furosemide to control edema, despite other standard heart failure therapy previously outlined. Acute pulmonary edema requiring hospitalization is managed as outlined in Box 3.1. Additional strategies for chronic CHF management are described here; they usually are instituted one at a time (not necessarily in the order presented) so that effectiveness can be evaluated. As always, therapy must be tailored for the individual patient's needs. Additional afterload reduction (amlodipine or hydralazine) can be helpful for dogs with MR and sometimes DCM; start with low doses and gradually titrate the dose upward as needed, while monitoring blood pressure. An arteriolar vasodilator is not recommended for cats with HCM or dogs with fixed ventricular outflow obstruction (e.g., subaortic stenosis). Pimobendan dosing frequency can be increased to every 8 hours, or dosage raised up to 0.4 to 0.5 mg/dose. For most cats with refractory CHF, pimobendan can be added to therapy or its dosage increased. For dogs with severe pulmonary hypertension and collapse episodes or right-sided CHF signs, addition of sildenafil (1-2 mg/kg q12h PO) can reduce clinical signs. Modification of diuretic therapy can be helpful for dogs that require very high furosemide doses. Torsemide can be used instead of furosemide, beginning at a total daily dose (mg) that is $\frac{1}{12}$ to $\frac{1}{10}$ of the total furosemide dose being given per day. An alternate strategy, if torsemide is not used, is the addition of a third diuretic (thiazide) to furosemide and spironolactone; however, very conservative dosing and close attention to renal function and electrolytes are necessary because severe derangements can develop quickly. Digoxin, if not previously used and not contraindicated, might be useful for additional inotropic support and its baroreceptor sensitizing effect. More stringent dietary salt restriction can be tried; however, it is important to support the patient's appetite and food intake. Dogs without pulmonary edema that persistently have a dry cough associated with bronchomalacia and/or main bronchus compression from marked LA enlargement often benefit from a cough suppressant. For dogs with concurrent airway disease, a bronchodilator also might be helpful as long as it does not provoke tachyarrhythmias.

Suggested Readings

Pathophysiology of Heart Failure

Cunningham SM, Rush JE, Freeman LM. Systemic inflammation and endothelial dysfunction in dogs with congestive heart failure. *J Vet Intern Med*. 2012;26:547–557.

Freeman LM, et al. Antioxidant status and biomarkers of oxidative stress in dogs with congestive heart failure. *J Vet Intern Med*. 2005;19:537–541.

Mochel JP, Danhof M. Chronobiology and pharmacologic modulation of the renin-angiotensin-aldosterone system in dogs: what have we learned? *Rev Physiol Biochem Pharmacol*. 2015;169: 43–69.

Scollan KF, Sisson DD. Pathophysiology of heart failure. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of veterinary internal medicine*. 8th ed. St. Louis: Elsevier; 2017:1153–1163.

Spratt DP, et al. Cardiac troponin I: evaluation of a biomarker for the diagnosis of heart disease in the dog. *J Small Anim Pract*. 2005;46:139–145.

Tidholm A, Haggstrom J, Hansson K. Vasopressin, cortisol, and catecholamine concentrations in dogs with dilated cardiomyopathy. *Am J Vet Res*. 2005;66:1709–1717.

Therapy of Heart Failure

Adin DB, et al. Intermittent bolus injection versus continuous infusion of furosemide in normal adult greyhound dogs. *J Vet Intern Med*. 2003;17:632–636.

Atkins C, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease. (ACVIM Consensus Statement). *J Vet Intern Med*. 2009;23:1142–1150.

Atkins CE, et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. *J Am Vet Med Assoc*. 2007;231:1061–1069.

Bernay F, et al. Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. *J Vet Intern Med*. 2010;24:331–341.

Bonagura JB, Lehmkuhl LB, de Morais HA. Fluid and diuretic therapy in heart failure. In: DiBartola SP, eds. *Fluid, electrolyte, and acid-base disorders in small animal practice*. 4th ed. St Louis: Elsevier Saunders; 2012:514.

Boswood A, et al. Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study—a randomized clinical trial. *J Vet Intern Med*. 2016;30: 1765–1779.

Boyle KL, Leech E. A review of the pharmacology and clinical uses of pimobendan. *J Vet Emerg Crit Care*. 2012;22:398–408.

Chetboul V, et al. Comparative adverse cardiac effects of pimobendan and benazepril monotherapy in dogs with mild degenerative mitral valve disease: a prospective, controlled, blinded, and randomized study. *J Vet Intern Med*. 2007;21:742–753.

Edwards TH, et al. Outcome of positive-pressure ventilation in dogs and cats with congestive heart failure: 16 cases (1992-2012). *J Vet Emerg Crit Care*. 2014;24:586–593.

Esposito CT, et al. Spironolactone improves the arrhythmogenic substrate in heart failure by preventing ventricular electrical activation delays associated with myocardial interstitial fibrosis and inflammation. *J Cardiovasc Electrophysiol*. 2013;24: 806–812.

Freeman LM. Cachexia and sarcopenia: emerging syndromes of importance in dogs and cats. *J Vet Intern Med*. 2012;26:3–17.

Freeman LM. Beneficial effects of omega-3 fatty acids in cardiovascular disease. *J Small Anim Pract*. 2010;51:462–470.

Freeman LM, Rush JE. Nutritional management of heart disease. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of veterinary internal medicine*. 8th ed. St. Louis: Elsevier; 2017:764–771.

Goutal CM, et al. Evaluation of acute congestive heart failure in dogs and cats: 145 cases (2007-2008). *J Vet Emerg Crit Care*. 2010;20:330–337.

Haggstrom J, et al. Short-term hemodynamic and neuroendocrine effects of pimobendan and benazapril in dogs with myxomatous mitral valve disease and congestive heart failure. *J Vet Intern Med*. 2013;27:1452–1462.

Haggstrom J, et al. Longitudinal analysis of quality of life, clinical, radiographic, echocardiographic, and laboratory variables in dogs with myxomatous mitral valve disease receiving pimobendan or benazepril: the QUEST study. *J Vet Intern Med*. 2013;27:1441–1451.

Haggstrom J, et al. Effect of pimobendan or benazepril HCl on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. *J Vet Intern Med*. 2008;22:1124–1135.

Helms SR, et al. Compounded pimobendan for canine chronic degenerative mitral valve disease and pulmonary hypertension. *Int J Pharm Compd*. 2012;16:34–41.

Hopper K, et al. Indications, management, and outcome of long-term positive-pressure ventilation in dogs and cats: 148 cases (1990-2001). *J Am Vet Med Assoc*. 2007;230:64–75.

Kvart C, et al. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation. *J Vet Intern Med*. 2002;16:80–88.

Lake-Bakaar GA, et al. Effect of pimobendan on the incidence of arrhythmias in small breed dogs with myxomatous mitral valve degeneration. *J Vet Cardiol*. 2015;17:120–128.

Lefebvre HP, et al. Safety of spironolactone in dogs with chronic heart failure because of degenerative valvular disease: a population-based, longitudinal study. *J Vet Intern Med*. 2013;27:1083–1091.

Lefebvre HP, et al. Angiotensin-converting enzyme inhibitors in veterinary medicine. *Curr Pharm Des*. 2007;13:1347–1361.

Lombarde CW, Jöns O, Bussadori CM. Clinical efficacy of pimobendan versus benazepril for the treatment of acquired atrioventricular valvular disease in dogs. *J Am Anim Hosp Assoc*. 2006;42:249–261.

O'Grady MR, et al. Efficacy of pimobendan on case fatality rate in Doberman Pinschers with congestive heart failure caused by dilated cardiomyopathy. *J Vet Intern Med*. 2008;22:897–904.

O'Grady MR, et al. Efficacy of benazepril hydrochloride to delay the progression of occult dilated cardiomyopathy in Doberman Pinschers. *J Vet Intern Med*. 2009;23:977–983.

Ohad DG, et al. Sleeping and resting respiratory rates in dogs with subclinical heart disease. *J Am Vet Med Assoc*. 2013;243:839–843.

Oyama MA, et al. Use of the loop diuretic torsemide in three dogs with advanced heart failure. *J Vet Cardiol*. 2011;13:287–292.

Oyama MA, et al. Perceptions and priorities of owners of dogs with heart disease regarding quality versus quantity of life for their pets. *J Am Vet Med Assoc*. 2008;233:104–108.

Peddle GD, et al. Effect of torsemide and furosemide on clinical, laboratory, radiographic and quality of life variables in dogs with heart failure secondary to mitral valve disease. *J Vet Cardiol*. 2012;14:253–259.

Porciello F, et al. Sleeping and resting respiratory rates in dogs and cats with medically-controlled left-sided congestive heart failure. *Vet J*. 2016;207:164–168.

Rush JE, et al. Clinical, echocardiographic and neurohormonal effects of a sodium-restricted diet in dogs with heart failure. *J Vet Intern Med*. 2000;14:512–520.

Schober KE, et al. Effects of treatment on respiratory rate, serum natriuretic peptide concentration, and Doppler echocardiographic indices of left ventricular filling pressure in dogs with congestive heart failure secondary to degenerative mitral valve disease and dilated cardiomyopathy. *J Am Vet Med Assoc*. 2011;239:468–479.

Schuller S, et al. Lack of efficacy of low-dose spironolactone as adjunct treatment to conventional congestive heart failure treatment in dogs. *J Vet Pharmacol Ther*. 2011;34:322–331.

Slupe JL, Freeman LM, Rush JE. Association of body weight and body condition with survival in dogs with heart failure. *J Vet Intern Med*. 2008;22:561–565.

Smith PJ, et al. Efficacy and safety of pimobendan in canine heart failure caused by myxomatous mitral valve disease. *J Small Anim Pract*. 2005;46:121–130.

Summerfield NJ, et al. Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with preclinical dilated cardiomyopathy (the PROTECT Study). *J Vet Intern Med*. 2012;26:1337–1349.

Suzuki S, et al. The effect of furosemide on left atrial pressure in dogs with mitral valve regurgitation. *J Vet Intern Med*. 2011;25:244–250.

Thomason JD, et al. The influence of enalapril and spironolactone on electrolyte concentrations in Doberman pinschers with dilated cardiomyopathy. *Vet J*. 2014;202:573–577.

Thomason JD, et al. Gingival hyperplasia associated with the administration of amlodipine to dogs with degenerative valvular disease (2004-2008). *J Vet Intern Med*. 2009;23:39–42.

Vollmar AC, Fox PR. Long-term outcome of Irish Wolfhound dogs with preclinical cardiomyopathy, atrial fibrillation, or both treated with pimobendan, benazepril hydrochloride, or methyldigoxin monotherapy. *J Vet Intern Med*. 2016;30:553–559.

Ward DM, et al. Treatment of severe chronic digoxin toxicosis in a dog with cardiac disease, using ovine digoxin-specific immunoglobulin G Fab fragments. *J Am Vet Med Assoc*. 1999;215:1808–1812.

CHAPTER 4

Cardiac Arrhythmias and Antiarrhythmic Therapy



GENERAL CONSIDERATIONS

Cardiac arrhythmias occur for many reasons. Although some arrhythmias are of no clinical consequence, others cause serious hemodynamic compromise and sudden death, especially in animals with underlying heart disease. It is important to make an accurate electrocardiographic diagnosis, as well as to consider the arrhythmia's clinical context, before deciding whether to use antiarrhythmic therapy. For example, the risk of death associated with ventricular tachyarrhythmias is higher in people when myocardial function is impaired. Dogs with cardiomyopathy also are known to have increased risk for sudden death, especially Doberman Pinschers and Boxers. In addition, an inherited disorder predisposing to sudden death has been identified in young German Shepherds. On the other hand, the ventricular premature activity that occurs commonly after thoracic trauma or splenectomy in previously healthy animals (see p. 41) usually is benign and resolves without therapy.

Occasional ventricular premature complexes (VPCs) occur without consequence in many animals. However, arrhythmias that compromise cardiac output and coronary perfusion promote myocardial ischemia, hypotension, reduced cardiac pump function, and sometimes sudden death. These arrhythmias tend to be either quite rapid (such as sustained ventricular or supraventricular tachyarrhythmias) or slow (such as advanced atrioventricular [AV] block with a slow or unstable ventricular escape rhythm). Sometimes, however, a lethal arrhythmia such as ventricular fibrillation (VF) occurs without an antecedent sustained arrhythmia. Sustained tachycardia of either supraventricular or ventricular origin reduces cardiac output acutely, and eventually (within weeks) it leads to myocardial dysfunction and congestive heart failure (CHF).

DEVELOPMENT OF ARRHYTHMIAS

Multiple factors underlie cardiac rhythm disturbances. Abnormalities of conduction or automaticity caused by cardiac structural or pathophysiologic remodeling can predispose to arrhythmias, even in the absence of overt cardiac disease. Genetic factors and environmental stresses contribute to this. However, additional triggering (such as a premature stimulus or abrupt change in heart rate) and/or modulating factors (such as changes in autonomic tone, circulating catecholamines, ischemia, or electrolyte disturbances) are thought to be necessary to provoke and sustain a rhythm disturbance. For example, episodes of anger or aggressive behavior have been linked to increased susceptibility to ischemic arrhythmias and sudden arrhythmic death in both dogs and people. Various stresses that lead to abnormal cardiac remodeling also could play a role in arrhythmia development. Remodeling can involve myocyte hypertrophy, changes in the structure or function of ion channels, tissue fibrosis, and other changes related to neurohormonal activity, cytokines, and other signaling systems (see Chapter 3). Although some of these changes act as positive compensatory mechanisms in the short term, they can have harmful and arrhythmogenic long-term effects. It is thought that if such underlying arrhythmogenic modulators could be controlled or reduced, arrhythmias would be lessened. The higher survival in human heart failure patients treated with angiotensin-converting enzyme inhibitors (ACEI), spironolactone, and some β-blockers supports this concept. There is similar evidence for ACEIs in dogs with dilated cardiomyopathy (DCM) and reason to suspect that other therapies might be beneficial as well.

APPROACH TO ARRHYTHMIA MANAGEMENT

Specific antiarrhythmic drug therapy may or may not be warranted in an individual patient (see guidelines later). If antiarrhythmic therapy is pursued, it should be with defined goals in mind. For example, usually an immediate goal is to restore hemodynamic stability. Although ideal goals might include conversion to sinus rhythm, correction of underlying cause, and prevention of further arrhythmia and sudden death, suppression of all abnormal beats generally is not a realistic goal. Successful therapy could mean sufficient reduction in frequency (e.g., by ≥70%-80%) or repetitive rate of ectopic beats to eliminate clinical signs. It must be

recognized, however, that even with apparently complete conversion to sinus rhythm, the risk of sudden death from a lethal arrhythmia may remain. It is also important to remember that all antiarrhythmic drugs can have adverse effects, including provoking additional arrhythmias (proarrhythmic effect).

Various arrhythmias and their electrocardiographic characteristics are described in Chapter 2. This section provides a general approach to managing cardiac rhythm disturbances. Nevertheless, much remains to be learned about effective arrhythmia management and the prevention of sudden death.

1. Record and interpret an electrocardiogram (ECG) (Box 4.1); identify and define any arrhythmia. An extended ECG recording period may be necessary (e.g., Holter or event monitoring or extended in-hospital monitoring).
2. Evaluate the whole patient, including history, physical examination findings, and clinical/laboratory test results. Are signs of hemodynamic impairment evident (e.g., episodic weakness, syncope, signs of CHF)? Are other signs of cardiac disease present (e.g., heart murmur, cardiomegaly)? Are there additional abnormalities (e.g., fever, abnormal blood chemistry or hemogram values, respiratory compromise with hypoxia, other extracardiac disease, trauma, or pain)? Is the animal receiving any medications? Correct what can be corrected!
3. Decide whether to use antiarrhythmic drug therapy. Consider signalment, history, clinical signs, and underlying disease, as well as the potential benefits/risks of the drug(s) under consideration.
4. If an antiarrhythmic drug is to be used, define the goals of therapy for this patient.
5. Initiate treatment and determine drug effectiveness. Adjust dose or try alternate agents, if needed.
6. Monitor patient status. Assess arrhythmia control (consider repeated Holter monitoring), manage underlying disease(s), and watch for adverse drug effects and other complications.



BOX 4.1

ECG Interpretation Guide

1. Determine the heart rate. Is it too fast, too slow, or normal?
2. Is the rhythm regular or irregular?
3. Is sinus rhythm present (with or without other abnormalities), or are there no consistent P-QRS-T relationships?
4. Are all P waves followed by a QRS and all QRS complexes preceded by a P wave?
5. If premature (early) complexes are present, do they look the same as sinus QRS complexes (implying atrial or junctional [supraventricular] origin), or are they wide and of different configuration than sinus complexes (implying a ventricular origin [or possibly abnormal ventricular conduction of a supraventricular complex])?
6. Are premature QRS complexes preceded by an abnormal P wave (suggesting atrial origin)?
7. Are there baseline undulations instead of clear and consistent P waves, with a rapid, irregular QRS occurrence (compatible with atrial fibrillation)?
8. Are there long pauses in the underlying rhythm before an abnormal complex occurs (escape beat)?
9. Is an intermittent AV conduction disturbance present?
10. Is there a lack of consistent temporal relationship between P waves and QRS complexes, with a slow and regular QRS occurrence (implying complete AV block with escape rhythm)?
11. For sinus and supraventricular complexes, is the mean electrical axis normal?
12. Are all measurements and waveform durations within normal limits?

See Chapter 2 for more specific information.

DIAGNOSIS AND MANAGEMENT OF COMMON ARRHYTHMIAS

Cardiac arrhythmias in a given animal often occur inconsistently and are influenced by drug therapy, prevailing autonomic tone, baroreceptor reflexes, and variations in heart rate. Treatment decisions are based on consideration of the origin (supraventricular or ventricular), timing (premature or escape), and severity of the rhythm disturbance, as well as the clinical context. Accurate ECG interpretation is important. Although a routine (resting) ECG documents arrhythmias present during the recording period, it provides only a glimpse of the cardiac rhythm occurring over time. Because marked variation in frequency and severity of arrhythmias can occur over time, potentially critical arrhythmias are easy to miss. For this reason, Holter (or other ambulatory ECG) monitoring can be useful in assessing the severity and frequency of arrhythmias and monitoring treatment efficacy. Some rhythm abnormalities do not require therapy, whereas others demand immediate aggressive treatment. Close patient monitoring is especially important in patients with more serious arrhythmias.

Supraventricular tachyarrhythmias occur from various mechanisms, including reentry involving the AV node, accessory pathways, or sinoatrial (SA) node, as well as abnormal automaticity within atrial or junctional tissue. Many patients have atrial enlargement. Common underlying heart diseases include chronic mitral or tricuspid valve degeneration with regurgitation, DCM, congenital malformations, and cardiac neoplasia. Other factors also may predispose to atrial tachyarrhythmias (Box 4.2).

VPCs occur with disorders that affect cardiac tissue directly or indirectly through neurohormonal effects (see Box 4.2). For instance, disorders of the central nervous system (CNS) can produce abnormal autonomic neural effects in the heart, and provoke ventricular or supraventricular arrhythmias (brain-heart syndrome). When VPCs

BOX 4.2

Factors Predisposing to Arrhythmias

Atrial Arrhythmias

Cardiac

Mitral or tricuspid insufficiency
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Cardiac neoplasia
Congenital malformation
Accessory AV nodal bypass tract(s)
Myocardial fibrosis
High sympathetic tone
Ischemia
Intra-atrial catheter placement

Extracardiac

Catecholamines
Electrolyte imbalances
Digoxin toxicity
Other drugs (anesthetic agents, bronchodilators)
Acidosis/alkalosis
Hypoxia
Thyrotoxicosis
Severe anemia
Electric shock
Thoracic surgery

Ventricular Arrhythmias

Cardiac

Congestive heart failure
Cardiomyopathy (especially Doberman Pinschers and Boxers)
Myocarditis
Pericarditis
Degenerative valvular disease with myocardial fibrosis
Ischemia
Trauma
Cardiac neoplasia
Heartworm disease
Congenital heart disease
Ventricular dilation
Mechanical stimulation (intracardiac catheter, pacing wire)

Extracardiac

Hypoxia
Electrolyte imbalances (especially K^+)
Acidosis/alkalosis
Thyrotoxicosis
Hypothermia
Fever
Sepsis/toxemia
Trauma (thoracic or abdominal)
Gastric dilation/volvulus
Splenic mass or splenectomy
Hemangiosarcoma
Pulmonary disease
Uremia
Pancreatitis
Pheochromocytoma
Other endocrine diseases (diabetes mellitus, Addison disease, hypothyroidism)
High sympathetic tone (pain, anxiety, fever)
Central nervous system disease (increases in sympathetic or vagal stimulation)
Electric shock
Drugs (digoxin, sympathomimetics, anesthetics, tranquilizers, anticholinergics, antiarrhythmics)

are infrequent or underlying cardiac function is normal, adverse hemodynamic effects may be negligible. However, hemodynamic impairment can be severe in dogs or cats with underlying heart disease, rapid ventricular rates, or myocardial depression stemming from a systemic disease.

Factors such as underlying hypoxia, electrolyte or acid-base imbalances, and abnormal hormone concentrations (e.g., hyperthyroidism) can exacerbate arrhythmias. Therefore, correcting these improves arrhythmia control. Because some drugs can provoke arrhythmias, reducing dosage or discontinuing the medication may be necessary.

CLINICAL PRESENTATION

Box 4.3 lists common arrhythmias according to a clinical description of the heartbeat.

TACHYARRHYTHMIAS

Rapid Irregular Rhythms

Irregular heart rhythms are common. The ECG is important for differentiating abnormal rhythms and sinus arrhythmia. Pulse deficits (see p. 6) and an irregular, weak pulse with heart sounds of varying intensity and regularity may be detected on physical examination. Premature contractions interrupt ventricular filling and reduce stroke volume, sometimes to the extent that there is no ejection at all for that cycle (Fig. 4.1). Rapid atrial fibrillation (AF) and premature contractions of any origin often cause such pulse deficits. VPCs can cause audible splitting of the heart sounds because of asynchronous ventricular activation. Ventricular and supraventricular tachycardias (SVTs) and AF cause more severe hemodynamic compromise than do isolated premature contractions, especially in patients with underlying heart disease.

Rapid Regular Rhythms

Rapid regular rhythms include sinus tachycardia, sustained SVT, and sustained ventricular tachycardia. Sinus tachycardia is caused by high sympathetic tone or drug-induced vagal blockade. Underlying factors include anxiety, pain, fever, thyrotoxicosis, heart failure, hypotension, shock, the

BOX 4.3

Clinical Characterization of Common Heart Rate and Rhythm Disturbances

Fast, Irregular Rhythms

Atrial or supraventricular premature contractions
Paroxysmal atrial or supraventricular tachycardia
Atrial flutter or fibrillation
Ventricular premature contractions
Paroxysmal ventricular tachycardia

Fast, Regular Rhythms

Sinus tachycardia
Sustained supraventricular tachycardia
Sustained ventricular tachycardia

Slow, Irregular Rhythms

Sinus bradyarrhythmia
Sinus arrest
Sick sinus syndrome
High-grade second-degree AV block

Slow, Regular Rhythms

Sinus bradycardia
Complete (third-degree) AV block with ventricular escape rhythm
Atrial standstill with ventricular escape rhythm

AV, Atrioventricular.

ingestion of stimulants or toxins (e.g., chocolate, caffeine), or drugs (e.g., catecholamines, anticholinergics, theophylline, and related agents). The heart rate in dogs and cats with sinus tachycardia usually is well under 300 beats/min, although it could be higher in those with thyrotoxicosis or in those (particularly cats) that have ingested exogenous stimulants or drugs. Alleviation of the underlying cause and intravenous (IV) fluid administration to reverse hypotension (in animals without edema) should cause sympathetic tone and sinus rate to decrease.

SVT of varying causes can be difficult to differentiate from sinus tachycardia. The heart rate with SVT may be greater than 300 beats/min, but it is uncommon for the sinus rate to be this rapid. Patients with SVTs usually have a normal QRS configuration (narrow and upright in lead II). However, if an intraventricular conduction disturbance is present, SVT may resemble ventricular tachycardia. A vagal maneuver (see p. 82) can be useful in differentiating among narrow QRS complex tachycardias.

Sustained, rapid arrhythmias lead to decreases in cardiac output, arterial blood pressure, and coronary perfusion. CHF eventually may result. Signs of poor cardiac output and hypotension include weakness, depression, pallor, prolonged capillary refill time, exercise intolerance, syncope, dyspnea, prerenal azotemia, worsening rhythm disturbances, and sometimes altered mentation, seizure activity, and sudden death.

Supraventricular Tachyarrhythmias

Occasional premature beats do not require specific therapy. Factors that predispose to these arrhythmias should be minimized as possible (e.g., discontinue or reduce dosage of predisposing drugs, manage heart failure if present, and treat metabolic or endocrine abnormalities).

Oral therapy for frequent supraventricular premature beats or paroxysmal tachycardia

Initial oral therapy for frequent atrial premature complexes (APCs) or paroxysmal SVT can involve either diltiazem, digoxin, a β-blocker, or a combination of these (Fig. 4.2). For patients with CHF, if the arrhythmia is not sufficiently controlled with diltiazem (or digoxin), along with other therapy indicated for heart failure, the combination of diltiazem with digoxin (or a β-blocker with digoxin) may be effective. Cats with hypertrophic cardiomyopathy (HCM) or hyperthyroidism usually are treated with a β-blocker such as atenolol, although diltiazem could be an alternative. Refractory, frequent supraventricular tachyarrhythmias may respond to amiodarone, sotalol, procainamide, or propafenone.

Acute therapy for supraventricular tachycardia

More aggressive therapy is warranted for rapid, sustained supraventricular tachyarrhythmias because of the hemodynamic impairment caused. A vagal maneuver can be tried initially (see p. 82). IV access is secured, and fluid administered to maintain blood pressure and enhance endogenous vagal tone. However, caution is necessary. Patients with known or suspected heart failure generally should not receive IV fluid or should receive only a small volume administered slowly. If a vagal maneuver does not terminate the arrhythmia, diltiazem IV (or oral loading) is a good first-choice agent. However, it has a negative inotropic effect, so low doses and slow administration are important when used IV, especially in patents with suspected DCM. A slowly administered IV β-blocker (such as esmolol or propranolol) is an alternative therapy but also has negative inotropic effects. Occasional cases of reentrant SVT or automatic atrial tachycardia respond to IV lidocaine, which may be worth trying given this drug's relative safety. Other strategies in refractory cases include IV amiodarone, oral sotalol, or a class IA or IC drug. Oral digoxin often is less effective than diltiazem but might be useful in some cases. Digoxin has a slower onset of action, and it increases vagal tone. IV digoxin is not recommended, as it also can increase central sympathetic output. Adenosine has been ineffective for terminating SVTs in dogs. Further cardiac diagnostic tests are indicated once conversion is achieved or the ventricular rate has decreased to fewer than 200 beats/min. Options for longer-term oral therapy to control recurrence include diltiazem, amiodarone, a β-blocker, digoxin, or propafenone; combination therapy may be necessary.

Paroxysmal AV reciprocating tachycardia (AVRT) is a reentrant tachycardia involving an accessory pathway and the AV node (see p. 44). It is interrupted by slowing conduction or prolonging the refractory period of either or both tissues. A vagal maneuver may slow AV conduction enough to terminate the rhythm. Diltiazem and β-blockers slow AV

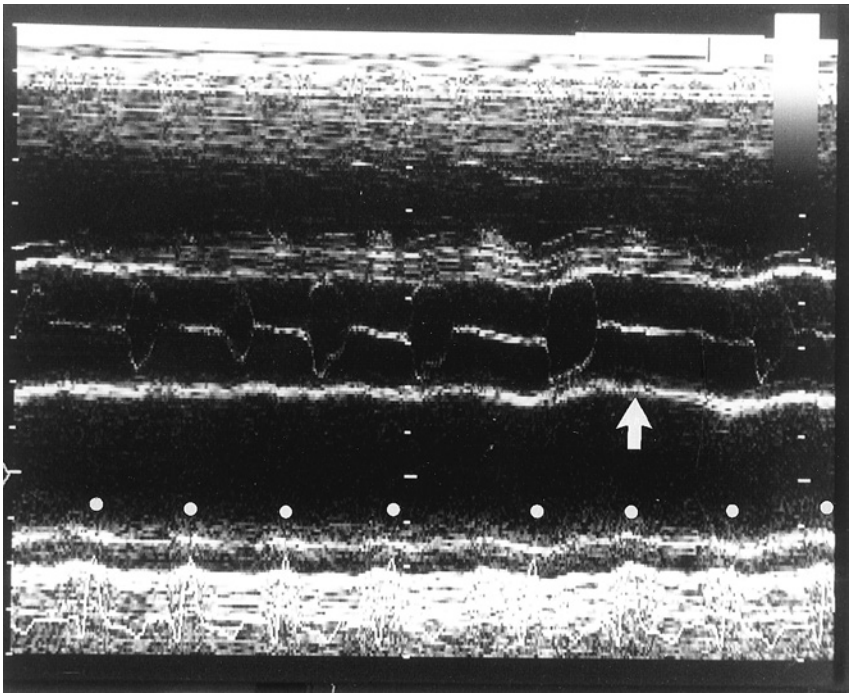


FIG 4.1
M-mode echocardiogram at the aortic root level in a Doberman Pinscher with dilated cardiomyopathy atrial fibrillation (AF) illustrates variable (or absent) opening of the aortic valve; this is caused by the AF-induced variation in ventricular filling leading to irregularly reduced stroke volume. Variable-intensity pulses and pulse deficits result. The motion of two aortic valve leaflets is seen within the parallel aortic root echoes. Irregular and abbreviated aortic valve opening occurs after most QRS complexes (indicated by white dots), but the aortic valve does not open at all after the sixth QRS complex from the left *(arrow)*.

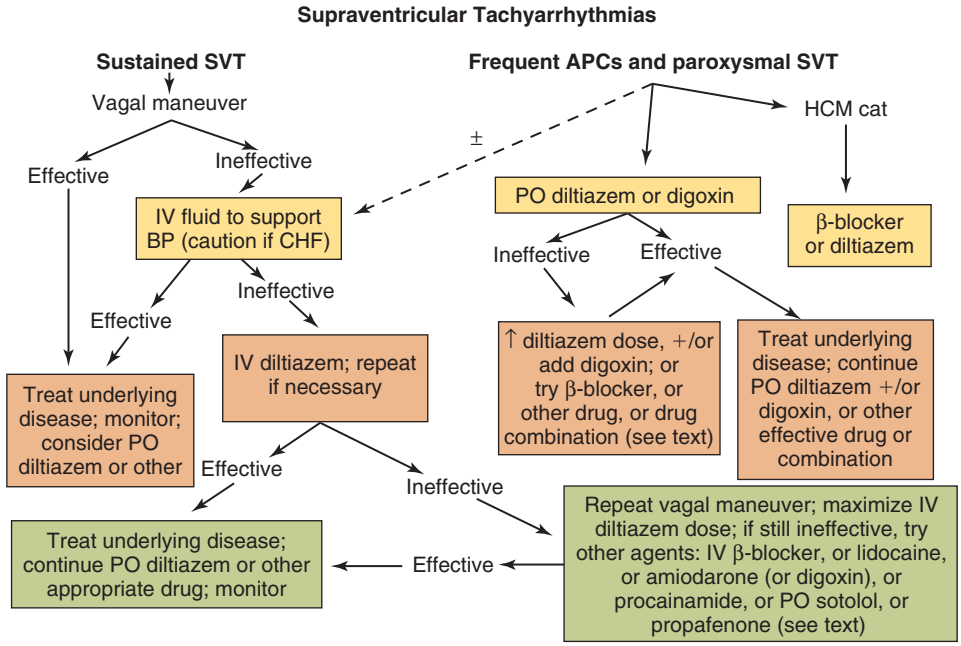


FIG 4.2
A therapeutic approach to supraventricular tachyarrhythmias. See Table 4.2 for drug doses and text for more information. *APCs,* Atrial premature complexes; *BP,* blood pressure; *CHF,* congestive heart failure; *HCM,* hypertrophic cardiomyopathy; *HF,* heart failure or myocardial dysfunction; *IV,* intravenous; *PO,* oral; *SVT,* supraventricular tachycardia.

conduction and increase refractoriness. Another approach is IV amiodarone or procainamide. Digoxin is not used in cases with preexcitation. Although it slows AV conduction, it can accelerate conduction in the accessory pathway and provoke ventricular tachycardia or fibrillation. Procainamide and quinidine may prevent AVRT because they lengthen the refractory period of the accessory pathway. Although high-dose procainamide, with or without a β-blocker or diltiazem, has prevented recurrent tachycardia in some cases, oral procainamide is no longer available in the United States. Intracardiac electrophysiologic mapping and catheter ablation of accessory pathways have been used successfully to abolish refractory AVRT in dogs, although this technique is not widely available.

Atrial tachycardia caused by a persistent automatic ectopic focus can be particularly difficult to suppress. If the antiarrhythmic strategies outlined in the preceding paragraphs are unsuccessful, the goal of therapy shifts to ventricular rate control. By prolonging AV conduction time and refractoriness, fewer atrial impulses are conducted, and ventricular rate is slowed (and often becomes irregular). Therapy with combinations of diltiazem or a β-blocker and digoxin, sotalol, or amiodarone can be effective. The animal with persistent automatic atrial tachycardia could be a candidate for a cardiac ablation procedure, if available. Alternatively, heart rate control could be achieved by AV node ablation with permanent pacemaker implantation.

Vagal maneuver

A vagal maneuver can help the clinician differentiate among tachycardias caused by an ectopic automatic focus, those dependent on a reentrant circuit involving the AV node, or excessively rapid sinus node activation. The vagal maneuver may transiently slow or intermittently block AV conduction, exposing abnormal P′ waves, and thus allow an ectopic atrial focus to be identified. Vagal maneuvers can terminate reentrant SVTs involving the AV node by interrupting the reentrant circuit. The maneuver tends to temporarily slow the rate of sinus tachycardia.

A vagal maneuver is performed either by firmly massaging the area over the carotid sinuses (below the mandible in the jugular furrows) or by applying firm bilateral ocular pressure for 15 to 20 seconds. Although initial attempts often are unsuccessful, repeating the vagal maneuver after antiarrhythmic drug injection may be more effective. Diltiazem, a β-blocker, digoxin, and other agents can increase a vagal maneuver's effect. The maneuver can be potentiated further in dogs by administering intramuscular (IM) morphine sulfate (0.2 mg/kg) or IV edrophonium chloride (but have atropine and an endotracheal tube readily available).

Ventricular Tachyarrhythmias

Occasional VPCs in an otherwise asymptomatic animal are not treated. Moderately frequent single VPCs generally do not require antiarrhythmic drug treatment either, if underlying heart function is reasonably normal. However, specific guidelines as to whether, when, and how best to treat intermittent ventricular tachyarrhythmias remain undefined. Besides their expense, antiarrhythmic drugs can have serious adverse effects, can provoke additional arrhythmias (proarrhythmic effects), and may not be efficacious. Pretreatment and posttreatment 24- to 48-hour ambulatory ECG recordings showing at least a 70% to 80% reduction in arrhythmia frequency provide the best indicator of a drug's efficacy in suppressing an arrhythmia. Intermittent ECG recordings cannot truly differentiate between drug effect (or lack thereof) and the spontaneous, marked variability in arrhythmia frequency that occurs commonly. However, in-hospital ECG recordings of 15 seconds to several minutes in duration often are used as a pragmatic, if not thorough, attempt to monitor arrhythmias.

Several factors influence the decision to use ventricular antiarrhythmic drug therapy. These factors include the nature of the animal's underlying disease, the perceived severity of the arrhythmia, and evidence of hemodynamic compromise. Diseases such as DCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), HCM, and subaortic stenosis, among others, frequently are associated with sudden death from arrhythmias. Therefore ventricular antiarrhythmic therapy would appear most urgent in animals with these diseases. However, the efficacy of a particular therapy to prolong survival and suppress the arrhythmia is difficult to accurately assess. Traditional guidelines for instituting ventricular antiarrhythmic therapy have been based on frequency, prematurity, and variability of the QRS configuration of the arrhythmia. Characteristics thought to imply increased electrical instability include rapid paroxysmal or sustained ventricular tachycardia, multiform (polymorphic) VPC configuration, or close coupling of VPCs to preceding complexes (R-on-T phenomenon). However, clear evidence that these guidelines predict greater risk of sudden death in all patients is lacking. It is probably more important to consider the animal's underlying heart disease and whether the arrhythmia is causing signs of hypotension or low cardiac output. Animals that are hemodynamically unstable or have a disease associated with sudden cardiac death are treated earlier and more aggressively.

Acute therapy for ventricular tachycardia

Sustained ventricular tachycardia should be treated aggressively because it can lead to marked decrease in arterial blood pressure, especially at faster rates. Lidocaine (IV) generally is the first-choice drug for controlling serious ventricular tachyarrhythmias in dogs. It is effective against arrhythmias caused by several underlying mechanisms and has minimal adverse hemodynamic effects. Because the effects of an IV lidocaine bolus last only about 10 to 15 minutes, constant-rate infusion (CRI) is warranted if the drug is effective. Small supplemental IV boluses can be given in addition to the CRI, if needed, to maintain therapeutic drug concentrations until steady state is achieved. IV infusion can be continued for several days, if necessary. When lidocaine is ineffective even at maximal recommended doses, several other strategies can be tried (Fig. 4.3).

IV amiodarone, oral sotalol, or oral mexiletine can be more effective in some cases. When using IV amiodarone,

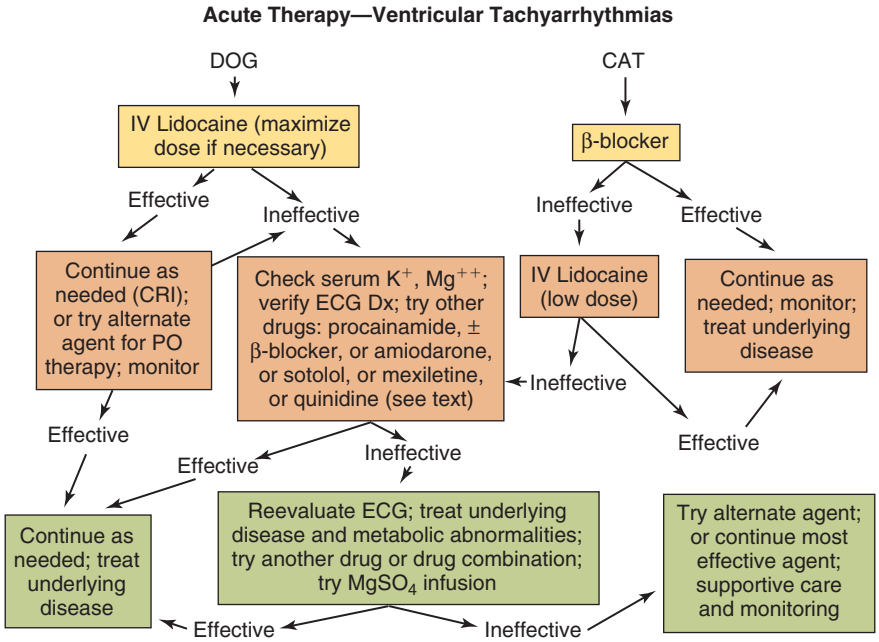


FIG 4.3
A therapeutic approach to ventricular tachyarrhythmias. See Table 4.2 for drug doses and text for more information. *CRI,* Constant-rate infusion; *Dx,* diagnosis; *ECG,* electrocardiogram.

only the newer aqueous preparation (e.g., Nexterone; Baxter International) should be used. Older amiodarone formulations can cause marked hypotension and hypersensitivity reactions because of the solvents used (see p. 95). Alternatively, procainamide (IV or IM) or quinidine (IM or PO) can be tried next. Effects of a single IM or oral loading dose should occur within 2 hours. If this is effective, lower doses can be given every 4 to 6 hours IM (or PO, if available). If ineffective, the dose can be increased or another antiarrhythmic drug chosen. Quinidine is not given IV because of its hypotensive effects; it also is not recommended in patients on digoxin or that have prolonged QT intervals. If the arrhythmia has not been controlled, a β-blocker can be added.

Cats with frequent ventricular tachyarrhythmias usually are given a β-blocker first. Alternatively, low doses of lidocaine can be administered. However, cats can be quite sensitive to the neurotoxic effects of this drug. Procainamide or sotalol also can be used.

Digoxin is not used to treat ventricular tachyarrhythmias. It can predispose to the development of ventricular arrhythmias. Patients with heart failure and/or supraventricular arrhythmias that are being treated with digoxin and that develop frequent or repetitive VPCs may need additional antiarrhythmic drug therapy (e.g., lidocaine) or digoxin withdrawal, as well as serum digoxin measurement. Ancillary KCl supplementation (if serum $K^+ \leq 4$ mEq/L) with or without $MgSO_4$ can increase antiarrhythmic efficacy.

Close ECG and patient monitoring and further diagnostic testing should follow initial therapy. Total suppression of persistent ventricular tachyarrhythmias is not expected. The patient's clinical status, the underlying disease(s), the success of the drug in controlling the arrhythmia, and the drug dosage (that is, whether it could be increased within recommended dosage range) all influence the decision whether to continue or discontinue current treatment or to use a different drug. Clinical status and results of diagnostic testing also guide decisions about chronic oral therapy.

If the ventricular tachyarrhythmia appears refractory to initial treatment attempts, one or more of the following considerations may be helpful:

1. Reevaluate the ECG—could the rhythm have been incorrectly diagnosed initially? For example, SVT with an intraventricular conduction disturbance (aberrant ventricular conduction) can mimic ventricular tachycardia. In such cases, IV diltiazem is usually more effective than lidocaine.
2. Reevaluate the serum K^+ (and Mg^{++}) concentration. Hypokalemia reduces the efficacy of class I antiarrhythmic drugs (such as lidocaine, procainamide, quinidine) and can predispose to the development of arrhythmias. If the serum K^+ concentration is less than 3 mEq/L, KCl can be infused at 0.5 mEq/kg/h; for serum K^+ between 3 to 3.5 mEq/L, KCl can be infused at 0.25 mEq/kg/h. A serum K^+ concentration in the high normal range is the goal. If the serum Mg^{++} concentration is less than 1 mg/dL, $MgSO_4$ or $MgCl_2$, diluted in D_5W, can be administered at 0.75 to 1 mEq/kg/day by CRI.
3. Try amiodarone (IV), sotalol (PO), or a β-blocker in conjunction with a class I drug (such as esmolol, propranolol,

or atenolol with procainamide or lidocaine) or a class IA drug with a IB drug (such as procainamide with lidocaine or mexiletine).
4. Maximize the dose of the antiarrhythmic drug having the greatest effect.
5. Consider the possibility that the drug therapy is exacerbating the rhythm disturbance (proarrhythmia). Polymorphic ventricular tachycardia (torsades de pointes) has been associated with quinidine, procainamide, and other drug toxicities.
6. $MgSO_4$ may be effective in animals with ventricular tachyarrhythmias associated with digoxin toxicity or with suspected polymorphous ventricular tachycardia (torsades de pointes). A slowly administered IV bolus of 25 to 40 mg/kg, diluted in D_5W, followed by an infusion of the same dose over 12 to 24 hours, has been suggested. Given that $MgSO_4$ contains 8.13 mEq magnesium per gram, a similar magnesium dose is provided by calculating 0.15 to 0.3 mEq/kg.
7. If the animal is tolerating the arrhythmia well, continue supportive care, correct other abnormalities as possible, and continue cardiovascular monitoring alone or with the most effective antiarrhythmic drug.
8. Direct current (DC) cardioversion or ventricular pacing may be available at some centers; ECG-synchronized equipment and anesthesia or sedation are required. High-energy, nonsynchronized shock (defibrillation) can be used for rapid polymorphic ventricular tachycardia or flutter degenerating into fibrillation.

Chronic oral therapy for ventricular tachyarrhythmias

The same drug that was most effective during acute therapy, or a similar one, often is continued orally when longer-term therapy is necessary. Although suppression of ventricular ectopy is one aim, reducing the risk of sudden arrhythmic death is the main goal for long-term therapy. Whereas the class IB drugs (lidocaine and mexiletine) appear to raise the fibrillation threshold more than the class IA agents (procainamide and quinidine), class III agents appear to have greater antifibrillatory effects than the class I drugs. Concurrent disease should be treated as thoroughly as possible. It is likely that animals with arrhythmias associated with underlying heart disease also benefit from β-blocker, ACEI, and other therapies, as do people. However, β-blockers alone do not appear effective in suppressing ventricular tachyarrhythmias in Doberman Pinschers with cardiomyopathy. Fish oil (omega-3 fatty acid) supplements appear to reduce the frequency of VPCs in Boxers with ARVC and possibly in other patients as well.

Several strategies are used for long-term oral therapy of patients with ventricular tachyarrhythmias. Presently, the most favored options include sotalol, mexiletine with atenolol, mexiletine with sotalol, or amiodarone. These are likely to provide a greater antifibrillatory effect than class I agents alone. The potential for serious adverse effects with long-term or high-dose use must be considered.

Frequent reevaluation is important for patients on long-term antiarrhythmic therapy (for any rhythm disturbance). When possible, continuous 24- to 48-hour ambulatory ECG recordings are most accurate for assessing efficacy. Although clearly not an ideal strategy, the patient's owner also can be shown how to use a stethoscope or palpate the chest wall to count the number of "skipped" beats per minute at home to approximate the frequency of arrhythmic events (either single or paroxysms). The decision to continue or discontinue successful antiarrhythmic therapy also is based on consideration of the clinical situation and any underlying cardiac disease.

Atrial Fibrillation

AF most often develops when there is marked atrial enlargement. It is a serious arrhythmia, especially when the ventricular response rate is high. Predisposing conditions include DCM, advanced degenerative mitral valve disease, congenital malformations that cause atrial enlargement, and hypertrophic or restrictive cardiomyopathy in cats. Clinical heart failure is common in these animals. AF is characterized by an irregular and usually rapid ventricular response rate. When little time is available for ventricular filling, stroke volume is compromised. Furthermore, atrial contraction (the "atrial kick"), which is especially important to ventricular filling at faster heart rates, is lost. In patients with underlying cardiac dysfunction, cardiac output tends to decrease considerably when AF develops. Therefore it is important to control the ventricular response rate (i.e., the heart rate) as soon as possible.

Long-lasting conversion to sinus rhythm is uncommon in the face of marked underlying cardiac disease, even after successful electrical cardioversion. Therefore treatment in most cases is directed at reducing the ventricular response rate by slowing AV conduction (Fig. 4.4). A slower heart rate allows more time for ventricular filling and lessens the relative importance of atrial contraction. In-hospital heart rates of fewer than 150 (or <180 in cats) beats/min are desirable. The patient's ventricular rate should be documented by ECG recording; counting the heart rate by auscultation or palpation can be highly inaccurate in animals with AF. Resting heart rate at home, which some owners can monitor, is a better indicator of drug effectiveness. Heart rates of 70 to 110 beats/min in dogs and 80 to 140 beats/min in cats are probably acceptable.

Therapy for atrial fibrillation

When the heart rate exceeds 180 to 200 beats/min at rest, especially in the setting of heart failure, it is important to expediently reduce the ventricular rate. IV diltiazem acts more quickly than oral dosing, but caution must be used especially in patients with DCM because the drug has negative inotropic effects. Tiny doses are used if given IV, along with immediate institution of pimobendan therapy (if not currently being given). Blood pressure, as well as heart rate, should be monitored. A more conservative approach is to use oral loading dose(s) of diltiazem, although the onset of effect is more gradual. Diltiazem's negative inotropic effect is

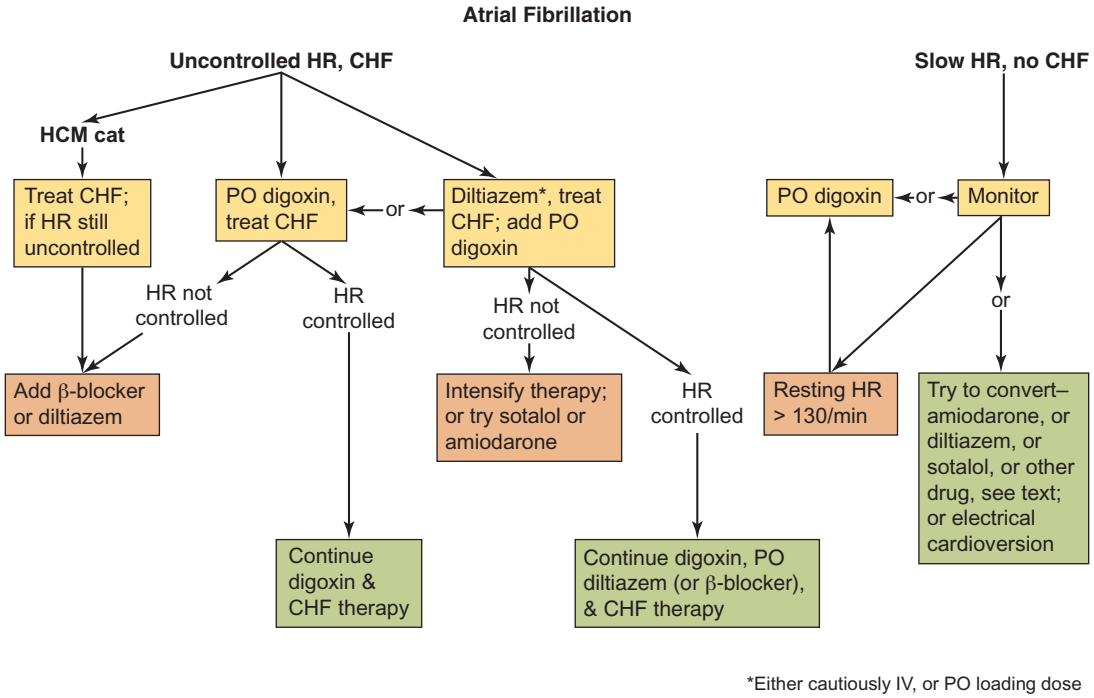


FIG 4.4
A therapeutic approach to atrial fibrillation. See Table 4.2 for drug doses and text for more information. *AF,* Atrial fibrillation; *CHF,* congestive heart failure; *HCM,* hypertrophic cardiomyopathy; *HR,* heart rate.

less than that of verapamil (which should not be used in CHF) or an IV β-blocker, although esmolol could be cautiously tried if necessary because of its short half-life. Oral digoxin at maintenance doses could be used for initial heart rate control (see Table 3.3), especially in dogs without CHF. However, twice the eventual oral maintenance dosage can be given for 1 to 2 days for more rapid effect, and this strategy can be used for dogs with CHF as well. Although IV digoxin has been used, it is generally avoided because of toxicity concerns. Acidosis and hypoxemia associated with severe pulmonary edema could increase myocardial sensitivity to digoxin-induced arrhythmias; furthermore, rapid IV digoxin administration can promote peripheral vasoconstriction by increasing central sympathetic output. If IV digoxin must be used, for lack of other options, it must be given slowly and in small doses. When dobutamine or dopamine infusion is necessary to support myocardial function during acute CHF management (see p. 63 and Box 3.1), a β-blocker usually is avoided. Diltiazem (cautiously IV, or PO) is recommended, but if unavailable, a PO loading dose of digoxin could be used. Ultimately, the combination of both diltiazem and digoxin typically is used because this has been shown to control heart rate in AF better than either agent alone.

Digoxin alone does not fully control the heart rate in many animals with AF. Increases in sympathetic tone from CHF, exercise, or excitement can override the vagal effect of digoxin on AV conduction. Either diltiazem or a β-blocker can be added PO, initially at a conservative dose and then titrated upward as needed to adequately slow AV conduction and control ventricular rate. The potential myocardial depressant effects of β- and Ca^{++}-blockers warrant caution in patients with myocardial failure. Concurrent pimobendan therapy or allowing 1 to 2 days of digoxin therapy before adding or increasing the dose is recommended. Digoxin is not used in cats with HCM and AF; a β-blocker or diltiazem is used instead. Amiodarone and sotalol are other agents that can be used for heart rate control in dogs. Occasionally, conversion to sinus rhythm occurs in response to amiodarone or even diltiazem therapy. In experimental dog models, fish oil administration has reduced the occurrence of AF.

When AF develops in patients that also have ventricular preexcitation, AV nodal blocking drugs (Ca^{++}-blockers, digoxin, and possibly β-blockers) should not be used because they can paradoxically increase the ventricular response rate. Amiodarone is recommended in these cases; sotalol or procainamide also can be used.

Electrical cardioversion of AF is successful in some animals, although not usually those with marked atrial enlargement. Use of biphasic current delivery combined with amiodarone (or other drug) therapy may increase effectiveness. However, most animals with significant underlying heart disease revert to AF.

Lone Atrial Fibrillation

AF sometimes develops in large or giant-breed dogs without cardiomegaly or other evidence of structural heart disease. This is known as "lone AF." AF with a slow ventricular response rate can be an incidental finding in such dogs. AF

occasionally occurs transiently, usually in association with trauma or surgery. Acute AF without signs of heart disease or failure may convert to sinus rhythm spontaneously or in response to drug therapy or electrical cardioversion. Drugs that might be effective include amiodarone, diltiazem (e.g., PO for ≈3 days), or possibly sotalol or other class III or IC agents. Acute-onset AF associated with high vagal tone may convert with IV lidocaine. Quinidine PO or IM has been used for acute AF conversion in large dogs without signs of heart disease, but adverse effects can include increased ventricular response rate from the drug's vagolytic effects, ataxia, and, most seriously, seizures or polymorphic ventricular tachycardia. If effective, the drug is discontinued after sinus rhythm is achieved. Dogs that do not convert to sinus rhythm are given either digoxin or diltiazem for rate control. Alternatively, if the ventricular rate is consistently low at rest, dogs can be monitored periodically without therapy, but rapid heart rates are still likely with exercise or excitement. Lone AF precedes the development of DCM in some cases.

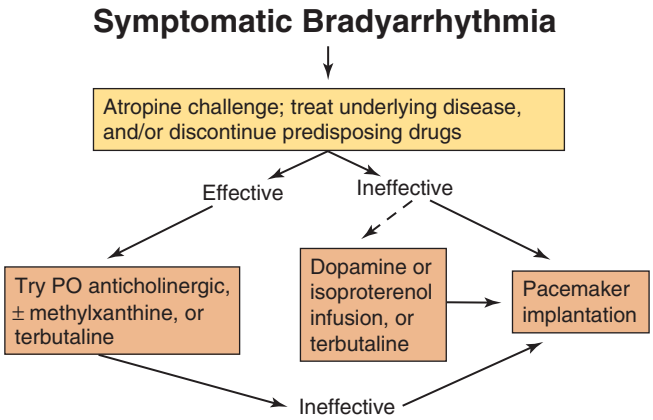


FIG 4.5
A therapeutic approach to managing symptomatic bradyarrhythmias. See Box 3.1 and Table 4.2 for drug doses and text for more information.

BRADYARRHYTHMIAS

Sinus Bradycardia

Slow sinus rhythm (or arrhythmia) can be a normal finding, especially in athletic dogs. Sinus bradycardia also has been associated with various drugs (e.g., xylazine, thorazine tranquilizers, some anesthetic agents, medetomidine, digoxin, calcium entry blockers, β-blockers, parasympathomimetic drugs), trauma or diseases of the CNS, organic disease of the sinus node, hypothermia, hyperkalemia, and hypothyroidism, among other disorders. Conditions that increase vagal tone (for example, respiratory or gastrointestinal [GI] disease or a mass involving the vagosympathetic trunk) can induce sinus bradycardia. Chronic pulmonary disease often is associated with pronounced respiratory sinus arrhythmia.

In most cases with sinus bradycardia, the heart rate increases in response to exercise or atropine administration, and no clinical signs are associated with the slow heart rate. Symptomatic dogs usually have a heart rate slower than 50 beats/min and/or pronounced underlying disease. Because sinus bradycardia and sinus bradyarrhythmia are extremely rare in cats, a search for underlying cardiac or systemic disease (such as hyperkalemia) is warranted in any cat with a slow heart rate.

When sinus bradycardia is associated with signs of weakness, exercise intolerance, syncope, or worsening underlying disease, an anticholinergic (or adrenergic) agent is given (Fig. 4.5). If sinus bradycardia is the result of a drug effect, discontinuation, dosage reduction, or other therapy should be used, as appropriate (e.g., reversal of anesthesia, calcium salts or atropine for calcium entry blocker overdose, dopamine or atropine for β-blocker toxicity). If there is inadequate increase in heart rate with medical therapy, temporary or permanent pacing is indicated (see Suggested Readings).

Sick Sinus Syndrome

Sick sinus syndrome is a condition of erratic SA function characterized by episodic weakness, syncope, and, sometimes, convulsive syncope (Stokes-Adams seizures) triggered by cerebral hypoxia. Older female Miniature Schnauzers and West Highland White Terriers most commonly are affected, but the syndrome also is seen in Dachshunds, Cocker Spaniels, Pugs, and mixed-breed dogs. Affected dogs have episodes of marked sinus bradycardia with sinus arrest (or SA block). Sick sinus syndrome is extremely rare in cats.

Abnormalities of the AV conduction system can coexist, causing the activity of subsidiary pacemakers to be depressed and leading to prolonged periods of asystole. Some affected dogs also have paroxysmal SVTs, prompting the name *bradycardia-tachycardia syndrome* (Fig. 4.6). Premature complexes can be followed by long pauses before sinus node activity resumes, indicating a prolonged sinus node recovery time. Intermittent periods of accelerated junctional rhythms and variable junctional or ventricular escape rhythms also occur.

Clinical signs result from bradycardia and sinus arrest, paroxysmal tachycardia, or both. Signs can mimic seizures stemming from neurologic or metabolic disorders. Concurrent degenerative mitral valve disease also is often present. Some dogs have evidence of CHF, usually secondary to mitral valve regurgitation, although the arrhythmias may be a complicating factor.

ECG abnormalities frequently are pronounced in dogs with long-standing sick sinus syndrome. Nevertheless, some dogs have one or more normal resting ECGs. Prolonged visual ECG monitoring or 24-hour ambulatory ECG can help establish a definitive diagnosis. An atropine challenge test is done in dogs with persistent bradycardia (see p. 97). The normal response is an increase in the heart rate of 150% or to more than 130 to 150 beats/min. Dogs with sick sinus syndrome generally have a subnormal response.

Therapy with an anticholinergic agent, methylxanthine bronchodilator, or terbutaline given orally might temporarily help some animals that respond positively to atropine challenge. Yet anticholinergic or sympathomimetic drugs



FIG 4.6
Electrocardiogram from an 11-year-old female Miniature Schnauzer with sick sinus syndrome illustrates typical bradycardia and tachycardia. The top portion of this continuous recording shows persistent sinus arrest with three different escape complexes, followed by an atrial premature complex. A 1-mV calibration mark is seen in the middle of the top strip. The bradycardia is interrupted by a run of atrial tachycardia at a rate of 250 beats/min, with 1 : 1 atrioventricular conduction initially; but starting in the middle of the bottom strip, every other P′ wave is blocked (2 : 1 atrioventricular conduction).

used to accelerate the sinus rate also can exacerbate tachyarrhythmias. Conversely, drugs used to suppress these supraventricular tachyarrhythmias can magnify the bradycardia. However, cautious use of diltiazem or digoxin could be helpful against paroxysmal SVT in some dogs, as long as sinus node function is not further depressed. Sick sinus syndrome with frequent or severe clinical signs is best managed by permanent artificial pacing (see sources in Suggested Readings for further details on pacing). Dogs that remain symptomatic because of paroxysmal SVT can more safely be given appropriate antiarrhythmic therapy once a normally functioning pacemaker is in place.

Atrial Standstill

Persistent atrial standstill is a rhythm disturbance characterized by loss of effective atrial electrical activity (with no P waves and a flat baseline); a junctional or ventricular escape rhythm controls the heart. This bradyarrhythmia is rare in dogs and extremely rare in cats. Most cases have occurred in English Springer Spaniels with muscular dystrophy, although infiltrative and inflammatory disease of the atrial myocardium also can result in atrial standstill. Organic disease of the atrial myocardium can involve the ventricular myocardium as well; persistent atrial standstill may be a harbinger of progressive cardiac disease.

Medical treatment for persistent atrial standstill rarely is rewarding; however, an anticholinergic drug or infusion of dopamine or isoproterenol sometimes will temporarily accelerate the escape rhythm. If ventricular tachyarrhythmias result from this treatment, the drug should be discontinued or the dose reduced. Oral terbutaline also may have some beneficial effect. Antiarrhythmic agents are contraindicated in these cases because they could suppress the escape focus in addition to the tachyarrhythmia. Permanent pacemaker implantation is the treatment of choice, although the prognosis is poor in dogs with concurrent ventricular myocardial dysfunction.

Hyperkalemia can mimic atrial standstill and should be ruled out in animals without P waves. The apparent lack of atrial electrical and mechanical activity ("silent atrium") caused by hyperkalemia is reversible with treatment. Sinus node activity (and P waves) become evident as the serum K^+ concentration returns to normal.

Atrioventricular Conduction Block

Second-degree, or intermittent, AV block usually causes an irregular heart rhythm. In contrast, the ventricular escape rhythm that occurs with third-degree (complete) AV block usually is quite regular, although premature beats or shifts in the ventricular escape focus can cause some irregularities. AV conduction disturbances can result from certain drugs (such as α_2 agonists, opioids, digoxin), high vagal tone, or organic disease of the AV node. Diseases that have been associated with AV conduction disturbances include aortic valve endocarditis, HCM, neoplastic infiltration of the myocardium, and myocarditis. Idiopathic heart block can occur in middle-aged and older dogs; congenital third-degree AV block also has been reported in dogs. Symptomatic third-degree AV block is less common in cats, but evidence of any AV conduction disturbance should prompt further

diagnostic evaluation, because most cases have been associated with HCM. Complete AV block occasionally is found in older cats without detectable organic heart disease.

Type I second-degree AV block and first-degree AV block are associated frequently with high vagal tone or drug effects in dogs. These animals often are asymptomatic; exercise or anticholinergic drug (atropine or glycopyrrolate) administration usually abolishes the conduction disturbance. High-grade second-degree AV block (many blocked P waves) and complete (3°) heart block usually cause lethargy, exercise intolerance, weakness, syncope, and other signs of low cardiac output. These signs become severe at heart rates consistently below 40 beats/min in dogs. CHF develops secondary to chronic bradycardia in some cases, especially if other cardiac disease is present.

An atropine challenge test (p. 97) is used to determine the degree of vagal influence on the AV block. Oral anticholinergic (or sympathomimetic) therapy can be attempted in symptomatic animals that are atropine-responsive (see Fig. 4.5). However, atropine and oral anticholinergic therapy often is ineffective, especially with high-grade second-degree AV block, so artificial pacing usually is indicated. An emergency infusion of dopamine (see Box 3.1) or isoproterenol might increase the ventricular escape rate in animals with high-grade second- or third-degree block, although it may also provoke ventricular tachyarrhythmias. Oral isoproterenol usually is ineffective. A thorough cardiac workup is indicated before permanent artificial pacemaker implantation because some underlying diseases (progressive myocardial disease, endocarditis) are associated with a poor prognosis, even after pacing. Temporary transvenous pacing could be attempted for 1 to 2 days in questionable cases to assess the animal's response to a normal heart rate before permanent pacemaker surgery is performed. More information on pacing therapy is found in Suggested Readings.

BOX 4.4

Formulas to Calculate Constant-Rate Infusion

Method 1

(Allows for "fine-tuning" fluid and drug administration rate)
Determine desired drug infusion rate: µg/kg/min × kg body weight = µg/min (A)
Determine desired fluid infusion rate: mL/hour ÷ 60 = mL/min (B)
(A) ÷ (B) = µg/min ÷ mL/min = µg drug/mL of fluid
Convert from µg to mg of drug needed (1 µg = 0.001 mg)
Mg drug/mL fluid × mL of fluid in bag (or bottle, etc.) = mg of drug to add to the fluid container

Method 2

(For total dose over a 6-hour period, must also calculate fluid volume and administration rate)
Total dose in mg to infuse over a 6-hour period = body weight (kg) × dose (µg/kg/min) × 0.36

Method 3 (for Lidocaine)

(Faster but less helpful if fluid rate is important or if fine drug-dosage adjustments are necessary)
For CRI of 44 µg/kg/min of lidocaine, add 25 mL of 2% lidocaine to 250 mL of D_5W
Infuse at 0.25 mL/25 lb of body weight/min

ANTIARRHYTHMIC AGENTS

Antiarrhythmic drugs can act by slowing the rate of a tachycardia, terminating a reentrant arrhythmia, or preventing abnormal impulse formation or conduction. These effects occur through modulation of tissue electrophysiologic properties and/or autonomic nervous system effects. The traditional (Vaughan-Williams) antiarrhythmic drugs are classified according to their main electrophysiologic effects on cardiac cell action potentials (Table 4.1). Although this classification system has several shortcomings (for example, some drugs with antiarrhythmic effects are excluded, several drugs have the multiclass effects, and attention to ion channel mechanisms is lacking), clinical reference to this classification persists. See Table 4.2 and Box 4.4 for antiarrhythmic drug dosages and CRI calculation methods.

Class I agents tend to slow conduction and decrease automaticity and excitability by means of their membrane-stabilizing effects; older ventricular antiarrhythmic drugs belong to this class. Class II drugs include the β-adrenergic antagonists (β-blockers), which act by inhibiting the effects of catecholamines on the heart. Class III drugs prolong the effective refractory period of cardiac action potentials without decreasing conduction velocity; they may be most effective in suppressing reentrant arrhythmias and in preventing VF. Class IV drugs are the calcium entry blockers; ventricular arrhythmias usually are not responsive to these agents, but they are important against supraventricular tachyarrhythmias. Antiarrhythmic agents within this classification scheme are contraindicated in animals with complete AV block and should be used only cautiously in animals with sinus bradycardia, sick sinus syndrome, and first- or second-degree AV block. Sometimes a designation of Class V is used for drugs with antiarrhythmic effects that work by other mechanisms than described for the original four classes.

CLASS I ANTIARRHYTHMIC DRUGS

Class I antiarrhythmic drugs block membrane Na^+ channels and depress the action potential upstroke (phase 0), which slows conduction velocity along the cardiac cells. They have been subclassified according to differences in other electrophysiologic characteristics. These differences (see Table 4.1) can influence their efficacy against specific arrhythmias. Most of the class I agents depend on extracellular K^+ concentration for their effects, and they lose effectiveness in patients with hypokalemia.

TABLE 4.1

Classification and Effects of Antiarrhythmic Drugs

CLASSIFICATION	DRUG	MECHANISM AND ECG EFFECTS
Class I		Decreases fast inward Na^+ current; membrane-stabilizing effects (decreased conductivity, excitability, and automaticity)
IA	Quinidine Procainamide	Moderately decreases conductivity, increases action potential duration; can prolong QRS complex and Q-T interval
IB	Lidocaine Mexiletine Phenytoin	Little change in conductivity, decreases action potential duration; QRS complex and Q-T interval unchanged
IC	Flecainide Propafenone	Markedly decreases conductivity without change in action potential duration
Class II	Atenolol Propranolol Esmolol Metoprolol Carvedilol Others	β-adrenergic blockade—reduces effects of sympathetic stimulation (no direct myocardial effects at clinical doses)
Class III	Sotalol Amiodarone Ibutilide Dofetilide Others	Selectively prolongs action potential duration and refractory period; antiadrenergic effects; Q-T interval prolonged
Class IV	Verapamil Diltiazem Others	Decreases slow inward Ca^{++} current (greatest effects on SA and AV nodes)
Other Antiarrhythmic Agents	Digoxin	Antiarrhythmic action results mainly from indirect autonomic effects (especially increased vagal tone)
	Atropine Glycopyrrolate Others	Anticholinergic agents oppose vagal effects on SA and AV nodes (glycopyrrolate and other drugs also have this effect)

AV, Atrioventricular; *ECG,* electrocardiogram; *SA,* sinoatrial.

Lidocaine

Lidocaine HCl generally is the first-choice IV ventricular antiarrhythmic agent in dogs. It usually is not effective against supraventricular arrhythmias, with the exception of some recent-onset, vagally induced AF or tachycardias. At recommended doses, it has little effect on sinus node rate, AV conduction, and refractoriness. Lidocaine suppresses automaticity in normal Purkinje fibers and diseased myocardial tissue, slows conduction, and reduces the supernormal period (during which the cell can be reexcited before complete repolarization occurs). It has greater effects on diseased and hypoxic cardiac cells and at faster stimulation rates. The electrophysiologic effects of lidocaine are influenced by extracellular potassium concentration. Hypokalemia may render the drug ineffective, and hyperkalemia intensifies its depressant effects on cardiac membranes. Lidocaine produces little or no depression of contractility at therapeutic doses when administered slowly IV. The lidocaine congener mexiletine similarly produces minimal negative inotropic and hypotensive effects. However, toxic concentrations of lidocaine can cause hypotension.

Lidocaine undergoes rapid hepatic metabolism by cytochrome P-450 (CYP) enzyme activity; some metabolites might contribute to its antiarrhythmic and toxic effects. Lidocaine is not effective orally because of its virtually complete first-pass hepatic elimination. IV administration, usually as slow boluses followed by CRI, is most effective. Antiarrhythmic effects after IV bolus occur within 2 minutes and abate within 10 to 20 minutes. CRI without a loading dose produces steady-state concentrations in 4 to 6 hours. The half-life is less than 1 hour in the dog. An initial bolus of 2 mg/kg is used in dogs and can be repeated two to three times if necessary. Lower doses should be used in cats to avoid toxicity (loading dose of 0.25-0.5 mg/kg slowly IV). The half-life in cats is 1 to 2 hours. Therapeutic plasma concentrations are thought to range from 1.5 to 6 μg/mL in dogs. Only lidocaine without epinephrine should be used for antiarrhythmic therapy. If IV access is not possible, IM administration could be used but is less effective.

The most common toxic effect of lidocaine in dogs is CNS excitation. Signs include agitation, disorientation or ataxia, muscle twitches, nystagmus, and generalized seizures; nausea also can occur. Worsening of arrhythmias (proarrhythmic effect) is seen occasionally, as with any drug that has cardiac electrophysiologic effects. There are anecdotal reports of respiratory depression and arrest after lidocaine administration to unconscious patients. Cats are particularly sensitive to the drug's toxic effects and can develop seizures, respiratory arrest, bradyarrhythmias, and sudden death. In the event of toxicity, lidocaine should be discontinued until the signs of toxicity disappear; a lower infusion rate may then be instituted. IV diazepam (0.25-0.5 mg/kg) is used to control lidocaine-induced seizures. Hepatic disease can



TABLE 4.2

Dosage of Antiarrhythmic Drugs

AGENT	DOSAGE
Class I	
Lidocaine	Dog: initial boluses of 2 mg/kg slowly IV, up to 8 mg/kg (over ≥10 min); or rapid IV infusion at 0.8 mg/kg/min; if effective, then 25-80 mcg/kg/min CRI Cat: initial bolus of 0.25-0.5 (- 1) mg/kg slowly IV; can repeat boluses of 0.15-0.25 mg/kg, up to total of 4 mg/kg; if effective, 10-40 mcg/kg/min CRI
Procainamide	Dog: 2 mg/kg IV over 2 minutes; repeat if necessary, up to cumulative dose of 20 mg/kg; 10-50 mcg/kg/minute CRI; 6-20 (up to 30) mg/kg IM q4-6h (PO, if available, 10-20 mg/kg q 8-12 [sustained-release prep.] hours) Cat: 1.0-2.0 mg/kg IV over 2 minutes, repeat if necessary, up to cumulative dose of 10 mg/kg; 10-20 mcg/kg/min CRI; 7.5-20 mg/kg IM q(6-)8h
Quinidine	Dog: 6-20 mg/kg IM q6h (loading dose, 14-20 mg/kg); 6-16 mg/kg PO q6h; sustained action preparations, 8-20 mg/kg PO q8h Cat: 6-16 mg/kg, IM or PO, q8h
Mexiletine	Dog: 4-6 (-8) mg/kg PO q8h Cat: —
Phenytoin	Dog: 10 mg/kg slowly IV; 20-50 mg/kg PO q8h Cat: do not use
Propafenone	Dog: 2-4 (up to 6?) mg/kg PO q8h (start low) Cat: —
Flecainide	Dog: 1-2 (up to 4?) mg/kg PO q(8-)12h (start low; not advised if CHF or impaired LV function present) Cat: —
Class II	
Atenolol	Dog: 0.2-1 mg/kg PO q12(-24)h, start low Cat: Same, or 6.25(-12.5) mg/cat PO q12(-24)h
Propranolol	Dog: 0.02 mg/kg initial bolus slowly IV (up to maximum of 0.1 mg/kg); initial oral dose, 0.1-0.2 mg/kg PO q8h, up to 1 mg/kg q8h Cat: Same IV instructions; 2.5 up to 10 mg/cat PO q8-12h
Esmolol	Dog: 50-100 mcg/kg IV over 5 minutes (loading dose), followed by infusion of 25-50 mcg/kg/min Cat: same
Metoprolol	Dog: initial dose, 0.1-0.2 mg/kg PO q24(-12)h, up to 1(-2) mg/kg q8(-12)h Cat: 2 up to 15 mg/cat PO q8(-12)h, start low
Class III	
Sotalol	Dog: 1-3 (up to 5?) mg/kg PO q12h Cat: 10-20 mg/cat PO q12h (or 2-4 mg/kg PO q12h)
Amiodarone	Dog: PO loading: 10 (up to 15) mg/kg PO q12h for 4-7 days, then same dose q24h for 7 days, then reduce to maintenance dose PO maintenance: 5-7.5 mg/kg PO q24h For IV administration use aqueous formulation (Nexterone, 1.5 mg/mL), not standard amiodarone, see p. 95): 3-5 mg/kg slow IV over 15 min; can continue 0.05 mg/kg/min CRI if needed Cat: IV aqueous formulation (1.5 mg/mL): 2.5 mg/kg slow IV bolus over 15 minutes (optimal dose uncertain)

TABLE 4.2

Dosage of Antiarrhythmic Drugs—cont'd

AGENT	DOSAGE
Class IV	
Diltiazem	Dog: Acute IV for rapid rate control of AF: 0.05-0.10 mg/kg IV over 2-5 minutes, can repeat if needed. Acute IV for SVT: 0.1-(0.2) mg/kg over 2-5 minutes IV, can repeat to cumulative IV dose of 0.3-0.4 mg/kg; monitor blood pressure. CRI (if frequent SVT recurrence): 0.002-0.006 mg/kg/min (or 0.12-0.35 mg/kg/h) PO loading dose: 0.5 mg/kg PO followed by 0.25 mg/kg PO q1h to a total of 1.5(-2.0) mg/kg or conversion Oral maintenance: initial dose 0.5-1 mg/kg (up to 2-3 mg/kg) PO q8h Extended release (diltiazem ER): 1-4 (up to 6) mg/kg PO q12h Cat: Same?; Or 1.5-2.5 mg/kg (or 7.5-10 mg/cat) PO q8h; sustained-release preparations: diltiazem ER, 30 mg/cat/day (one half of a 60 mg controlled-release tablet within the 240-mg gelatin capsule), can increase to 60 mg/day in some cats if necessary Cardizem-CD, 10 mg/kg/day (45 mg/cat ≅ 105 mg of Cardizem-CD ≅ amount that fits into small end of No. 4 gelatin capsule)
Verapamil	Dog: initial dose, 0.02-0.05 mg/kg slowly IV, can repeat q5min up to a total of 0.15(-0.2) mg/kg; 0.5-2 mg/kg PO q8h. (*Note:* diltiazem preferred instead) Cat: initial dose, 0.025 mg/kg slowly IV, can repeat q5min up to a total of 0.15(-0.2) mg/kg; 0.5-1 mg/kg PO q8h. (*Note:* diltiazem preferred instead)
Anticholinergic	
Atropine	Dog: 0.02-0.04 mg/kg IV, IM, SC; 0.04 mg/kg PO q6-8h Cat: same Atropine challenge test: 0.04 mg/kg IV (see text, p. 97)
Glycopyrrolate	Dog: 0.005-0.01 mg/kg, IV or IM; 0.01-0.02 mg/kg SC Cat: same
Propantheline	Dog: 0.25-0.5 mg/kg or 3.73-7.5 (-15) mg/dog PO q8-12h Cat: —
Hyoscyamine	Dog: 0.003-0.006 mg/kg PO q8h Cat: —
Sympathomimetic	
Isoproterenol	Dog: 0.04-0.08 mcg/kg/min CRI Cat: same
Theophylline (extended rel.)	Dog: 10 mg/kg PO q12h Cat: 10-15 mg/kg q24h
Terbutaline	Dog: 0.14 mg/kg, or 2.5-5 mg/dog, PO q8-12h Cat: 0.1-0.2 mg/kg, or 0.625-1.25 mg/cat, PO q12h
Other Agents	
Digoxin	See Table 3.3 for PO dosing; see Box 3.1 and p. 85 for IV
Edrophonium	Dog: 0.05-0.1 mg/kg IV (have atropine and endotracheal tube available) Cat: same?
Phenylephrine	Dog: 0.004-0.01 mg/kg IV Cat: same?

CRI, Constant-rate infusion; —, effective dosage not known.

slow the drug's metabolism. Drugs that decrease liver blood flow (such as propranolol, cimetidine, and chloramphenicol) also slow lidocaine's metabolism and predispose to toxicity. Animals with heart failure could have reduced hepatic blood flow and so might require a lower dosage of the drug.

Procainamide

Procainamide HCl has electrophysiologic effects similar to those of quinidine. These include both direct and indirect (vagolytic) effects. Procainamide is indicated for the treatment of premature ventricular (and sometimes atrial)

depolarizations and tachycardias. It is less effective than quinidine for atrial tachyarrhythmias. Procainamide prolongs the effective refractory period and slows accessory pathway conduction in dogs with orthodromic AVRT. Procainamide should be used only with caution in animals with hypotension.

Procainamide is well absorbed orally in the dog, with a half-life of 2.5 to 4 hours; sustained-release procainamide's half-life was 3 to 6 hours. Unfortunately, oral procainamide is no longer available in the United States, but it may be elsewhere. The drug undergoes hepatic metabolism and renal excretion in proportion to the creatinine clearance. Procainamide can be given IM without marked hemodynamic effect, but rapid IV injection can cause hypotension and cardiac depression, although to a much lesser degree than IV quinidine. Administration by CRI can be used if the arrhythmia responds to an IV bolus; a steady state is reached in 12 to 22 hours. Therapeutic plasma concentration range is thought to be 4 to 10 μg/mL.

The toxic effects of procainamide are similar to those of quinidine (see later) but usually are milder. GI upset and prolongation of the QRS or QT intervals can occur. Procainamide can enhance the ventricular response rate to AF (that is, the heart rate) if used without diltiazem, digoxin, or a β-blocker. More serious toxic effects include hypotension, depressed AV conduction (sometimes causing 2° or 3° AV block), and proarrhythmia. The latter can cause syncope or VF. Hypotension should respond to IV fluid, and catecholamine or calcium-containing solutions.

Quinidine

Quinidine, the prototype IA drug, has been used to treat ventricular and some supraventricular tachyarrhythmias. In large dogs with recent-onset AF and normal ventricular function (lone AF), quinidine might cause conversion to sinus rhythm. This drug must be used cautiously in animals with heart failure or hyperkalemia. The characteristic electrophysiologic effects of quinidine are depression of automaticity and conduction velocity, and prolongation of the effective refractory period. Corresponding dose-dependent ECG changes include PR, QRS, and QT prolongation. Quinidine also has indirect vagolytic effects. At low doses, these vagolytic effects can increase the sinus rate or the ventricular response rate to AF by antagonizing the drug's direct effects. As with other class I agents, hypokalemia reduces quinidine's antiarrhythmic effectiveness.

The drug is well absorbed orally but is rarely used now for chronic oral therapy because of its frequent adverse effects. Quinidine is metabolized extensively by the liver; the half-life is about 6 hours in dogs and 2 hours in cats. Quinidine is highly protein-bound; severe hypoalbuminemia can predispose to toxicity. Cimetidine, amiodarone, and antacids can also predispose to toxicity by slowing the drug's elimination. Quinidine can precipitate digoxin toxicity (when used concurrently) by displacing digoxin from skeletal muscle binding sites and reducing its renal clearance. IV administration is not recommended because of quinidine's propensity to cause vasodilation (by means of nonspecific α-adrenergic receptor blockade), cardiac depression, and hypotension. The oral and IM routes usually do not cause adverse hemodynamic effects, but close monitoring is warranted initially. Therapeutic blood concentrations (2.5-5 μg/mL) usually are achieved in 12 to 24 hours after oral or IM administration. Slow-release sulfate (83% active drug), gluconate (62% active drug), and polygalacturonate (80% active drug) salts of quinidine prolong the drug's absorption and elimination. The sulfate salt is more rapidly absorbed than the gluconate; peak effect is usually achieved 1 to 2 hours after oral administration.

Marked QT prolongation, right bundle branch block, or QRS widening by more than 25% of pretreatment value suggests quinidine toxicity; various conduction blocks and ventricular tachyarrhythmias are other manifestations. The QT prolongation implies increased temporal dispersion of myocardial refractoriness; this predisposes to torsades de pointes (see p. 41) and VF. Transient episodes of these serious arrhythmias are thought to underlie syncopal attacks in people taking quinidine. Lethargy, weakness, and CHF can result from the negative inotropic and vasodilatory effects of the drug and subsequent hypotension. Cardiotoxicity and hypotension can be partially reversed by sodium bicarbonate (1 mEq/kg IV), which temporarily decreases serum K^+ concentration, enhances quinidine's binding to albumin, and reduces its cardiac electrophysiologic effects. GI signs (e.g., nausea, vomiting, diarrhea) are common with orally administered quinidine. Thrombocytopenia (reversible after quinidine discontinuation) can occur in people and possibly in dogs and cats.

Mexiletine

Mexiletine HCl is similar to lidocaine in its electrophysiologic, hemodynamic, toxic, and antiarrhythmic properties. It can be effective in suppressing ventricular tachyarrhythmias in dogs. The combination of sotalol or a traditional β-blocker with mexiletine may be more efficacious and associated with fewer adverse effects than mexiletine alone (by allowing lower dosage). The drug is easily absorbed when administered orally, but delayed gastric emptying, narcotics, and magnesium-aluminum hydroxide antacids reportedly slow its absorption in people. Mexiletine undergoes hepatic metabolism (influenced by liver blood flow) and some renal excretion (which is slower if the urine is markedly alkaline). Cimetidine can have variable effects on mexiletine plasma concentration; however, omeprazole and famoditine are unlikely to affect its metabolism. Moderate to severe liver disease can impair mexiletine's metabolism. Hepatic microsomal enzyme inducers can accelerate its clearance. The half-life in dogs is from 4.5 to 7 hours (depending to some degree on the urine pH). Approximately 70% of the drug is protein-bound. The therapeutic serum concentration is thought to range from 0.5 to 2 μg/mL (as in people). The effects of mexiletine in cats are not well known. Adverse effects have included vomiting, anorexia, tremor, disorientation, sinus bradycardia, and thrombocytopenia.

Phenytoin

The only indication for phenytoin as an antiarrhythmic agent is for digoxin-induced ventricular tachyarrhythmias in dogs that are not responsive to lidocaine or other agents. Thus it is now almost never used. Electrophysiologically, it is similar to lidocaine, but it also has some slow-calcium channel inhibitory and CNS effects that contribute to its effectiveness against digitalis-induced arrhythmias. Slow IV infusion (of 10 mg/kg) and oral administration (of 20-50 mg/kg PO q8h) have minimal hemodynamic effects; however, oral bioavailability is poor. Rapid IV injection can depress myocardial contractility, exacerbate arrhythmias, and cause vasodilation, hypotension, or respiratory arrest related to the propylene glycol vehicle. The half-life of phenytoin in the dog is about 3 hours. The drug is metabolized in the liver; drugs that inhibit CYP enzyme activity increases phenytoin's serum concentration. IV administration of phenytoin has been associated with bradycardia, AV block, ventricular tachycardia, and cardiac arrest. CNS toxicity signs include depression, nystagmus, disorientation, and ataxia. The drug is not used in cats because of its long half-life (>40 hours) and toxicity.

Other Class I Agents

Flecainide and propafenone are class IC agents. Flecainide prolongs the sinus cycle length and AV conduction time and refractoriness. It also has a potassium current (delayed rectifier, I_K) blocking effect similar to class III agents; however, action potential prolongation is offset by its Na^+ channel blocking effect, so little change in action potential duration occurs. Because of its effects to prolong refractoriness and slow conduction, it can increase risk for proarrhythmia and sudden death, especially at high doses and in patients with prior myocardial damage. Propafenone increases AV node refractory period, slows intraatrial conduction, and reduces ventricular excitability. It also has weak β- and calcium channel blocking activity, and a vagolytic effect. Adverse effects in people include lightheadedness, nausea, vomiting, and proarrhythmia. Higher doses of these agents depress automaticity in the sinus node and specialized conducting tissues. Vasodilation, myocardial depression, and severe hypotension have occurred after IV injection. Bradycardia, intraventricular conduction disturbances, and consistent (although transient) hypotension, as well as nausea, vomiting, and anorexia, have occurred in dogs. Proarrhythmia is a serious potential adverse effect of these agents. Flecainide can be useful against paroxysmal SVT or AF but is not used for long-term therapy of AF, or in patients with myocardial dysfunction, ventricular hypertrophy, valvular disease, or ischemic heart disease. Propafenone has been effective in suppressing various SVTs, including those involving an accessory pathway.

CLASS II ANTIARRHYTHMIC DRUGS: β-ADRENERGIC BLOCKERS

Class II antiarrhythmic drugs act by blocking catecholamine effects. They slow heart rate, reduce myocardial O_2 demand, and increase AV conduction time and refractoriness. The antiarrhythmic effect of β-blockers relates to β_1-receptor blockade rather than direct electrophysiologic effects. They are often used in combination with a class I agent (such as procainamide or mexiletine), although their negative inotropic effect demands caution when used in animals with myocardial failure. β-receptor blockers are used in animals with supraventricular and ventricular tachyarrhythmias (especially those induced by enhanced sympathetic tone), certain congenital and acquired ventricular outflow obstructions, hyperthyroid heart disease, HCM, and other diseases or toxicities that cause excessive sympathetic stimulation. A β-blocker, rather than diltiazem, sometimes is used in conjunction with digoxin to slow the ventricular response rate to AF. A β-blocker, such as atenolol or propranolol, is considered the first-line antiarrhythmic agent in cats for both supraventricular and ventricular tachyarrhythmias.

β-adrenergic receptors have been classified into subtypes. β_1-receptors are located mainly in the myocardium and mediate increases in contractility, heart rate, AV conduction velocity, and automaticity in specialized fibers. Extracardiac β_2-receptors mediate bronchodilation and vasodilation, as well as renin and insulin release. There also are some β_2- and β_3-receptors in the heart. "Nonselective" β-blockers inhibit catecholamine binding to both β_1- and β_2-adrenergic receptors. Other β-blockers are more selective; they antagonize mainly one or the other receptor subtype (Table 4.3). The first-generation β-blockers (e.g., propranolol) have nonselective β-blocking effects. Second-generation agents (e.g., atenolol, metoprolol) are relatively β_1 selective. The third-generation β-blockers affect both β_1 and β_2 receptors but also antagonize α_1 receptors and may have other effects. A few β-blockers have some degree of intrinsic sympathomimetic activity.

The clinical antiarrhythmic effect of class II drugs is thought to relate to β_1-receptor blockade rather than to direct electrophysiologic mechanisms. In normal animals β-receptor blockers have little negative inotropic effect. However, they must be used cautiously in animals with underlying myocardial disease because increased sympathetic drive may be necessary to maintain cardiac output; marked depression of cardiac contractility, conduction, or heart rate can result in such cases, and CHF could be precipitated. β-blockers generally are contraindicated in patients with sinus bradycardia, sick sinus syndrome, high-grade AV block, or severe CHF and in animals also receiving a Ca^{++}-blocking drug. Nonselective β-blockers could increase peripheral vascular resistance (because of unopposed α-adrenergic effects) and provoke bronchoconstriction. β-blockers also can mask the early signs of acute hypoglycemia in diabetics (such as tachycardia, blood pressure changes) and reduce the release of insulin in response to hyperglycemia. Because the effect of β-blockers depends on the level of sympathetic activation, individual patient response is quite variable. Therefore initial dosages should be low and titrated upward cautiously, as needed.

TABLE 4.3

Characteristics of Selected β-Blockers

DRUG	ADRENERGIC RECEPTOR SELECTIVITY	LIPID SOLUBILITY	MAIN ROUTE OF ELIMINATION
Atenolol	β_1	0	RE
Carvedilol	β_1, β_2, α_1	+	HM
Esmolol	β_1	0	BE
Labetalol	β_1, β_2, α_1	++	HM
Metoprolol	β_1	++	HM
Nadolol	β_1, β_2	0	RE
Pindolol*	β_1, β_2	++	B
Propranolol	β_1, β_2	++	HM
Sotalol†	β_1, β_2	0	RE
Timolol	β_1, β_2	0	RE

B, Both renal excretion and hepatic metabolism are important; *BE,* blood esterases; *HM,* hepatic metabolism; *RE,* renal excretion.
*Has intrinsic sympathomimetic activity.
†Also has class III antiarrhythmic activity.

β-blockers enhance the depression of AV conduction produced by Ca^{++}-blockers, class I antiarrhythmic drugs, and digoxin. Use of a β-blocker and a Ca^{++}-blocker simultaneously can markedly decrease heart rate and myocardial contractility. Because of possible β-receptor upregulation (increased number or affinity of receptors) associated with long-term β-blockade, therapy should not be discontinued abruptly. Chronic β-blocker therapy might increase risk for hypotension and bradycardia during anesthesia.

Atenolol

Atenolol is a selective β_1-blocker. It is used commonly to slow sinus rate and AV conduction and to suppress sympathetically mediated ventricular premature beats. The half-life of atenolol is slightly more than 3 hours in dogs and about 3.5 hours in cats. Its oral bioavailability in both species is high (≈90%). Atenolol is excreted in the urine; renal dysfunction delays its clearance. Atenolol's β-blocking effect lasts more than 12 hours but less than 24 hours in normal cats. This drug is hydrophilic. Adverse CNS effects are unlikely because atenolol does not readily cross the blood-brain barrier. As with other β-blockers, weakness or exacerbation of heart failure can occur.

Propranolol

Propranolol HCl is a nonselective β-blocker. It is not recommended for patients with pulmonary edema, asthma, or chronic small airway disease because of the potential for bronchoconstriction caused by β_2-receptor antagonism.

Propranolol undergoes extensive first-pass hepatic metabolism, and oral bioavailability is low; however, bioavailability increases with hepatic enzyme saturation. Propranolol reduces hepatic blood flow, which prolongs its elimination as well as that of other drugs dependent on liver blood flow for their metabolism (such as lidocaine). Feeding delays oral absorption and increases drug clearance after IV dosing (by increasing hepatic blood flow). The half-life of propranolol in the dog is only about 1.5 hours (0.5-4.2 hours in cats); active metabolites exist. Dosing every 8 hours appears to be adequate in both species. IV propranolol is used mainly for refractory ventricular tachycardia (in conjunction with a class I drug) and for emergency treatment of atrial or junctional tachycardia.

Toxicity most often is related to excessive β-blockade; this can develop at relatively low doses in some animals. Bradycardia, heart failure, hypotension, bronchospasm, and hypoglycemia can occur. Infusion of a catecholamine (dopamine or dobutamine) will help reverse these effects. Propranolol and other lipophilic β-blockers can cause CNS effects such as depressed attitude and disorientation.

Esmolol

Esmolol HCl is an ultra-short-acting β_1-selective agent. It is metabolized rapidly by blood esterases and has a half-life of less than 10 minutes. Steady state occurs in 5 minutes after a loading dose, or 30 minutes without. Esmolol's effects end within 10 to 20 minutes after infusion is stopped. This drug is used for acute therapy of tachyarrhythmias and feline hypertrophic obstructive cardiomyopathy.

Other β-Blockers

Many other β-blocking drugs are available. Their receptor selectivity and pharmacologic characteristics vary. Sotalol is a β-blocker that also prolongs action potential duration at higher doses; therefore it is usually considered a class III agent (see later). Certain β-blockers have been useful in people with chronic, stable myocardial failure by reducing the cardiotoxic effects of excessive sympathetic stimulation,

improving cardiac function, and increasing survival time. These include the third-generation β-blocker, carvedilol; the second-generation agent, metoprolol; and some others. Despite theoretical and some experimental benefit, β-blocker therapy has not been shown to delay CHF or increase survival in dogs and cats.

Carvedilol blocks β_1-, β_2-, and α_1-adrenergic receptors; has antioxidant effects; reduces endothelin release; has some Ca^{++}-blocking effect; and is also thought to promote vasodilation by affecting either NO or prostaglandin mechanisms. Oral doses in dogs produce a wide range of peak plasma concentrations. Carvedilol is eliminated mainly through hepatic metabolism; the terminal half-life in dogs is less than 1 to 2 hours (i.e., shorter than in people), and the drug is highly protein-bound. Its β-blocking effect lasts for 12 hours, and some residual effect persists for up to 24 hours, consistent with active metabolite(s). In healthy dogs, low doses of carvedilol cause minimal hemodynamic effect, but, as with all β-blockers, animals in heart failure may not tolerate even small doses.

Metoprolol tartrate is another β_1-selective agent. It is well absorbed orally, but bioavailability is reduced by a large first-pass effect. There is minimal protein-binding. The drug is metabolized in the liver and excreted in the urine. Half-life is 1.6 hours in dogs and 1.3 hours in cats.

CLASS III ANTIARRHYTHMIC DRUGS

Common features of class III drugs include prolongation of the cardiac action potential and effective refractory period without a decrease in conduction velocity. Their effects are mediated by inhibition of potassium channels responsible for repolarization (delayed rectifier current). These agents are useful against ventricular arrhythmias, especially those caused by reentry. Class III drugs have antifibrillatory effects as well. They share some characteristics of other antiarrhythmic drug classes in addition to their class III effects.

Sotalol

Sotalol HCl is a nonselective β-blocker that has class III effects at higher doses. Its oral bioavailability is high, although absorption is reduced when given with food. Sotalol's half-life is about 5 hours in dogs. It is eliminated unchanged by the kidneys, and renal dysfunction prolongs elimination. Sotalol's β-blocking effect outlasts its plasma half-life. The drug has minimal hemodynamic effects, although it can cause slowed sinus rate, first-degree AV block, and hypotension. Proarrhythmia can occur (as with all antiarrhythmic agents), including torsades de pointes (a type of multiform ventricular tachycardia). Sotalol's class III effects occur at higher doses in dogs than in people. Doses used clinically in dogs may be producing primarily β-blocking effects. A high incidence of proarrhythmia (especially torsades de pointes), which is of concern in people taking sotalol, has not been reported clinically in dogs. Experimentally, in dogs with hypokalemia, co-administration of mexiletine reduced the proarrhythmic potential.

Sotalol may worsen heart failure in animals with DCM. However, sotalol is thought to have less negative inotropic effect than propranolol. Other adverse effects of sotalol have included hypotension, depression, nausea, vomiting, diarrhea, and bradycardia. There are sporadic anecdotal reports of aggression that resolved after sotalol was discontinued. Sotalol may induce or worsen neurogenic bradycardia in some Boxers with ventricular tachycardia. Like other β-blockers, sotalol therapy should not be discontinued abruptly.

Amiodarone

Amiodarone HCl is thought to produce its antiarrhythmic effects by prolonging the action potential duration and effective refractory period in both atrial and ventricular tissues. Although considered a class III agent, it shares properties with all three other antiarrhythmic drug classes. Amiodarone is an iodinated compound that also has noncompetitive α_1- and β-blocking effects, as well as Ca^{++} channel-blocking effects. The β-blocking effects occur soon after administration, but maximal class III effects (and prolongation of action potential duration and QT interval) are not achieved for weeks with chronic administration. Its Ca^{++}-blocking effects may inhibit triggered arrhythmias by reducing afterdepolarizations. Therapeutic doses slow the sinus rate, decrease AV conduction velocity, and minimally depress myocardial contractility and blood pressure. Indications for amiodarone include refractory atrial and ventricular tachyarrhythmias, especially reentrant arrhythmias using an accessory pathway. The IV form has been used for ventricular tachycardia and AF. However, use of the standard (older) IV formulation often precipitates hypotension and anaphylactoid reactions, related to the solvents (polysorbate 80 and benzyl alcohol) used to keep the drug in solution. Therapy for acute hypersensitivity reaction has included discontinuing the drug, and using diphenhydramine (e.g., 1 mg/kg IV), a corticosteroid (e.g., prednisolone 1-2 mg/kg IV), IV fluids and other supportive care as needed. Although antihistamine pretreatment, conservative dosing, and slow injection over 10 to 20 minutes have been helpful in some cases, use of standard amiodarone IV is NOT currently recommended. A newer amiodarone formulation (Nexterone) without polysorbate 80 and benzyl alcohol is available and thought to be safer.

The pharmacokinetics of amiodarone are complex. Chronic oral use is associated with a prolonged time to steady state (of several weeks), concentration of drug in myocardial and other tissues, and accumulation of an active metabolite (desethylamiodarone). Therapeutic serum concentration range is thought to be 1 to 2.5 μg/mL. Amiodarone has less of a proarrhythmic effect than other agents and could reduce the risk of sudden death because of its uniform prolongation of repolarization throughout the ventricles, as well as suppression of Purkinje fiber automaticity. In normal dogs IV amiodarone does not adversely affect contractility at cumulative doses less than 12.5 to 15 mg/kg. However, the potential exists for more profound cardiac depression and

hypotension in dogs with myocardial disease. Amiodarone use is not described in cats.

Amiodarone is associated with many potential adverse effects. Hepatopathy, GI abnormalities, and a positive Coombs test have been reported in Dobermans receiving amiodarone. Other long-term adverse effects can include depressed appetite, GI upset, pneumonitis leading to pulmonary fibrosis, thyroid dysfunction, thrombocytopenia, and neutropenia. Hypersensitivity reactions (with acute erythema, angioedema, pruritus, agitation), hypotension, or tremors have occurred in dogs, especially with IV administration (of the older formulation). Other adverse effects observed in people have included corneal microdeposits, photosensitivity, bluish skin discoloration, and peripheral neuropathy. Amiodarone can increase the serum concentration of digoxin, diltiazem, and possibly procainamide and quinidine.

Other Class III Agents

Ibutilide fumarate is somewhat effective for converting recent-onset AF in people, but there is little veterinary experience with this drug. In experimental dog studies, it suppressed sinus and AV node conduction, increased refractoriness, and prolonged the QT interval; it was only moderately effective in suppressing AF and has caused torsades de pointes. Dofetilide is another drug that selectively blocks the rapid component of the repolarizing K^+ current. It too is used in people for converting AF and to maintain sinus rhythm, but it may be more effective in preventing rather than terminating AF. Experimentally in dogs it prolongs the QT interval and can induce torsades de pointes, although it does not exacerbate left ventricular dysfunction. Dofetilide is metabolized in the liver and has both hepatic and renal clearance; the half-life is about 4.5 hours in dogs.

CLASS IV ANTIARRHYTHMIC DRUGS: CALCIUM ENTRY BLOCKERS

The Ca^{++} entry blockers are a diverse group of drugs that have the common property of decreasing cellular Ca^{++} influx by blocking transmembrane L-type calcium channels. As a group, these drugs can cause coronary and systemic vasodilation, enhance myocardial relaxation, and reduce cardiac contractility. The dihydropyridine group of Ca^{++}-blockers (such as amlodipine) primarily have vasodilating effects and do not appreciably alter cardiac conduction or contractility. The nondihydropyridine group (including diltiazem) slows conduction in tissues dependent on the slow inward Ca^{++} current, such as the sinus and AV nodes, thereby exerting some antiarrhythmic effects.

Possible adverse effects of Ca^{++}-blockers include reduced contractility, hypotension, depression, anorexia, lethargy, bradycardia, and AV block. Low initial doses are used and increased as needed to effect or to maximal recommended dose. Contraindications to Ca^{++} channel blocker use include sinus bradycardia, AV block, sick sinus syndrome, myocardial failure (for agents with pronounced negative inotropic effect), and digoxin toxicity. They usually are not prescribed in patients receiving a β-blocker because of additive negative effects on contractility, AV conduction, and heart rate. An overdose or exaggerated response to a Ca^{++}-blocker is treated with supportive care, including atropine for bradycardia or AV block, dopamine or dobutamine (see Box 3.1) and furosemide for heart failure, and dopamine or IV calcium salts for hypotension.

Diltiazem

Diltiazem HCl is a benzothiazepine Ca^{++} channel blocker. It slows AV conduction, causes potent coronary and mild peripheral vasodilation, and has a lesser negative inotropic effect than the prototypical Ca^{++} entry blocker, verapamil. Diltiazem is often combined with digoxin to further slow the ventricular response rate to AF in dogs with heart failure. It is indicated for other supraventricular tachyarrhythmias as well. Diltiazem has been used in cats with HCM, based on its potential to decrease heart rate, contractility, and myocardial oxygen demand and to enhance myocardial relaxation and perfusion. However, diltiazem has not been shown to improve clinical outcome.

Peak effects are seen within 2 hours of oral dosing; effects last at least 6 hours in dogs. Extensive first-pass effect limits bioavailability, especially in dogs. The half-life of diltiazem in the dog is just over 2 hours, but chronic dosing prolongs it because of enterohepatic circulation. In cats, the half-life is about 2 to 3 hours; plasma concentrations peak within 30 to 90 minutes and effects last for 8 hours, although much variability in pharmacokinetics exists among individual cats. The therapeutic range is 50 to 300 ng/mL. Diltiazem is metabolized in the liver; active metabolites exist. Drugs that inhibit hepatic CYP enzyme systems decrease the metabolism of diltiazem. Propranolol and diltiazem decrease each other's clearance when used simultaneously. Diltiazem ER is a sustained-release preparation; the 240 mg capsules contain four tablets of 60 mg each. Doses of 30 to 60 mg q24h produced serum concentrations >200 ng/mL for 24 hours in cats, although some cats on the lower dose reached <50 ng/mL by 24 hours. The 60-mg dose (~9-15 mg/kg) caused lethargy, GI signs, and weight loss in about one third of cats on chronic therapy. Another sustained-release preparation (Cardizem-CD capsules) at 10 mg/kg daily in cats produces plasma concentrations that peak in 6 hours and remain in the therapeutic range for 24 hours. A dose of 45 mg per cat is approximately equal to 105 mg of Cardizem-CD (or the amount that fits into the small end of a No. 4 gelatin capsule; a 300-mg capsule provides about 6.5 doses); this is given once daily.

Adverse effects of diltiazem are uncommon at therapeutic doses, although anorexia, nausea, and bradycardia may occur. Rarely, other GI, cardiac, and neurologic adverse effects develop. High liver enzyme activities and anorexia occur sporadically in cats. Some cats have become aggressive or shown other personality change when treated with diltiazem.

Verapamil

Verapamil HCl is a phenylalkylamine with potent cardiac effects, however it is rarely used now in dogs and cats; diltiazem is far preferred. Verapamil causes dose-related slowing of the sinus rate and AV conduction. Although it can be effective for supraventricular and atrial tachycardias, it has important negative inotropic and some vasodilatory effects that can cause cardiac decompensation, hypotension, and even death in animals with underlying myocardial disease. If used, a low IV dose is given very slowly; this can be repeated at 5- (or more) minute intervals if no adverse effects have occurred and the arrhythmia persists. Blood pressure should be monitored because of the potential for hypotension. Verapamil should not be used in animals with heart failure. Toxic effects of verapamil include sinus bradycardia, AV block, hypotension, reduced myocardial contractility, and cardiogenic shock. Verapamil reduces the renal clearance of digoxin.

Other Calcium Channel Blockers

Amlodipine besylate is a dihydropyridine Ca^{++}-blocker recommended as the first-line antihypertensive agent in cats. It is also used in some hypertensive dogs (see Chapter 11), usually with an ACEI. Amlodipine also is used to provide additional afterload reduction for dogs with chronic refractory heart failure from mitral valve disease (see Table 3.3). Amlodipine is not useful as an antiarrhythmic agent. Nifedipine is another potent vasodilator without antiarrhythmic effects.

SO-CALLED CLASS V DRUGS

Digoxin

Digoxin is mainly considered a positive inotropic drug (see Chapter 3); however, it also is used to slow the ventricular response rate (heart rate in animals with AF). Digoxin also can suppress some supraventricular premature depolarizations. These effects are mediated by the drug's enhancement of parasympathetic tone, which mainly affects the SA and AV nodes and atrial tissue, and its direct effects that prolong AV nodal conduction and refractory period.

Ivabradine

Ivabradine is a selective sinus node "funny" current (I_f) inhibitor that causes a dose-related slowing of heart rate. It has minimal effect on other ion channels and cardiac mechanical function. Heart rate reduction can reduce myocardial oxygen requirement and improve coronary perfusion. Ivabradine could prove useful for heart rate control in cats with cardiomyopathy or animals with heart failure and persistent sinus tachycardia despite reasonable control of congestive signs. However, currently there is little clinical veterinary experience with this agent. Ivabradine and its major active metabolite appear to reach peak plasma concentrations in ~1 hour after oral dosing in dogs and cats, with peak negative chronotropic effect in ~3 hours. Plasma half-life of ivabradine is ~2 hours in dogs and ~3.5 hours in cats. Ivabradine is metabolized by hepatic cytochrome P450 enzyme pathways. Dosing at 12-hour intervals appears appropriate in healthy cats. The drug should be avoided in patients with sick sinus syndrome.

ANTICHOLINERGIC DRUGS

Atropine and Glycopyrrolate

Anticholinergic drugs increase sinus node rate and AV conduction when vagal tone is increased (see Table 4.2). Parenteral atropine or glycopyrrolate is indicated for bradycardia or AV block induced by anesthesia, CNS lesions, and certain other diseases or toxicities. Atropine is a competitive muscarinic receptor antagonist. It is used to determine whether excess vagal tone is responsible for bradyarrhythmias caused by sinus and/or AV nodal dysfunction via the *atropine challenge test* (or *atropine response test*). Response to atropine challenge is most consistent with IV administration of 0.04 mg/kg. An ECG is recorded within 5 to 10 minutes after atropine injection. If the heart rate has not increased by at least 150%, the ECG is repeated 15 to 20 minutes after atropine injection; sometimes, an initial vagomimetic effect on the AV node lasts longer than 5 minutes. The normal sinus node response is a rate increase to 150 to 160 beats/min (or >135 beats/min). However, a positive atropine response test may not predict oral anticholinergic therapy efficacy. Atropine has little to no effect on bradyarrhythmias caused by intrinsic disease of the sinus or AV node.

Atropine given by any parenteral route can transiently exacerbate vagally mediated AV block when the atrial rate increases faster than AV conduction can respond. However, IV administration causes the fastest and most consistent onset and resolution of the exacerbated block, as well as the most rapid post-bradycardia heart rates, compared with the IM and SC routes. Unlike atropine, glycopyrrolate does not have centrally mediated effects and its effects are longer lasting than those of atropine.

Oral Anticholinergic Drugs

Some animals that respond to parenteral atropine or glycopyrrolate will also respond to an oral anticholinergic agent. Clinical signs may be relieved in these animals, at least for a time. Nevertheless, most animals with symptomatic bradyarrhythmias eventually require permanent pacemaker implantation to effectively control heart rate. Propantheline bromide and hyoscyamine sulfate are commonly used, but other oral anticholinergic agents also are available. Individual dosage is adjusted to effect. Oral absorption of propantheline is variable; food may decrease drug absorption.

Vagolytic drugs can aggravate paroxysmal supraventricular tachyarrhythmias (as in sick sinus syndrome) and should be used only cautiously as chronic therapy in those patients. Other adverse effects of anticholinergic therapy include vomiting, dry mouth, constipation, keratoconjunctivitis sicca, increased intraocular pressure, and drying of respiratory secretions.

SYMPATHOMIMETIC DRUGS

Isoproterenol HCl is a β-receptor agonist that has been used to treat symptomatic AV block or bradycardia refractory to atropine, although electrical pacing is safer and more effective. It can also be effective for torsades de pointes, although it could exacerbate this arrhythmia in some. Because of its affinity for β_2-receptors, isoproterenol can cause hypotension. It is not used for treating either heart failure or cardiac arrest. Isoproterenol can be arrhythmogenic, as can other catecholamines. The lowest effective dose (see Table 4.2) is used, and the animal is monitored closely for arrhythmias. Oral administration is not effective because of marked first-pass hepatic metabolism.

Terbutaline sulfate is a β_2-receptor agonist that could have a mild stimulatory effect on heart rate when given orally. Methylxanthine bronchodilators (such as aminophylline and theophylline) increase heart rate in some dogs with sick sinus syndrome or AV block when used at higher doses.

OTHER DRUGS

Edrophonium chloride is a short-acting anticholinesterase with nicotinic and muscarinic effects. Although mainly used for diagnosing myasthenia gravis, it slows AV conduction, which can help in the diagnosis and resolution of some cases of acute SVT. The drug's effect begins within 1 minute and lasts up to 10 minutes after IV injection. Adverse effects are primarily cholinergic and include GI (vomiting, diarrhea, salivation), respiratory (bronchospasm, respiratory paralysis, edema), cardiovascular (bradycardia, hypotension, cardiac arrest), and muscular (twitching, weakness) signs. Atropine and supportive care are used if necessary.

Phenylephrine HCl is an α-adrenergic agonist that increases blood pressure by peripheral vasoconstriction. A baroreflex-mediated increase in vagal tone slows AV conduction and is thought to underlie its effects on SVT. Phenylephrine's pressor effect begins rapidly after IV injection and persists for up to 20 minutes. The drug is contraindicated in patients with hypertension or ventricular tachycardia. Extravasation can cause ischemic necrosis of surrounding tissue.

Suggested Readings

Arrhythmias and Antiarrhythmic Drugs

Bicer S, et al. Effects of chronic oral amiodarone on left ventricular function, ECGs, serum chemistries and exercise tolerance in healthy dogs. *J Vet Intern Med*. 2002;16:247–254.

Bright JM, Martin JM, Mama K. A retrospective evaluation of transthoracic biphasic electrical cardioversion for atrial fibrillation in dogs. *J Vet Cardiol*. 2005;7:85–96.

Brundel BJJM, et al. The pathology of atrial fibrillation in dogs. *J Vet Cardiol*. 2005;7:121.

Cober RE, et al. Pharmacodynamic effects of ivabradine, a negative chronotropic agent, in healthy cats. *J Vet Cardiol*. 2011;13:231–242.

Cober RE, et al. Adverse effects of intravenous amiodarone in 5 dogs. *J Vet Intern Med*. 2009;23:657–661.

Coronel R, et al. Electrophysiological changes in heart failure and their implications for arrhythmogenesis. *Biochim Biophys Acta*. 2013;1832:2432–2441.

Cote E, et al. Atrial fibrillation in cats: 50 cases (1979-2002). *J Am Vet Med Assoc*. 2004;225:256–260.

Estrada AH, Pariaut R, Moise NS. Avoiding medical error during electrical cardioversion of atrial fibrillation: prevention of unsynchronized shock delivery. *J Vet Cardiol*. 2009;11:137–139.

Finster ST, et al. Supraventricular tachycardia in dogs: 65 cases (1990-2007). *J Vet Emerg Crit Care*. 2008;18:503–510.

Gelzer AR, et al. Combination therapy with digoxin and diltiazem controls ventricular rate in chronic atrial fibrillation in dogs better than digoxin or diltiazem monotherapy: a randomized crossover study in 18 dogs. *J Vet Intern Med*. 2009;23:499–508.

Gelzer AR, et al. Combination therapy with mexiletine and sotolol suppresses inherited ventricular arrhythmias in German Shepherd dogs better than mexiletine or sotolol monotherapy: a randomized cross-over study. *J Vet Cardiol*. 2010;12:93–106.

Johnson MS, Martin M, Smith P. Cardioversion of supraventricular tachycardia using lidocaine in five dogs. *J Vet Intern Med*. 2006;20:272–276.

Kellum HB, Stepien RL. Third degree atrioventricular block in 21 cats (1997-2004). *J Vet Intern Med*. 2006;20:97–103.

Kovach JA, Nearing BD, Verrier RL. Anger-like behavioral state potentiates myocardial ischemia-induced T-wave alternans in canines. *J Am Coll Cardiol*. 2001;37:1719–1725.

Kraus MS, et al. Toxicity in Doberman Pinschers with ventricular arrhythmias treated with amiodarone. *J Vet Intern Med*. 2009;23:1–6.

Menaut P, et al. Atrial fibrillation in dogs with and without structural or functional cardiac disease: a retrospective study of 109 cases. *J Vet Cardiol*. 2005;7:75–83.

Meurs KM, et al. Use of ambulatory electrocardiography for detection of ventricular premature complexes in healthy dogs. *J Am Vet Med Assoc*. 2001;218:1291–1292.

Meurs KM, et al. Comparison of the effects of four antiarrhythmic treatments for familial ventricular arrhythmias in Boxers. *J Am Vet Med Assoc*. 2002;221:522–527.

Miyamoto M, et al. Acute cardiovascular effects of diltiazem in anesthetized dogs with induced atrial fibrillation. *J Vet Intern Med*. 2001;15:559–563.

Moneva-Jordan A, et al. Sick sinus syndrome in nine West Highland White Terriers. *Vet Rec*. 2001;148:142–147.

Oyama MA, Prosek R. Acute conversion of atrial fibrillation in two dogs by intravenous amiodarone administration. *J Vet Intern Med*. 2006;20:1224–1227.

Pariaut R, et al. Lidocaine converts acute vagally associated atrial fibrillation to sinus rhythm in German Shepherd dogs with inherited arrhythmias. *J Vet Intern Med*. 2008;22:1274–1282.

Penning VA, et al. Seizure-like episodes in three cats with intermittent high-grade atrioventricular dysfunction. *J Vet Intern Med*. 2009;23:200–205.

Riesen SC, et al. Pharmacokinetics of oral ivabradine in healthy cats. *J Vet Pharmacol Ther*. 2011;34:469–475.

Riesen SC, et al. Effects of ivabradine on heart rate and left ventricular function in healthy cats and cats with hypertrophic cardiomyopathy. *Am J Vet Res*. 2012;73:202–212.

Santilli RA, et al. Utility of 12-lead electrocardiogram for differentiating paroxysmal supraventricular tachycardias in dogs. *J Vet Intern Med*. 2008;22:915–923.

Saunders AB, et al. Oral amiodarone therapy in dogs with atrial fibrillation. *J Vet Intern Med*. 2006;20:921–926.

Smith CE, et al. Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med*. 2007;21:265–273.

Stafford Johnson M, Martin M, Smith P. Cardioversion of supraventricular tachycardia using lidocaine in five dogs. *J Vet Intern Med*. 2006;20:272–276.

Thomason JD, et al. Bradycardia-associated syncope in seven Boxers with ventricular tachycardia (2002-2005). *J Vet Intern Med*. 2008;22:931–936.

Thomasy SM, et al. Pharmacokinetics of lidocaine and its active metabolite, monoethylglycinexylidide, after intravenous administration of lidocaine to awake and isoflurane-anesthetized cats. *Am J Vet Res*. 2005;66:1162–1166.

Wall M, et al. Evaluation of extended-release diltiazem once daily in cats with hypertrophic cardiomyopathy. *J Am Anim Hosp Assoc*. 2005;41:98–103.

Wright KN, Knilans TK, Irvin HM. When, why, and how to perform cardiac radiofrequency catheter ablation. *J Vet Cardiol*. 2006;8: 95–107.

Cardiac Pacing

Bulmer BJ, et al. Physiologic VDD versus nonphysiologic VVI pacing in canine third degree atrioventricular block. *J Vet Intern Med*. 2006;20:257–271.

Côté E, Laste NJ. Transvenous cardiac pacing. *Clin Tech Small Anim Pract*. 2000;15:165–176. (erratum: *Clin Tech Small Anim Pract* 2000; 15: 260).

Fine DM, Tobias AH. Cardiovascular device infections in dogs: report of eight cases and review of the literature. *J Vet Intern Med*. 2007;21:1265–1271.

Francois L, et al. Pacemaker implantation in dogs: results of the last 30 years. *Schweiz Arch Tierheilkd*. 2004;146:335–344.

Genovese DW, et al. Procedure times, complication rates, and survival times associated with single-chamber versus dual-chamber pacemaker implantation in dogs with clinical signs of bradyarrhythmia: 54 cases (2004-2009). *J Am Vet Med Assoc*. 2013;242: 230–236.

Johnson MS, et al. Results of pacemaker implantation in 104 dogs. *J Small Anim Pract*. 2007;48:4–11.

Oyama MA, Sisson DD, Lehmkuhl LB. Practices and outcomes of artificial cardiac pacing in 154 dogs. *J Vet Intern Med*. 2001;15:229–239.

Santilli RA, et al. Long-term intrinsic rhythm evaluation in dogs with atrioventricular block. *J Vet Intern Med*. 2016;30:58–62.

Visser LC, et al. Outcomes and complications associated with epicardial pacemakers in 28 dogs and 5 cats. *Vet Surg*. 2013;42: 544–550.

Ward JL, et al. Complication rates associated with transvenous pacemaker implantation in dogs with high-grade atrioventricular block performed during versus after normal business hours. *J Vet Intern Med*. 2015;29:157–163.

Wess G, et al. Applications, complications, and outcomes of transvenous pacemaker implantation in 105 dogs (1997-2002). *J Vet Intern Med*. 2006;20:877–884.

CHAPTER 5

Congenital Cardiac Disease



GENERAL CONSIDERATIONS

Common congenital cardiac malformations, as well as some that occur more sporadically, are described in this chapter. Most congenital heart defects produce an audible murmur (Fig. 5.1), although some serious malformations do not. Murmurs caused by congenital disease range in intensity from very loud to very soft depending on the type and severity of the defect and on hemodynamic factors. In addition to murmurs of congenital disease, clinically irrelevant "innocent" murmurs are relatively common in puppies and kittens. The physiologic cause of these murmurs is incompletely understood but may involve mismatch in growth rate between the heart and great vessels, relative anemia, or high sympathetic tone compared to adult animals. Innocent murmurs are usually soft systolic ejection–type murmurs heard best at the left heart base; their intensity may vary with heart rate or body position. Innocent murmurs tend to get softer and usually disappear by about 4 months of age. Murmurs caused by congenital disease usually persist beyond 6 months of age and may get louder with time, although this is not always the case. Careful examination and auscultation are important, not only in animals intended for breeding but also in working dogs and pets. Puppies and kittens with a soft left basilar systolic murmur and no other clinical or radiographic signs can be auscultated repeatedly as they grow to determine whether the murmur disappears. Further diagnostic tests are indicated in puppies or kittens with a murmur that is loud (audible on both sides of the chest), is heard loudest on the right hemithorax, or has a diastolic component, or with any murmur that persists beyond 4 to 6 months of age. Additional reasons to pursue diagnostic testing early include patients with clinical signs and those for which economic or breeding-potential decisions are pending.

Congenital heart defects most often involve either a valve (or valve region) or an abnormal communication between the systemic and pulmonary circulations. Abnormally formed valves can be insufficient, stenotic, or both. Other malformations can exist, and multiple anomalies occur in some patients. Congenital malformations vary widely in type and severity. The patient's prognosis and options for therapy depend on the definitive diagnosis and severity. Initial noninvasive testing usually includes thoracic radiographs, a complete echocardiogram (M-mode, two-dimensional [2-D], and color and spectral Doppler), and sometimes an electrocardiogram (ECG). A packed cell volume (PCV) is indicated in cases of right-to-left shunting to document erythrocytosis. Cardiac catheterization with selective angiocardiography can be useful to define some structural abnormalities and is used to guide transvascular interventional procedures. Surgical repair or palliation, balloon valvuloplasty, transcatheter shunt occlusion, or other interventional techniques may be helpful for some cases.

Patent ductus arteriosus (PDA), pulmonic stenosis (PS), and subaortic stenosis (SAS) have been identified in different surveys as the most common congenital cardiovascular anomalies in the dog. Persistent right aortic arch (a vascular ring anomaly), ventricular septal defect (VSD), malformations (dysplasia) of the atrioventricular (AV) valves, atrial septal defect (ASD), and tetralogy of Fallot (T of F) occur less frequently but are not rare. The most common congenital malformation in cats is VSD; other lesions include AV valve dysplasias, stenotic lesions (SAS and PS), ASD, T of F, and PDA. An AV septal (endocardial cushion) defect occurs more commonly in cats and consists of all or some of the following: a high VSD, a low ASD, and malformations of one or both AV valves. Endocardial fibroelastosis, mainly in Burmese and Siamese cats, also has been reported. Congenital malformations are more prevalent in male than female cats. Congenital malformations in both species can occur as isolated defects, which is most often the case, or in various combinations.

The prevalence of congenital defects is higher in purebred than in mixed-breed animals. In some studies, a polygenic inheritance pattern has been suggested, although there is more recent focus on a single major gene effect influenced by other modifying genes. Recognized breed predispositions are listed in Table 5.1; animals of other breeds can be affected with any of these defects as well.

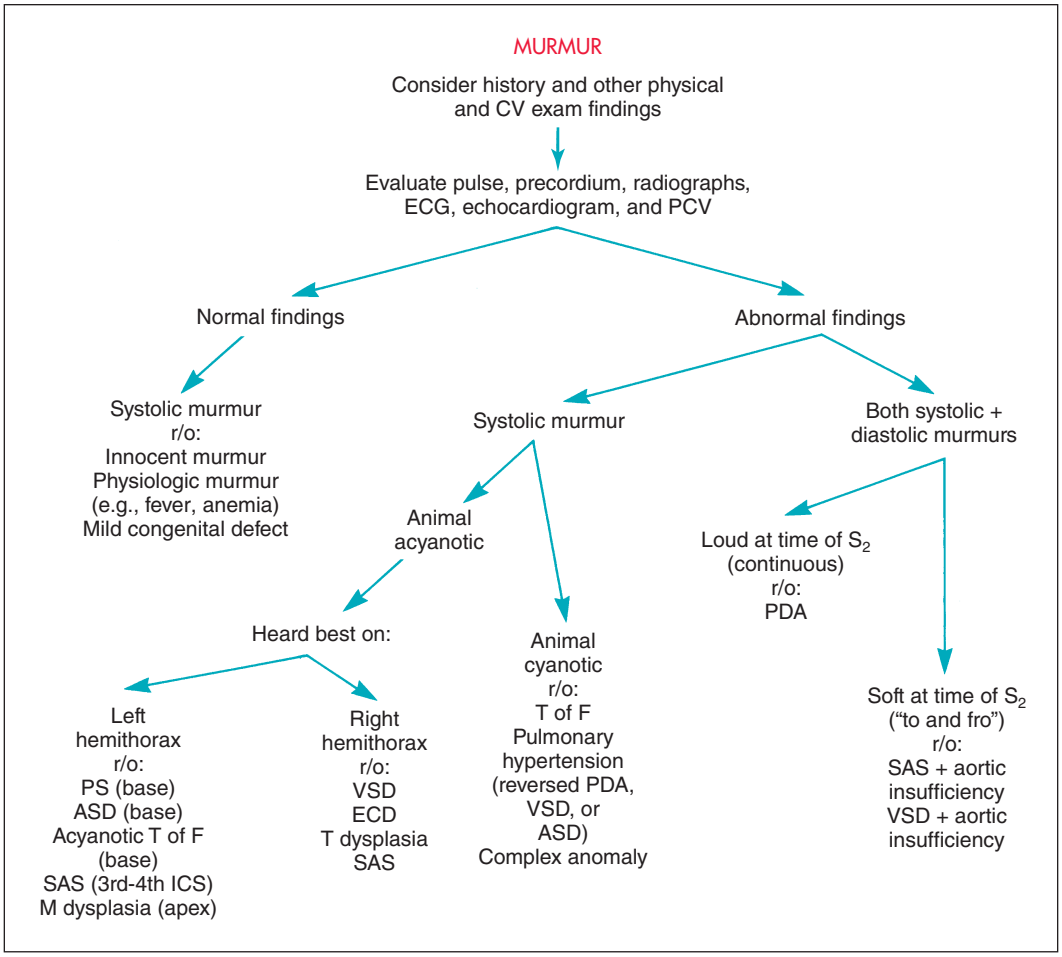


FIG 5.1
Flow chart for differentiating murmurs in puppies and kittens. Thoracic radiographs, ±ECG, also can help screen for structural abnormalities; however, referral to a veterinary cardiologist is recommended for more definitive evaluation. *ASD,* Atrial septal defect; *ECD,* endocardial cushion defect; *ECG,* electrocardiogram; *ICS,* intercostal space; *M,* mitral valve; *PCV,* packed cell volume; *PDA,* patent ductus arteriosus; *r/o,* rule out; *SAS,* subaortic stenosis; *T,* tricuspid valve; *T of F,* tetralogy of Fallot; *VSD,* ventricular septal defect.

EXTRACARDIAC ARTERIOVENOUS SHUNT

The most common congenital arteriovenous shunt is PDA. Rarely, similar hemodynamic and clinical abnormalities are caused by an aorticopulmonary window (a communication between the ascending aorta and pulmonary artery) or some other functionally similar communication in the hilar region.

PATENT DUCTUS ARTERIOSUS

Etiology and Pathophysiology

The ductus normally constricts to become functionally closed within hours of birth. Structural changes and permanent closure occur over the ensuing weeks. The ductal wall in animals with an inherited PDA is histologically abnormal and contains less smooth muscle and a greater proportion of elastic fibers, similar to the aortic wall. It is therefore unable to constrict effectively. When the ductus fails to close, blood shunts through it from the descending aorta into the pulmonary artery. Because aortic pressure normally is higher than pulmonic pressure throughout the cardiac cycle, shunting occurs continuously during both systole and diastole. This left-to-right shunt causes a volume overload of the pulmonary circulation, left atrium (LA), and left ventricle (LV). The shunt volume is directly related to the pressure difference (gradient) between the two circulations and the diameter of the ductus.

Hyperkinetic ("bounding") arterial pulses are characteristic of PDA. Blood runoff from the aorta into the pulmonary system allows diastolic aortic pressure to decrease rapidly below normal. The widened pulse pressure (difference between systolic and diastolic pressure) causes palpably stronger arterial pulses (Fig. 5.2).

TABLE 5.1

Breed Predispositions for Congenital Heart Disease

DISEASE	BREED
Patent ductus arteriosus	Maltese, Pomeranian, Shetland Sheepdog, English Springer Spaniel, Keeshond, Bichon Frise, Toy and Miniature Poodles, Yorkshire Terrier, Collie, Cocker Spaniel, German Shepherd Dog, Chihuahua, Kerry Blue Terrier, Labrador Retriever, Newfoundland, Welsh Corgi; female > male
Subaortic stenosis	Newfoundland, Golden Retriever, Rottweiler, Boxer, German Shepherd Dog, Great Dane, German Short-Haired Pointer, Bouvier des Flandres, Samoyed (valvular aortic stenosis: Bull Terrier)
Pulmonic stenosis	English Bulldog (male > female), Mastiff, Samoyed, Miniature Schnauzer, West Highland White Terrier, Cocker Spaniel, Beagle, Labrador Retriever, Basset Hound, Newfoundland, Airedale Terrier, Boykin Spaniel, Chihuahua, Scottish Terrier, Boxer, Chow, Miniature Pinscher, other terriers & spaniels
Ventricular septal defect	English Bulldog, English Springer Spaniel, Keeshond, West Highland White Terrier; cats
Atrial septal defect	Samoyed, Doberman Pinscher, Boxer
Tricuspid dysplasia	Labrador Retriever, German Shepherd Dog, Boxer, Weimaraner, Great Dane, Old English Sheepdog, Golden Retriever; other large breeds (male > female?); cats
Mitral dysplasia	Bull Terrier, German Shepherd Dog, Great Dane, Golden Retriever, Newfoundland, Mastiff, Dalmatian, Rottweiler (?); cats (male > female)
Tetralogy of Fallot	Keeshond, English Bulldog
Persistent right aortic arch	German Shepherd Dog, Great Dane, Irish Setter

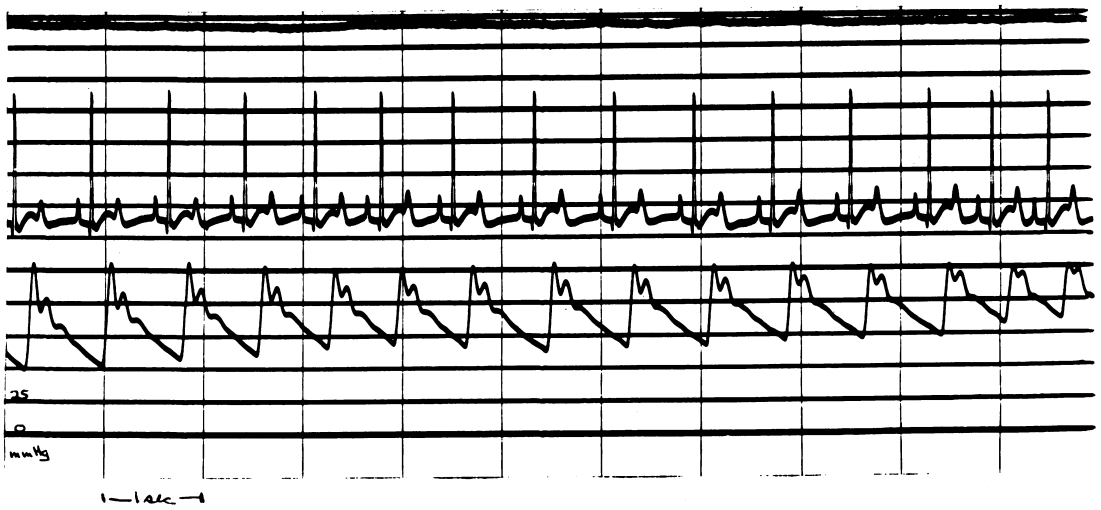


FIG 5.2
Continuous femoral artery pressure recording during surgical ligation of a patent ductus arteriosus in a Poodle. The wide pulse pressure (left side of trace) narrows as the ductus is closed (right side of trace). Diastolic arterial pressure rises because blood runoff into the pulmonary artery is curtailed. (Courtesy Dr. Dean Riedesel.)

Compensatory mechanisms that promote increased heart rate and volume retention maintain adequate systemic blood flow. However, the LV is subjected to a great hemodynamic burden, especially when the ductus is large, because the increased stroke volume is pumped into the relatively high pressure aorta. Left ventricular (LV) and mitral annulus dilation in turn cause mitral regurgitation and further volume overload. Excess fluid retention, declining myocardial contractility stemming from the chronic volume overload, and arrhythmias contribute to the development of left-sided congestive heart failure (CHF).

In rare cases, excessive pulmonary blood flow from a large ductus causes pulmonary vascular changes, abnormally high resistance, and pulmonary hypertension (see p. 114). As

pulmonary artery pressure rises toward aortic pressure, progressively less blood shunting occurs. If pulmonary artery pressure exceeds aortic pressure, shunt reversal (right-to-left flow) occurs. Approximately 15% of dogs with PDA have reversed (right-to-left) shunting. However, as most such shunts are already "reversed" (right-to-left) by the time of first evaluation, it is difficult to know whether these patients have retained fetal pulmonary vascular resistance (congenital pulmonary hypertension) causing right-to-left shunting from birth or whether shunt flow actually reversed postnatally following pulmonary vascular changes from volume overload.

Clinical Features

The left-to-right shunting PDA is by far the most common form; clinical features of reversed PDA are described on page 115. The prevalence of PDA is higher in certain breeds of dogs; a polygenic inheritance pattern is thought to exist, particularly in miniature Poodles. The prevalence is two or more times greater in female than male dogs. Most animals are asymptomatic when first diagnosed, although some patients may present with clinical signs of left-sided CHF including exercise intolerance, tachypnea, or cough. A continuous murmur heard best high at the left base (see p. 11), often with a precordial thrill, is typical for a left-to-right PDA; sometimes only the systolic component of the murmur is heard more caudally near the mitral valve area. Other findings include hyperkinetic (bounding, "water hammer") arterial pulses and pink mucous membranes.

Diagnosis

Radiographs usually show cardiac elongation (left heart dilation), left atrial (LA) and auricular enlargement, and pulmonary overcirculation (Table 5.2). A bulge often is evident in the descending aorta ("ductus bump"), main pulmonary trunk, or both (Fig. 5.3). The triad of all three bulges (i.e., pulmonary trunk, aorta, and left auricle), located in that order from the 1 to 3 o'clock position on a dorsoventral (DV) radiograph, is a classic finding but not always seen. Animals with left-sided CHF also show evidence of pulmonary edema. Characteristic ECG findings suggest LV and LA enlargement, including wide P waves, tall R waves, and often deep Q waves in leads II, aVF, and CV_6LL. Changes in the ST-T segment secondary to LV enlargement can occur. However, the ECG is normal in some animals with PDA. Most patients have normal sinus rhythm, although ventricular or supraventricular arrhythmias (including atrial fibrillation) can occur.

Echocardiography also shows left heart enlargement and pulmonary trunk dilation. LV fractional shortening can be normal or decreased, and the E point–septal separation is often increased. The ductus itself can be difficult to visualize because of its location between the descending aorta and pulmonary artery; angulation from the left cranial short axis view usually is most helpful. Doppler interrogation documents continuous, turbulent flow into the pulmonary artery (Fig. 5.4). The maximum aortic-to-pulmonary artery pressure gradient can be estimated using velocity of systolic PDA flow. Cardiac catheterization generally is unnecessary for

TABLE 5.2

Radiographic Findings in Common Congenital Heart Defects

DEFECT	HEART	PULMONARY VESSELS	OTHER
PDA	LAE, LVE; left auricular bulge; ±increased cardiac width	Overcirculated	Bulge(s) in descending aorta + pulmonary trunk; ±pulmonary edema
SAS	±LAE, LVE	Normal	Wide cranial cardiac waist (dilated ascending aorta)
PS	RAE, RVE; reverse D	Normal to undercirculated	Pulmonary trunk bulge
VSD	LAE, LVE; ±RVE	Overcirculated	±Pulmonary edema; ±pulmonary trunk bulge (large shunts)
ASD	RAE, RVE	±Overcirculated	±Pulmonary trunk bulge
T dys	RAE, RVE; ±globoid shape	Normal	Caudal cava dilation; ±pleural effusion, ascites, hepatomegaly
M dys	LAE, LVE	±Venous hypertension	±Pulmonary edema
T of F	RVE, RAE; reverse D	Undercirculated; ±prominent bronchial vessels	Normal to small pulmonary trunk; ±cranial aortic bulge on lateral view
PRAA	Normal	Normal	Focal leftward and ventral tracheal deviation ± narrowing cranial to heart; wide cranial mediastinum; megaesophagus (±aspiration pneumonia)

ASD, Atrial septal defect; *LAE,* left atrial enlargement; *LVE,* left ventricular enlargement; *M dys,* mitral dysplasia; *PDA,* patent ductus arteriosus; *PRAA,* persistent right aortic arch; *PS,* pulmonic stenosis; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement; *SAS,* subaortic stenosis; *T dys,* tricuspid dysplasia; *T of F,* tetralogy of Fallot; *VSD,* ventricular septal defect.

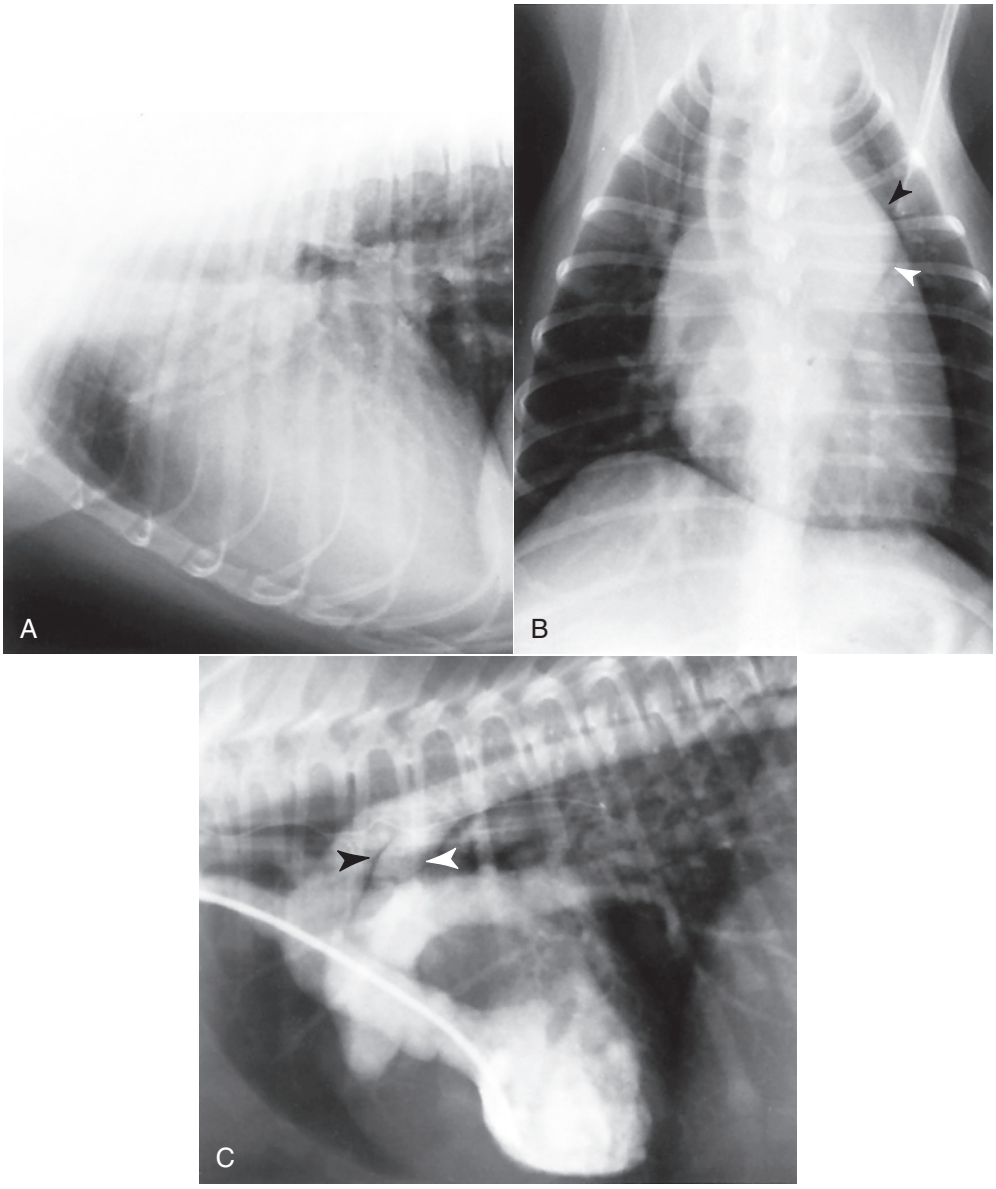


FIG 5.3
Lateral **(A)** and dorsoventral (DV) **(B)** radiographs from a dog with a patent ductus arteriosus. Note the large and elongated heart and prominent pulmonary vasculature. A large bulge is seen in the descending aorta on the DV view (*arrowheads* in **B**). **(C)** Angiocardiogram obtained using a left ventricular injection outlines the left ventricle, aorta, patent ductus *(arrowheads),* and pulmonary artery.

diagnosis, although it is important during interventional procedures. Angiocardiography shows left-to-right shunting through the ductus and facilitates measurement of the minimal ductal diameter (see Fig. 5.3, *C*).

Treatment and Prognosis

Closure of a left-to-right PDA is recommended as soon as is feasible in almost all cases, either by surgical or transcatheter methods. Surgical ligation via left lateral thoracotomy is successful in most cases. A perioperative mortality of about 5% has been reported. Several methods of transcatheter PDA occlusion are available and involve placement of a vascular occluding device within the ductus, such as the Amplatz canine ductal occluder (ACDO) or wire coils with attached thrombogenic tufts. Vascular access usually is via the femoral artery, although some have used a venous approach to the ductus. Where available, transcatheter PDA occlusion offers a much less invasive alternative to surgical ligation. Overall, ACDO occlusion has shown the highest success and lowest complication rates among occlusion methods and is considered the treatment of choice; however, the minimal device size (3 mm) is a limitation for very small puppies. Complications can occur with both surgical and interventional closure, including hemorrhage, residual ductal flow, and aberrant

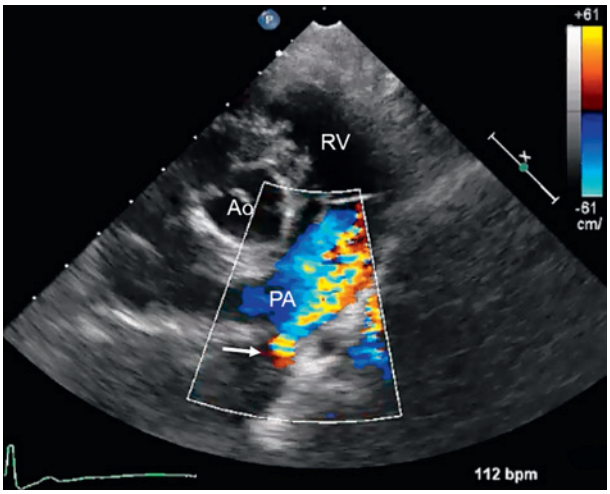


FIG 5.4
Continuous turbulent flow into the pulmonary artery from the area of the patent ductus arteriosus *(arrow)* is illustrated in a color flow Doppler image from the left cranial parasternal position, in an adult female Boston Terrier. *Ao,* Aorta; *PA,* main pulmonary artery; *RV,* right ventricle.

device embolization. Reverse remodeling of LV and LA enlargement occurs in most dogs after successful occlusion. Although LV systolic dimension and function may never completely normalize, residual changes generally are clinically insignificant. A normal life span can be expected after uncomplicated ductal closure.

Animals with left-sided CHF are treated with furosemide, pimobendan, an angiotensin-converting enzyme inhibitor (ACEI), rest, and dietary sodium restriction (see Chapter 3). Arrhythmias are treated as needed. Ductal closure is recommended as soon as feasible once CHF is stabilized. Tapering or discontinuation of CHF medications may be possible following successful closure.

If the ductus is not corrected, prognosis depends on ductal size and the level of pulmonary vascular resistance. Left-sided CHF is the eventual outcome for most patients that do not undergo ductal closure; more than 50% of affected dogs die within the first year of life. In animals with pulmonary hypertension and shunt reversal, ductal closure generally is contraindicated because the ductus acts as a "pop-off" valve for the high right-sided pressures. Ductal ligation in animals with reversed PDA is unlikely to produce improvement and can lead to acute right ventricular (RV) failure.

VENTRICULAR OUTFLOW OBSTRUCTION

Ventricular outflow obstruction can occur at the semilunar valve, just below the valve (subvalvular), or above the valve in the proximal great vessel (supravalvular). SAS and PS are most common in dogs and cats. Stenotic lesions impose a pressure overload on the affected ventricle, requiring higher systolic pressure and a slightly longer time to eject blood across the narrowed outlet. A systolic pressure gradient is generated across the stenotic region, as downstream pressure is normal. The magnitude of this gradient is related to the severity of the obstruction and strength of ventricular contraction.

Concentric myocardial hypertrophy typically develops in response to a systolic pressure overload; some dilation of the affected ventricle also can occur. Ventricular hypertrophy can impede diastolic filling (by increasing ventricular stiffness) or lead to secondary AV valve regurgitation. Heart failure results when ventricular diastolic and atrial pressures are elevated. Cardiac arrhythmias can contribute to the onset of CHF. Furthermore, the combination of outflow obstruction, paroxysmal arrhythmias, and/or inappropriate bradycardia reflexively triggered by ventricular baroreceptor stimulation can result in signs of low cardiac output. These signs are more often associated with severe outflow tract obstruction and include exercise intolerance, syncope, and sudden death.

SUBAORTIC STENOSIS

Etiology and Pathophysiology

Subvalvular narrowing caused by a fibrous or fibromuscular ring is the most common type of LV outflow stenosis in dogs. Certain larger breeds of dog are predisposed to this defect, including Newfoundlands, Golden Retrievers, and Rottweilers. SAS is thought to be inherited as an autosomal dominant trait with modifying genes that influence its phenotypic expression; a causative genetic mutation has been identified in Newfoundland dogs. SAS occurs occasionally in cats; supravalvular lesions have been reported in this species as well. Valvular aortic stenosis is reported in Bull Terriers.

The spectrum of SAS severity varies widely; three grades of SAS have been described in Newfoundland dogs. The mildest (grade I) causes no clinical signs or murmur and only subtle subaortic fibrous tissue ridging seen on postmortem examination. Moderate (grade II) SAS causes mild clinical and hemodynamic evidence of the disease, with an incomplete fibrous ring below the aortic valve found at postmortem. Dogs with grade III SAS have severe disease and a complete fibrous ring around the outflow tract. Some cases have an elongated, tunnel-like obstruction. Malformation of the mitral valve apparatus can exist as well, and a component of dynamic LV outflow tract obstruction (with or without systolic anterior motion of the mitral valve) might be important in some dogs.

Unlike many other congenital heart defects, the lesion itself is not present at birth; rather, patients are born with abnormal tissue in the subvalvular region of the conotruncal septum that retains the ability to proliferate and undergo chondrogenic differentiation. The obstructive lesion of SAS therefore develops postnatally during the first several months of life and may continue to worsen until the dog is fully grown (1-2 years of age). Murmur intensity therefore often increases over time and usually increases dynamically with exercise or excitement. Because of such factors, as well as the presence of physiologic murmurs in some animals,

definitive diagnosis and genetic counseling to breeders can be difficult.

The severity of the stenosis determines the degree of LV pressure overload and resulting concentric hypertrophy. Coronary perfusion is easily compromised in animals with severe LV hypertrophy. Myocardial capillary density can become inadequate as hypertrophy progresses. Furthermore, the high systolic wall tension, along with coronary narrowing, can cause systolic flow reversal in small coronary arteries. These factors contribute to intermittent myocardial ischemia and secondary fibrosis. Clinical sequelae include arrhythmias, syncope, and sudden death. Many animals with SAS also have aortic or mitral valve regurgitation because of related malformations or secondary changes; this imposes an additional volume overload on the LV. Left-sided CHF develops in some cases. Animals with SAS are thought to be at higher risk for aortic valve endocarditis because of jet lesion injury to the underside of the valve (see p. 132 and Figs. 6.5 and 6.6).

Clinical Features

Most patients with SAS are asymptomatic on initial presentation. Clinical signs of fatigue, exercise intolerance or exertional weakness, syncope, or sudden death occur in about one third of dogs with SAS. Low-output signs can result from severe outflow obstruction, tachyarrhythmias, or sudden reflex bradycardia and hypotension resulting from the activation of ventricular mechanoreceptors. Signs of left-sided CHF can develop, usually in conjunction with concurrent mitral or aortic regurgitation, other cardiac malformations, or acquired endocarditis. Dyspnea is the most commonly reported sign in cats with SAS.

The characteristic murmur of SAS is a harsh systolic ejection murmur heard near the aortic valve area at the left heart base, with or without a precordial thrill. This murmur often radiates equally or more loudly to the right heart base because of the orientation of the aortic arch. The murmur typically is heard over the carotid arteries as well and, in severe cases, sometimes even radiates to the calvarium. Aortic regurgitation can produce a diastolic murmur at the left base or may be inaudible. Other common physical examination findings in dogs with moderate to severe stenosis include weak and late-rising femoral pulses *(pulsus parvus et tardus)*, although concurrent severe aortic regurgitation can increase the arterial pulse strength. There may be evidence of pulmonary edema or arrhythmias.

In mild cases, a soft, poorly radiating ejection murmur at the left and sometimes right heart base may be the only abnormality found on physical examination. Low-grade functional LV outflow murmurs that are not associated with SAS are common in normal Greyhounds, other sighthounds, and Boxers; presence of such physiologic flow murmurs can complicate diagnosis of SAS.

Diagnosis

Radiographic abnormalities (see Table 5.2) can be subtle, especially in animals with mild SAS. The LV can appear normal or enlarged; mild to moderate LA enlargement is more likely with severe SAS or concurrent MR. Poststenotic dilation in the ascending aorta can cause a prominent cranial waist in the cardiac silhouette (especially on a lateral view) and cranial mediastinal widening. The ECG often is normal, although evidence of LV hypertrophy (left axis deviation) or enlargement (tall R waves) can be present. Depression of the ST segment in leads II and aVF can occur from myocardial ischemia or secondary to hypertrophy; exercise induces further ischemic ST-segment changes in some animals. Ventricular tachyarrhythmias are common.

Echocardiography reveals the extent of LV hypertrophy and subaortic narrowing. A discrete tissue ridge below the aortic valve is evident in many animals with moderate to severe disease (Fig. 5.5). Increased LV subendocardial

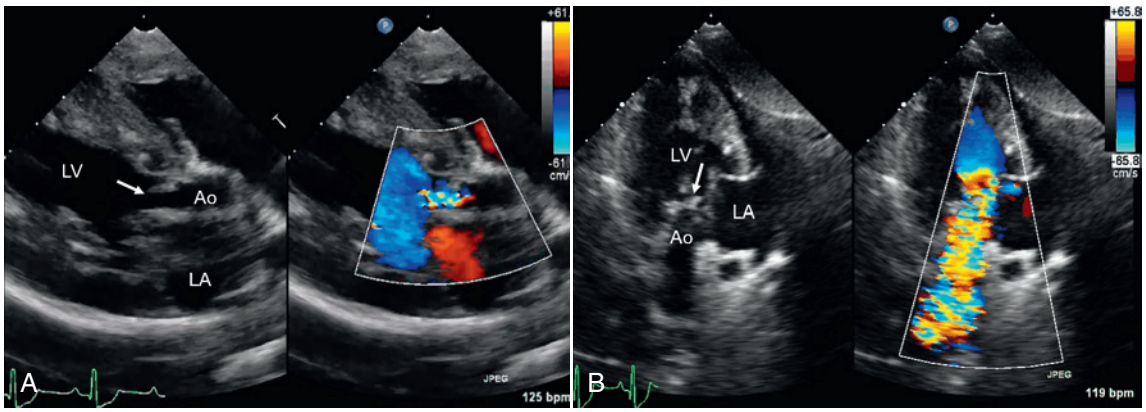


FIG 5.5
Right parasternal long-axis **(A)** and subcostal **(B)** echocardiographic images from a 3-month-old male Rottweiler with severe subaortic stenosis. Note the ridge of tissue causing a tunnel-like defect *(arrow)* below the aortic valve, creating a fixed outflow tract obstruction. Color Doppler reveals turbulent, high-velocity flow through the left ventricular outflow tract and ascending aorta in systole **(B),** as well as mild aortic insufficiency **(A).** *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

echogenicity (probably from fibrosis) is common in animals with severe obstruction; systolic anterior motion of the anterior mitral leaflet and mid-systolic partial aortic valve closure suggest concurrent dynamic LV outflow obstruction. Ascending aorta dilation, aortic valve thickening, and LA enlargement with hypertrophy may also be seen. In mildly affected animals, 2-D and M-mode findings may be unremarkable. Doppler echocardiography reveals systolic turbulence originating below the aortic valve and extending into the aorta, as well as high peak systolic outflow velocity (see Fig. 5.5). Some degree of aortic or mitral regurgitation is common. Spectral Doppler studies are used to estimate the stenosis severity by calculating the pressure gradient across the LV outflow tract (between the LV and aorta). A pressure gradient of <50 mm Hg is defined as mild stenosis, 50 to 80 mm Hg is moderate stenosis, and >80 mm Hg indicates severe stenosis. The LV outflow tract should be interrogated from more than one position to achieve the best possible alignment with blood flow. The subcostal (subxiphoid) position usually yields the highest-velocity signals, although the left apical position is optimal in some animals. Doppler-estimated systolic pressure gradients in unanesthetized animals are usually 40% to 50% higher than those recorded during cardiac catheterization under anesthesia.

The Doppler-estimated aortic outflow velocity might be only equivocally high in animals with mild SAS, especially with suboptimal Doppler beam alignment. With optimal alignment, aortic root velocities of less than 1.9 m/sec are typical in normal unsedated dogs; velocities over approximately 2.25 m/sec are generally considered abnormal. Peak velocities in the equivocal range between these values could indicate the presence of mild SAS, especially if other evidence of disease exists, such as a subaortic ridge, aortic regurgitation, or disturbed flow in the outflow tract or ascending aorta with an abrupt increase in velocity. This mainly is of concern when selecting animals for breeding. In some breeds (e.g., Boxer, Golden Retriever, Greyhound), outflow velocities in this equivocal range (1.8-2.25 m/sec) are common in normal dogs. This could reflect breed-specific variation in LV outflow tract anatomy or response to sympathetic stimulation, rather than SAS. A limitation of using the estimated pressure gradient to assess outflow obstruction severity is the dependence of this gradient on blood flow. Factors causing sympathetic stimulation and increased cardiac output (e.g., excitement, exercise, fever) will increase outflow velocities, whereas myocardial failure, cardiodepressant drugs, and other causes of reduced stroke volume will decrease recorded velocities. Cardiac catheterization and angiocardiography rarely are used now to diagnose or quantify SAS, except in conjunction with balloon dilation of the stenotic area.

Treatment and Prognosis

Several palliative surgical techniques have been attempted in dogs with severe SAS. Although some have reduced the LV systolic pressure gradient and possibly improved exercise ability, because of high complication rates, expense, and lack of a long-term survival advantage, surgery is not recommended. Likewise, transvascular balloon dilation of the stenotic area can reduce the measured gradient in some dogs; however, significant survival benefit has not been documented with this procedure. More recently, a combined valvuloplasty procedure involving cutting balloon valvuloplasty followed by high-pressure balloon dilation has been tried, with the goal of "scoring" (disrupting) the fibrous ring to make the subvalvular region more amenable to balloon dilation. This procedure can reduce LV pressure gradient and appears to be safe, although serious complications can occur. However, some degree of re-stenosis is common by 6 to 12 months postprocedure. As with other interventions for SAS, long-term survival benefit of this combined cutting and high-pressure balloon dilation procedure has not been documented.

Medical therapy with a β-blocker has been advocated in patients with moderate to severe SAS, to reduce myocardial oxygen demand and minimize the frequency and severity of arrhythmias. Animals with a high pressure gradient, marked ST-segment depression, frequent ventricular premature beats, or a history of syncope might be more likely to benefit from this therapy. Whether β-blockers prolong survival is unclear. Exercise restriction is advised for animals with moderate to severe SAS. Prophylactic antibiotic therapy is recommended for animals with SAS before any procedures with the potential to cause bacteremia (e.g., dentistry) are done, although the efficacy of this practice in preventing endocarditis is unclear.

The prognosis in dogs and cats with severe stenosis (pressure gradient > 80 mm Hg) is guarded. Median survival time is approximately 4.5 years, with a bimodal age distribution describing cause of death. Sudden death is more common in dogs younger than 3 years of age; overall, approximately 20% of dogs with SAS die suddenly. In contrast, infective endocarditis and CHF are more likely to develop later in life (8-10 years) in surviving dogs. Atrial and ventricular arrhythmias and worsened mitral regurgitation are complicating factors. Dogs with mild stenosis (pressure gradient < 50 mm Hg) could live a normal life span without clinical signs.

PULMONIC STENOSIS

Etiology and Pathophysiology

PS is more common in small breeds of dogs. Some cases of valvular PS result from simple fusion of the valve cusps, but valve dysplasia is more common. Dysplastic valve leaflets are variably thickened, asymmetric, and partially fused, with or without a hypoplastic valve annulus. RV pressure overload leads to concentric hypertrophy, as well as secondary dilation of the RV. Severe ventricular hypertrophy promotes myocardial ischemia and its sequelae. Excessive muscular hypertrophy in the infundibular region below the valve can create a dynamic subvalvular component to the stenosis. Other variants of PS, including supravalvular stenosis and RV muscular partition (double-chamber RV), occur rarely.

Turbulence caused by high-velocity flow across the stenotic orifice leads to poststenotic dilation in the main

pulmonary trunk. Right atrial (RA) dilation from secondary tricuspid insufficiency and high RV filling pressure predisposes to atrial tachyarrhythmias and right-sided CHF. The combination of PS and a patent foramen ovale or ASD can allow right-to-left shunting at the atrial level.

A single anomalous coronary artery has been described in some Bulldogs and other brachycephalic breeds with PS and is thought to contribute to the outflow obstruction. In such cases, palliative surgical procedures and balloon valvuloplasty can cause death secondary to transection or avulsion of the major left coronary branch that wraps circumferentially around the stenotic pulmonic valve annulus.

Clinical Features

Many dogs with PS are asymptomatic when diagnosed, although some have right-sided CHF or a history of exercise intolerance or syncope. Clinical signs might not develop until the animal is several years old, even in those with severe stenosis. Physical examination findings characteristic of moderate to severe stenosis include a prominent right precordial impulse and a systolic ejection murmur heard best high at the left heart base, with or without precordial thrill. The murmur can radiate cranioventrally and to the right in some cases but usually is not heard over the carotid arteries. An early systolic click sometimes is identified; this is probably caused by abrupt checking of a fused valve at the onset of ejection. A murmur of tricuspid insufficiency or arrhythmias can be heard in some cases. Femoral pulses are typically normal and mucous membranes usually pink. Ascites, jugular venous distension or pulsation, and other signs of right-sided CHF are present in some cases. Occasionally, cyanosis accompanies right-to-left shunting through a concurrent atrial or VSD.

Diagnosis

Radiographic findings typically seen with PS are outlined in Table 5.2. Marked RV hypertrophy shifts the cardiac apex dorsally and to the left. The heart can appear as a "reverse D" shape on a DV or ventrodorsal (VD) view. A variably sized pulmonary trunk bulge (poststenotic dilation) is best seen at the 1 o'clock position on a DV or VD view (Fig. 5.6). The size of the poststenotic dilation does not necessarily correlate with the severity of the pressure gradient. Diminutive peripheral pulmonary vasculature and/or a dilated caudal vena cava may be apparent. ECG changes are more common with moderate to severe stenosis. These include an RV hypertrophy pattern, right axis deviation, and sometimes an RA enlargement pattern or tachyarrhythmias.

Echocardiographic findings characteristic of moderate to severe stenosis include RV concentric hypertrophy and enlargement. The interventricular septum appears flattened when pressure in the RV exceeds that in the LV and pushes it toward the left; paradoxical septal motion may occur. Secondary RA enlargement is common as well, especially with concurrent tricuspid regurgitation (TR). A thickened, asymmetric, or otherwise malformed pulmonic valve usually can be identified (see Fig. 5.7), although the outflow region sometimes is narrow and difficult to clearly visualize. Poststenotic dilation of the main pulmonary trunk is expected. Ascites or pleural effusion accompany secondary right-sided CHF. Doppler evaluation along with anatomic findings provide an estimate of PS severity. The pressure gradient between the RV and PA is estimated by measuring peak blood flow velocity across the valve. PS generally is considered mild if the Doppler-derived gradient is <50 mm Hg, moderate if pressure gradient is 50 to 80 mm Hg, and severe if it is >80 mm Hg. Cardiac catheterization and angiocardiography also can be used to assess the pressure gradient across the stenotic valve, diameter of the valve annulus, and other anatomic features. Doppler-estimated systolic pressure gradients in unanesthetized animals usually are 40% to 50% higher than those recorded during cardiac catheterization.

Treatment and Prognosis

Balloon valvuloplasty is recommended for palliation of severe (and sometimes moderate) stenosis, especially if infundibular hypertrophy is not excessive. This procedure can reduce or eliminate clinical signs and improves long-term survival in severely affected animals. Balloon valvuloplasty, done in conjunction with cardiac catheterization and angiocardiography, involves passing a specially designed balloon catheter across the valve and inflating the balloon to enlarge the stenotic orifice. Pulmonary valves with mild to moderate thickening and simple fusion of the leaflets with normal annulus size are likely to be easier to effectively dilate. Dysplastic valves with annular hypoplasia can be more difficult to dilate effectively, but good results are possible in some cases. Successful balloon valvuloplasty is generally defined as at least 50% reduction in prevalvuloplasty pressure gradient or reduction to pressure gradient of less than 50 mm Hg. Various surgical procedures also have been used to palliate moderate to severe PS in dogs, including pulmonary arteriotomy for valvulotomy and patch grafting, or placement of a valved RV-PA conduit. Balloon valvuloplasty usually is attempted before a surgical procedure because it is less risky. Animals with a single anomalous coronary artery generally should not undergo balloon or surgical dilation procedures because of increased risk of death, although conservative ballooning reportedly has been palliative in a few cases. Placement of a valved RV-PA conduit to bypass the pulmonic valve could be an option for such patients. Coronary anatomy can be evaluated initially using echocardiography, but definitive diagnosis of coronary artery anomalies may require either aortic root angiography or computed tomography with angiography.

Exercise restriction is advised for animals with moderate to severe stenosis. β-blocker therapy could be helpful in cases of moderate to severe PS, especially in those with prominent RV infundibular hypertrophy and a dynamic component to their right ventricular outflow tract (RVOT) obstruction. β-blockade also decreases myocardial oxygen demand and arrhythmias, improves coronary perfusion, and

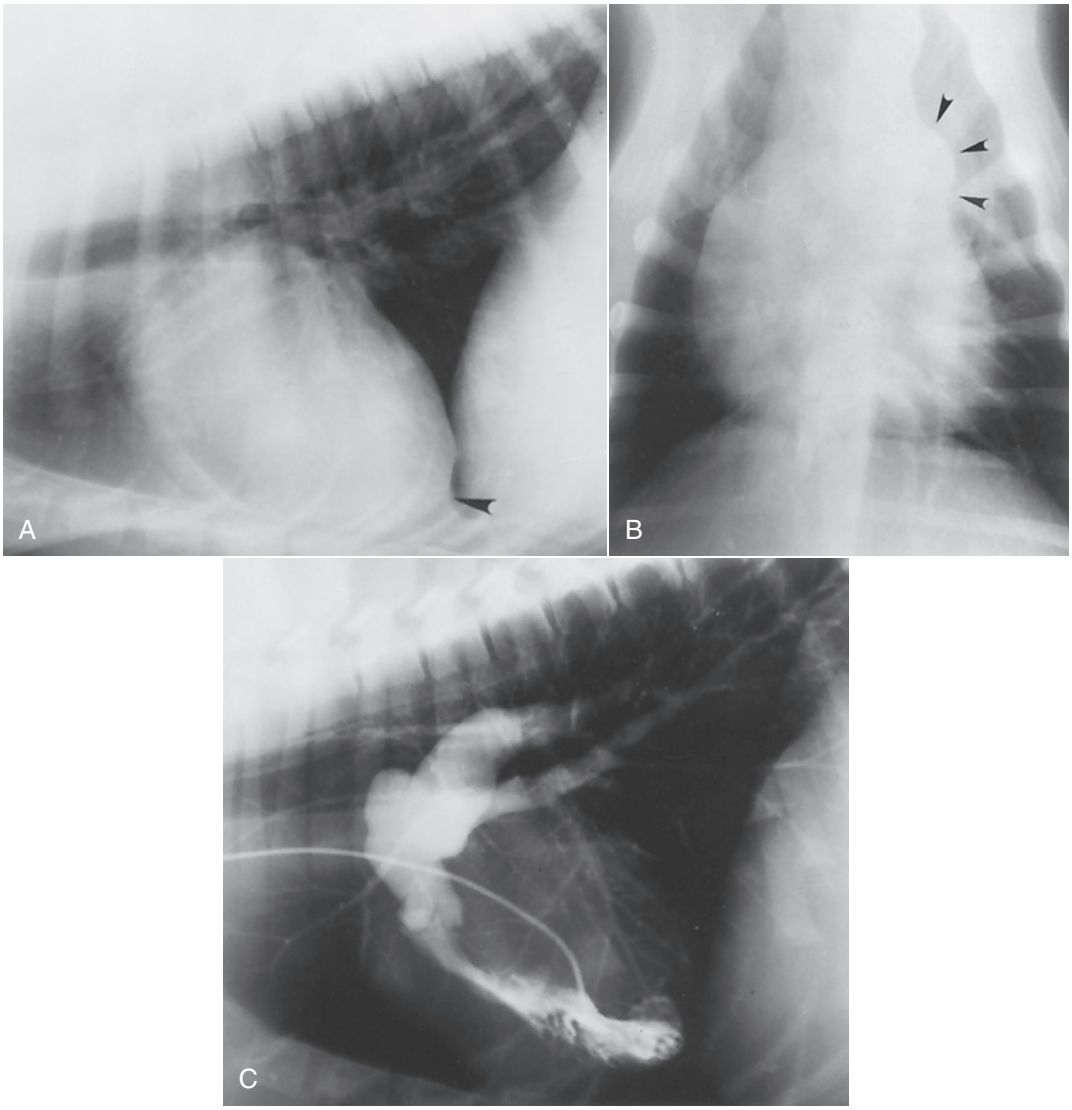


FIG 5.6
Lateral **(A)** and dorsoventral (DV) **(B)** radiographs from a dog with pulmonic stenosis, showing right ventricular enlargement (apex elevation on lateral view [*arrowhead* in **A**] and reverse D configuration on DV view) along with a pulmonary trunk bulge (*arrowheads* in **B**) seen on a DV view. **(C)** Angiocardiogram using a selective right ventricular injection demonstrates poststenotic dilation of the main pulmonary trunk and pulmonary arteries. The thickened pulmonic valve is closed in this diastolic frame.

can reduce syncope. Signs of CHF are managed medically with abdomino- or thoracocentesis, furosemide, pimobendan, an ACEI, and spironolactone (see Chapter 3).

The prognosis in patients with PS is variable and depends on the severity of the lesion and any complicating factors. Life span often is normal in those with mild PS, whereas animals with severe PS often die within 3 years of diagnosis. Sudden death occurs in some; development of right-sided CHF is more common. The prognosis is considerably worse in animals with TR, atrial fibrillation or other tachyarrhythmias, or CHF. Successful balloon dilation improves prognosis in dogs with severe PS; some dogs may live normal life spans after the procedure.

INTRACARDIAC SHUNT

Blood flow volume across an intracardiac shunt depends on the size of the defect and the pressure gradient driving flow across it. In most cases, flow direction is from left to right, causing pulmonary overcirculation. A volume overload is imposed on all heart chambers that receive "extra" shunted blood flow. Compensatory increases in blood volume and cardiac output occur in response to the partial diversion of blood away from the systemic circulation. If right heart pressures increase due to increased pulmonary resistance or a concurrent PS, shunt flow may equilibrate or reverse (i.e., become right to left).

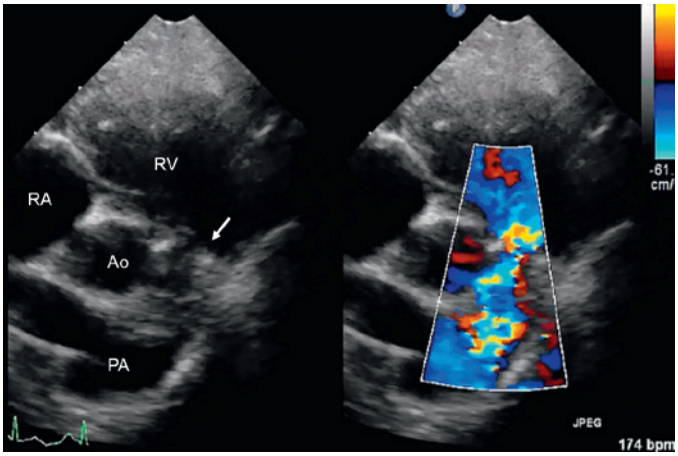


FIG 5.7
Right parasternal short-axis echocardiographic image at the level of the heart base from a 3-month-old female English Bulldog with severe pulmonic stenosis. Thickened, partially fused leaflets of the malformed pulmonary valve *(arrow)* cause turbulent, high-velocity flow across the pulmonic valve on color Doppler. Note the severe right ventricular enlargement and hypertrophy. *Ao,* Aortic root; *PA,* main pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

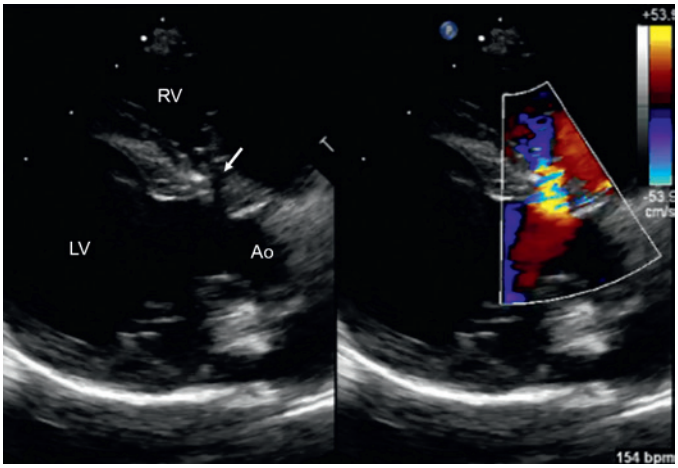


FIG 5.8
Right parasternal long-axis echocardiographic image in a 4-month-old male Bassett Hound. A small perimembranous ventricular septal defect (*arrow*) can be seen just below the aortic root. Color Doppler in systole reveals turbulent flow (from left to right) through the defect. *Ao,* Aortic root; *LV,* left ventricle; *RV,* right ventricle.

VENTRICULAR SEPTAL DEFECT

Etiology and Pathophysiology

Most VSDs are located in the membranous part of the septum, just below the aortic valve and beneath the septal tricuspid leaflet (perimembranous VSD). VSDs also occur sporadically in other septal locations, including the muscular septum (muscular VSD), below and between AV valves (inlet VD), and just below the pulmonary valve (juxta-arterial, outlet, or supracristal VSD). A VSD may be accompanied by other AV septal (endocardial cushion) malformations, especially in cats. Usually, VSDs cause volume overloading of the pulmonary circulation, LA, LV, and RV outflow tract. However, because most VSDs occur very high in the RV outflow tract (in the membranous septum), significant volume overload of the RV itself is rare. Small defects may be clinically unimportant. Moderate to large defects tend to cause left heart dilation and can lead to left-sided CHF. A very large VSD causes the ventricles to function as a common chamber and induces RV dilation and hypertrophy. Pulmonary hypertension secondary to overcirculation is more likely to develop with large shunts. Some animals with perimembranous or juxta-arterial VSDs also have aortic regurgitation, with diastolic prolapse of a valve leaflet. Presumably this occurs because the deformed septum provides inadequate support for the aortic root. Aortic regurgitation places an additional volume load on the LV.

Clinical Features

Most animals with VSDs are asymptomatic at time of diagnosis. If clinical disease does occur, the most common manifestations are exercise intolerance and signs of left-sided CHF. The characteristic auscultatory finding is a holosystolic murmur, heard loudest at the cranial right sternal border (which corresponds to the usual direction of shunt flow). A large shunt volume can produce a murmur of relative or functional PS (systolic ejection murmur at the left base). With concurrent aortic regurgitation, a corresponding diastolic decrescendo murmur may be audible at the left base. A split S_2 sound may be audible due to delayed closure of the pulmonic valve, though this is usually obscured by the loud heard murmur.

Diagnosis

Radiographic findings associated with VSD vary with the size of the defect and the shunt volume (see Table 5.2). Large shunts typically cause left heart enlargement, main pulmonary artery enlargement, and pulmonary overcirculation.

The ECG may be normal or suggest LA or LV enlargement. In some cases, disturbed intraventricular conduction is suggested by "fractionated" or splintered QRS complexes or right bundle-branch block. An RV enlargement pattern usually indicates a large defect, pulmonary hypertension, or a concurrent RV outflow tract obstruction.

Echocardiography allows visualization of the defect. Perimembranous VSDs usually are seen best just below the aortic valve in the right parasternal long-axis LV outflow view (Fig. 5.8). The septal tricuspid leaflet is located to the right of the defect. Because echo "dropout" at the thin membranous septum can mimic a VSD, the area of a suspected defect should be visualized in more than one plane. The size of the VSD often is indexed to aortic diameter. Color Doppler is used to demonstrate shunt flow across the defect (see Fig. 5.8). Spectral Doppler assessment of

peak shunt flow velocity is used to estimate the systolic pressure gradient between the LV and RV. Small (restrictive) VSDs cause a high-velocity shunt flow (≈4.5-5 m/sec) because of the normally large systolic pressure difference between the ventricles. Lower peak shunt velocity (nonrestrictive VSD) implies increased RV systolic pressure, either from PS or pulmonary hypertension. Left heart dilation is evident when the shunt is large; RV dilation occurs uncommonly as most VSDs are located high in the interventricular septum with blood shunting nearly immediately into the RV outflow tract. Echocardiography should be repeated when patients reach adult size (usually approximately 1 year of age).

Cardiac catheterization, oximetry, and angiocardiography uncommonly are performed clinically but can allow measurement of intracardiac pressures, indicate the presence of an oxygen step-up at the level of the RV outflow tract, and show the pathway of abnormal blood flow.

Treatment and Prognosis

Small restrictive VSDs (less than 40% of aortic diameter, shunt velocity greater than 4.5 m/s) have an excellent prognosis; animals typically live a normal life span with no treatment required. There are sporadic reports of spontaneous VSD closure within the first 2 years of life, either from myocardial hypertrophy around the VSD or a seal formed by the septal tricuspid leaflet or a prolapsed aortic leaflet. Animals with large nonrestrictive VDSs (greater than 60% of aortic diameter, shunt velocity less than 4.0 m/s) have a more guarded prognosis; left-sided CHF is the most common outcome, although in some cases pulmonary hypertension with shunt reversal develops instead. Animals that develop clinical complications related to a large VSD typically display clinical signs at an early age. In a large retrospective case series of VSDs in dogs and cats, the vast majority of patients with VSDs (81%) were asymptomatic at time of diagnosis and remained asymptomatic throughout an average 12-year life span.

For asymptomatic patients with a small restrictive VSD, no treatment is indicated. For patients with a larger nonrestrictive VSD, left-sided CHF is managed medically when and if it occurs. Definitive therapy for large nonrestrictive VSDs generally requires cardiopulmonary bypass for open-heart surgery (patch grafting). Transcatheter delivery of an occlusion device can be successful in medium- to large-breed dogs with muscular VSDs; other VSD locations generally are less amenable to interventional closure due to proximity of the defect to the aortic or pulmonic valve. Historically, large left-to-right shunts sometimes have been palliated by surgically placing a constrictive band around the pulmonary trunk to create a mild supravalvular PS. This raises RV systolic pressure in response to the increased outflow resistance, decreasing shunt volume from the LV to RV. However, an excessively tight band can cause right-to-left shunting (functionally analogous to a T of F). Palliative surgery should not be attempted in the presence of pulmonary hypertension and shunt reversal.

ATRIAL SEPTAL DEFECT

Etiology and Pathophysiology

Several types of ASD exist. Those located in the region of the fossa ovalis (ostium secundum defects) are more common in dogs. An ASD in the lower interatrial septum (ostium primum defect) is likely to be part of the AV septal (endocardial cushion or common AV canal) defect complex, especially in cats. Other ASD locations (sinus venosus or coronary sinus defects) are rare. Animals with ASD commonly have other cardiac malformations as well. In most cases of ASD, blood shunts from the LA to RA and results in a volume overload to both the right heart and pulmonary circulation. However, if PS or pulmonary hypertension is present, right-to-left shunting and cyanosis can occur. Patent foramen ovale, where embryonic atrial septation has occurred normally but the overlap between the septum primum and septum secundum does not seal closed, is not considered a "true" ASD, but is a common cause of right-to-left shunting in the presence of abnormally high RA pressure (as in PS or pulmonary hypertension).

Clinical Features

The clinical history in animals with an ASD is usually nonspecific. Physical examination findings associated with an isolated ASD often are unremarkable. Because the pressure difference between right and left atria is minimal, no murmur is expected across the ASD, although large left-to-right shunts can cause a murmur of relative PS. Fixed splitting (i.e., with no respiratory variation) of the second heart sound (S_2) is the classic auscultatory finding, caused by delayed pulmonic and early aortic valve closures. Rarely, a soft diastolic murmur of relative tricuspid stenosis might be audible. Large ASDs can lead to signs of right-sided or biventricular CHF.

Diagnosis

Right heart enlargement, with or without pulmonary trunk dilation, is found radiographically in patients with large shunt volumes (see Table 5.2). Pulmonary overcirculation can be apparent unless pulmonary hypertension has developed. Left heart enlargement is not generally evident unless another defect such as mitral insufficiency is present. The ECG can be normal or show evidence of RV and RA enlargement.

Echocardiography is likely to show RA and RV dilation, with or without paradoxical interventricular septal motion; larger ASDs can be visualized. Care must be taken not to confuse the thinner fossa ovalis region of the interatrial septum with an ASD, because echo dropout also occurs here. Doppler echocardiography can allow identification of smaller shunts that cannot be clearly visualized on 2-D examination, but venous inflow streams can complicate this. An agitated saline contrast study can be used to identify right-to-left shunting ASDs. Although rarely performed clinically, cardiac catheterization shows an oxygen step-up at the level of the right atrium (RA). Abnormal flow through the shunt might be evident after the injection of contrast material into the pulmonary artery.

Treatment and Prognosis

Large shunts can be treated with open-heart surgery and patch-grafting under cardiopulmonary bypass, similarly to VSDs. Ostium secundum defects can sometimes be treated with transcatheter device occlusion depending on patient size, ASD size, and presence of an adequate rim of atrial septal tissue around the defect. Otherwise, animals are managed medically if CHF develops. The prognosis is variable and depends on shunt size, concurrent defects, and the level of pulmonary vascular resistance.

ATRIOVENTRICULAR VALVE MALFORMATION

MITRAL DYSPLASIA

Congenital malformations of the mitral valve apparatus can be variable and include the following: shortened, fused, or overly elongated chordae tendineae; direct attachment of the valve cusp to a papillary muscle; thickened, cleft, or shortened valve cusps; prolapse of valve leaflets; abnormally positioned or malformed papillary muscles; and excessive dilation of the valve annulus. Mitral valve dysplasia (MD) is most common in large-breed dogs and also occurs in cats; MD is the most common concurrent congenital malformation among dogs with SAS. Valvular regurgitation is the predominant functional abnormality, and it may be severe; the pathophysiology and sequelae resemble those of acquired mitral regurgitation (see p. 119). Left-sided CHF is the most common clinical manifestation. Mitral valve stenosis occurs uncommonly; when present, the ventricular inflow obstruction increases LA pressure and can precipitate the development of pulmonary edema. Mitral regurgitation usually accompanies stenosis.

Clinical signs associated with MD are similar to those seen with degenerative mitral valve disease, except for the younger patient age. Reduced exercise tolerance, respiratory signs of left-sided CHF, inappetence, and atrial arrhythmias (especially atrial fibrillation) are common in affected animals. Mitral regurgitation typically causes a holosystolic murmur heard best at the left apex. Animals with severe MD, especially those with stenosis, can also develop syncope with exertion, postcapillary pulmonary hypertension, and, occasionally, signs of right-sided (in addition to left-sided) CHF.

Radiographic, ECG, echocardiographic, and catheterization findings are similar to those of patients with acquired mitral insufficiency. Echocardiography can depict the specific mitral apparatus malformations, as well as the degree of chamber enlargement and functional changes. Animals with mitral stenosis have a typical mitral inflow pattern with prolonged high velocity, reflecting the diastolic pressure gradient between LA and LV.

Therapy consists of medical management for CHF. Animals with mild to moderate mitral valve dysfunction may do well clinically for years. However, for those with severe mitral regurgitation or stenosis, the prognosis is poor. Surgical valve reconstruction or replacement under cardiopulmonary bypass might be possible in some cases.

TRICUSPID DYSPLASIA

Animals with tricuspid dysplasia (TD) have variable malformations of the tricuspid valve and related structures, similar to those of MD. The tricuspid valve can be displaced ventrally into the ventricle (an Ebstein-like anomaly) in some cases. TD is identified most frequently in large-breed dogs, particularly in Labrador Retrievers, and in males; cats are also affected. Tricuspid valve dysplasia occurs concurrently with PS in some dogs.

The pathophysiologic features of TD are the same as those of acquired TR. Severe cases result in marked enlargement of the right heart chambers. Progressive increase in RA and RV end-diastolic pressures eventually result in right-sided CHF. Tricuspid stenosis can occur but is rare.

The historical signs and clinical findings likewise are similar to those of degenerative tricuspid disease. Initially, the animal may be asymptomatic. However, exercise intolerance, abdominal distention resulting from ascites, dyspnea resulting from pleural effusion, anorexia, and cardiac cachexia often develop. The right-sided holosystolic murmur of TR is characteristic. However, not all cases have an audible murmur because the dysplastic leaflets may gap so widely in systole that there is little resistance to backflow and therefore minimal turbulence. Jugular pulsations are common. Additional signs that accompany right-sided CHF include jugular vein distention, muffled heart and lung sounds, and ballotable abdominal fluid.

Radiographs demonstrate RA and RV enlargement. The round appearance of the heart shadow in some cases is similar to that seen in patients with pericardial effusion or dilated cardiomyopathy. A distended caudal vena cava, pleural or peritoneal effusion, and hepatomegaly suggest right-sided CHF.

RV and occasionally RA enlargement patterns are seen on ECG. A splintered QRS complex configuration may be seen. Atrial fibrillation or other atrial tachyarrhythmias occur commonly. Evidence for ventricular preexcitation is seen in some cases, particularly in patients with the Ebstein-like anomaly.

Echocardiography reveals right heart dilation, which can be massive. Malformations of the valve apparatus can be evident in several views (Fig. 5.9), although the left apical four-chamber view is especially useful. Doppler flow patterns are similar to those of MD. Intracardiac electrocardiography is necessary to confirm an Ebstein anomaly, which is suggested by ventral displacement of the tricuspid valve annulus; a ventricular electrogram recorded on the RA side of the valve is diagnostic. CHF and arrhythmias are managed medically. Periodic abdomino- or thoracocentesis may be necessary in animals with cavitary effusions that cannot be controlled with medication and diet. The prognosis depends on degree of valve dysfunction. Dogs with severe TR and marked cardiomegaly have a guarded to poor prognosis, but some dogs survive for many years. Surgical replacement of

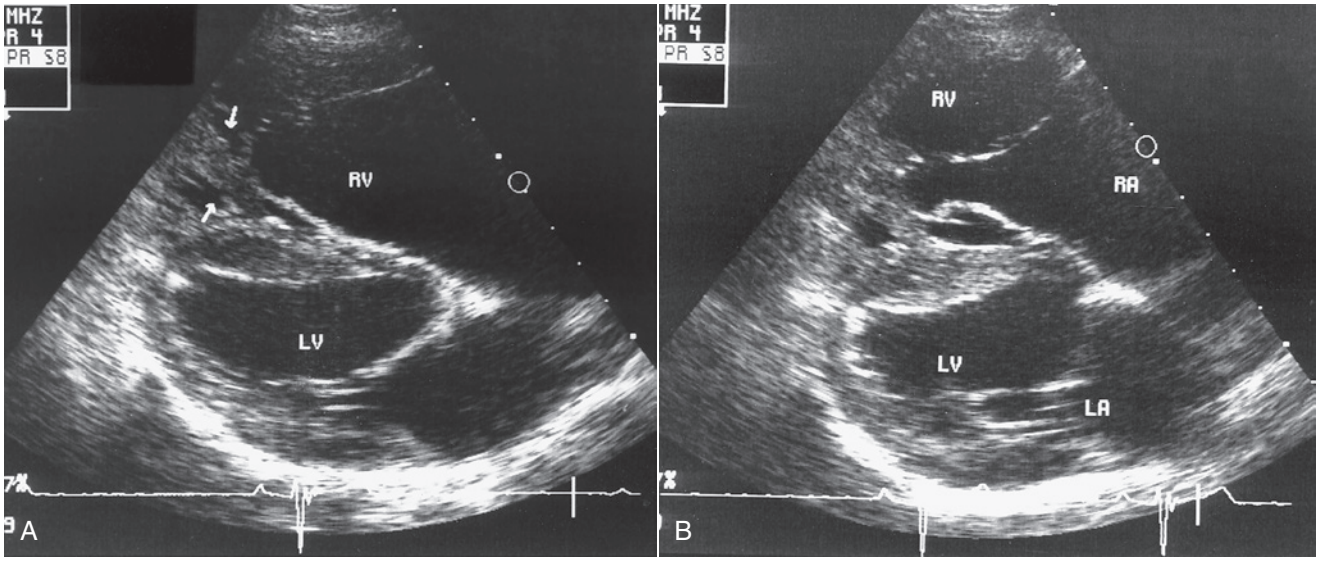


FIG 5.9
Right parasternal long-axis echo images from a 1-year-old male Labrador Retriever with tricuspid valve dysplasia in diastole **(A)** and systole **(B).** The valve annulus appears to be ventrally displaced; the leaflet tips are tethered to a malformed, wide papillary muscle (*arrows* in **A**). Wide leaflet tip separation in systole **(B)** caused severe tricuspid regurgitation and clinical congestive heart failure. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

the tricuspid valve under cardiopulmonary bypass has been described in a small number of dogs. Balloon dilation has occasionally been successful for treating tricuspid stenosis.

CARDIAC ANOMALIES CAUSING CYANOSIS

Malformations that allow deoxygenated blood to reach the systemic circulation (right-to-left shunts) result in hypoxemia. Right-to-left shunting requires (1) the presence of an anomalous connection between the systemic and pulmonary circulations, and (2) suprasystemic right heart pressures, usually due to pulmonary hypertension or PS. Visible cyanosis occurs when the desaturated hemoglobin concentration is greater than 5 g/dL. Arterial hypoxemia stimulates increased red blood cell production, leading to a compensatory erythrocytosis that increases oxygen carrying capacity. However, blood viscosity and resistance to flow also rise with the increase in PCV. Severe erythrocytosis (PCV ≥ 65%) results in hyperviscosity, which can lead to microvascular sludging, poor tissue oxygenation, intravascular thrombosis, hemorrhage, and cardiac arrhythmias. Erythrocytosis can become extreme, with a PCV of greater than 80% in some animals.

Usually the earliest clinical sign in animals with cyanotic heart disease is exercise-induced weakness or syncope. Such "hypercyanotic" events occur because exercise stimulates systemic vasodilation to increase blood flow to skeletal muscles; the resulting decrease in systemic vascular resistance transiently increases right-to-left shunt volume. Later complications of cyanotic heart disease generally are related to hyperviscosity associated with erythrocytosis, including metabolic and hemostatic abnormalities, seizures, and cerebrovascular accidents. The possibility of a venous embolus crossing the shunt to the systemic circulation poses another danger in these cases. Despite the pressure overload on the right heart, CHF is rare in cyanotic heart disease; the shunt provides an alternate pathway for high pressure flow.

Anomalies that most often cause cyanosis in dogs and cats include T of F, PS in conjunction with an intracardiac shunt (VSD or ASD), or pulmonary arterial hypertension in conjunction with an intracardiac or extracardiac shunt (PDA, VSD, or ASD). Other complex but uncommon anomalies such as transposition of the great vessels or truncus arteriosus also send deoxygenated blood to the systemic circulation.

TETRALOGY OF FALLOT

Etiology and Pathophysiology

T of F is classically defined by its four components: VSD, PS, a dextropositioned aorta, and RV hypertrophy. However, T of F is actually caused by a single embryologic defect: incomplete rotation and faulty partitioning of the conotruncus during septation of the great vessels. The malalignment of the aorta and pulmonary artery with respect to the interventricular septum causes a large nonrestrictive VSD, obstruction of the RV outflow tract (PS), and an aortic root that extends over the right side of the interventricular septum; all of these components facilitate RV-to-aortic shunting. The PS usually is subvalvular or infundibular, but can involve the valve; in some cases, the pulmonary artery is hypoplastic or

not open at all (atretic). RV hypertrophy occurs in response to the pressure overload imposed by the PS and systemic arterial circulation. The volume of blood shunted from the RV into the aorta depends on the balance of outflow resistance caused by the fixed PS compared with systemic arterial resistance, which varies with exercise and autonomic tone. Pulmonary vascular resistance is generally normal in animals with T of F. A polygenic inheritance pattern for T of F has been identified in the Keeshond. The defect also occurs in other dog breeds, particularly terrier breeds, and in cats.

Clinical Features

Exertional weakness, dyspnea, syncope, cyanosis, and stunted growth are common in the history. Physical examination findings are variable, depending on the relative severity of the malformations. Cyanosis may be seen at rest in some animals, whereas others are cyanotic only with exercise. The precordial impulse is usually of equal intensity or stronger on the right chest wall than on the left. A holosystolic murmur at the right sternal border consistent with a VSD, a systolic ejection murmur at the left base compatible with PS, or both may be heard on auscultation. However, some animals have no audible murmur because hyperviscosity associated with erythrocytosis diminishes blood turbulence and therefore murmur intensity.

Diagnosis

Thoracic radiographs depict variable cardiomegaly, usually of the right heart (see Table 5.2). The main pulmonary artery usually appears small, in contrast to typical valvular PS. Reduced pulmonary vascular markings are common. The malpositioned aorta can create a cranial bulge in the heart shadow on lateral view. RV hypertrophy causes dorsal displacement of the cardiac apex on lateral views and an upturned cardiac apex on VD views, leading to a classically described "boot-shaped" heart. The ECG typically suggests RV enlargement, although a left axis deviation has been seen in some affected cats.

Echocardiography depicts the VSD, a large aortic root shifted rightward and overriding the ventricular septum, PS, and RV hypertrophy. Doppler studies reveal the right-to-left shunt and high-velocity stenotic pulmonary outflow jet. An echo-contrast study can also document the right-to-left shunt. Typical clinicopathologic abnormalities include increased PCV and arterial hypoxemia.

Treatment and Prognosis

Definitive repair of T of F requires open-heart surgery. Palliative surgical procedures can increase pulmonary blood flow by creating a left-to-right shunt. Anastomosis of a subclavian artery to the pulmonary artery (a modified Blalock-Taussig shunt) is the most commonly used palliative procedure in small animals.

Severe erythrocytosis and clinical signs associated with hyperviscosity (e.g., weakness, shortness of breath, seizures) can be treated with periodic phlebotomy (see p. 116) or, alternatively, hydroxyurea (see p. 116). The goal is to maintain PCV at a level where clinical signs are minimal (a general goal is 62%-65%); further reduction of PCV (into the normal range) can exacerbate signs of hypoxia. A β-blocker such as atenolol or propranolol might help reduce clinical signs in some dogs with T of F by decreasing sympathetic tone, RV (muscular) outflow obstruction, and myocardial oxygen consumption. Additionally, β-blockers help limit exercise-induced peripheral vasodilation that can exacerbate right-to-left shunting and cause hypercyanotic episodes. Exercise restriction is also advised. Drugs with systemic vasodilator effects should not be given. Supplemental O_2 has negligible benefit in patients with T of F.

The prognosis for animals with T of F depends on the severity of PS and erythrocytosis. Mildly affected animals and those that have had a successful palliative surgical shunting procedure may survive well into middle age. Nevertheless, progressive hypoxemia, erythrocytosis, and sudden death at an earlier age are common. Overall median survival time following diagnosis is approximately 2 years.

PULMONARY HYPERTENSION WITH SHUNT REVERSAL

Etiology and Pathophysiology

In dogs and cats, pulmonary overcirculation typically results in left-sided CHF. Left-to-right shunts rarely lead to reactive vasoconstriction and pulmonary arterial hypertension in small animals, because the low-resistance pulmonary vascular system (with significant capacity for collateral circulation) normally can accept a large increase in blood flow without marked rise in pulmonary arterial pressure. However, a small percentage of dogs and cats with shunts do develop pulmonary arterial hypertension causing shunt reversal (right-to-left shunting). It is not clear why pulmonary hypertension develops in some animals, although the defect size in affected animals is usually quite large. Possibly the high fetal pulmonary resistance may not regress normally in these animals, or their pulmonary vasculature may react abnormally to an initially large left-to-right shunt flow. In any case, irreversible histologic changes are present in the pulmonary arteries that increase vascular resistance. These include intimal thickening, medial hypertrophy, and characteristic plexiform lesions.

As pulmonary vascular resistance increases, pulmonary artery pressure rises and the extent of left-to-right shunting diminishes. If right heart and pulmonary pressures exceed those of the systemic circulation, the shunt reverses direction and deoxygenated blood flows into the aorta. These changes typically develop in very young animals (usually by 6 months of age), supporting the notion that pulmonary hypertension in these cases may represent retention of fetal pulmonary vascular resistance. The term *Eisenmenger physiology* refers to severe pulmonary hypertension with shunt reversal; affected animals with clinical signs sometimes are described as having *Eisenmenger syndrome*.

Right-to-left shunts that result from pulmonary hypertension cause pathophysiologic and clinical sequelae similar

to those resulting from T of F. The major difference is that the impediment to pulmonary flow occurs at the level of the pulmonary arterioles rather than at the pulmonic valve. Clinical manifestations include hypoxemia, cyanosis (worsened with exercise), RV hypertrophy and enlargement, and erythrocytosis and its sequelae. Right-sided CHF is uncommon but can develop in response to secondary myocardial failure or tricuspid insufficiency. The right-to-left shunt potentially allows venous emboli to cross into the systemic arterial system and cause stroke or other arterial embolization.

Clinical Features

The history and clinical presentation of animals with pulmonary hypertension and shunt reversal are similar to those associated with T of F. Exercise intolerance, shortness of breath, syncope (especially in association with exercise or excitement), and sudden death are common. Cyanosis might be evident only during exercise or excitement. Intracardiac shunts cause equally intense cyanosis throughout the body, whereas a reversed PDA causes cyanosis of the caudal mucous membranes alone (differential cyanosis). In reversed PDA, normally oxygenated blood flows to the cranial body via the brachycephalic trunk and left subclavian artery (from the aortic arch); because the ductus is located in the descending aorta, the caudal body receives desaturated blood (Fig. 5.10). Rear limb weakness is common in animals with reversed PDA.

A murmur typical of the underlying defect(s) might be heard. However, in many cases, no murmur is audible because right and left heart pressures are nearly equivalent, minimizing pressure gradient and thus velocity of shunting blood flow. Additionally, high blood viscosity caused by erythrocytosis minimizes turbulence. There is no continuous murmur in patients with reversed PDA. Pulmonary hypertension often causes a loud and "snapping" or split S_2 sound. Other physical examination findings can include a pronounced right precordial impulse and jugular pulsations.

Diagnosis

Thoracic radiographs typically reveal right heart enlargement, a prominent pulmonary trunk, and tortuous, proximally widened pulmonary arteries. A bulge in the descending aorta is common in dogs with reversed PDA. In animals with a reversed PDA or VSD, the left heart may be enlarged as well. The ECG usually suggests RV and sometimes RA enlargement, with a right axis deviation.

Echocardiography reveals the RV hypertrophy, intracardiac anatomic defects, and sometimes a large ductus, as well

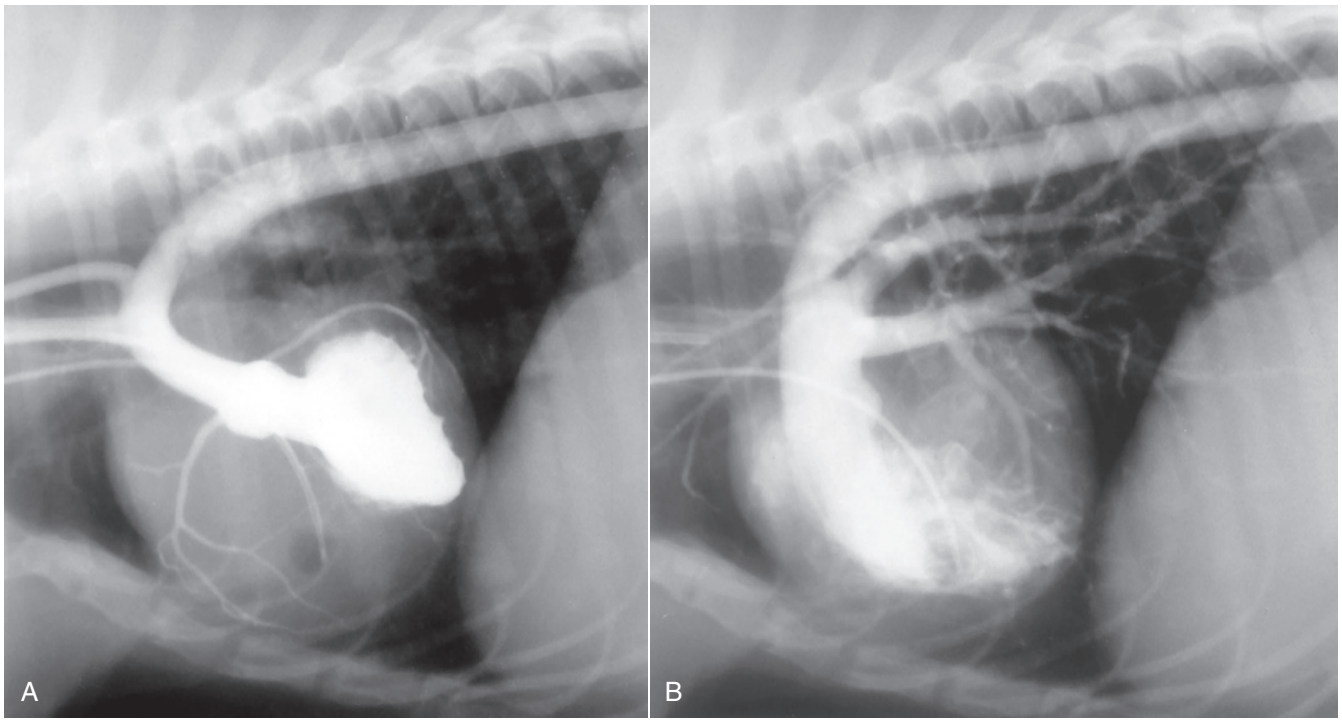


FIG 5.10
Angiocardiograms from an 8-month-old female Cocker Spaniel with patent ductus arteriosus, pulmonary hypertension, and shunt reversal. Left ventricular injection **(A)** shows dorsal displacement of the left ventricle by the enlarged right ventricle. Note the dilution of radiographic contrast solution in the descending aorta (from mixing with nonopacified blood from the ductus) and the prominent right coronary artery. Right ventricular injection **(B)** illustrates right ventricular hypertrophy and pulmonary trunk dilation secondary to severe pulmonary hypertension. Opacified blood courses through the large ductus into the descending aorta.

as pulmonary trunk dilation. Doppler or echo-contrast study can confirm an intracardiac right-to-left shunt. Imaging the abdominal aorta during venous echo-contrast injection can show reversed PDA flow. Peak RV (and in the absence of PS, pulmonary artery) pressure can be estimated by measuring the peak velocity of a TR jet. Pulmonary insufficiency flow can be used to estimate diastolic pulmonary artery pressure. Cardiac catheterization can confirm the diagnosis and quantify the pulmonary hypertension and systemic hypoxemia.

Treatment and Prognosis

Therapy is aimed at reducing pulmonary arterial pressure, as well as managing secondary erythrocytosis to minimize signs of hyperviscosity. Exercise restriction is also advised.

Sildenafil citrate is a selective phosphodiesterase-5 inhibitor that reduces pulmonary resistance via nitric oxide–dependent pulmonary vasodilation. It can reduce the degree of right-to-left shunting in dogs with pulmonary hypertension, leading to improved clinical signs and exercise tolerance, as well as decreased erythrocytosis. Doses of 1 to 3 mg/kg q12h or q8h generally are well tolerated and may produce some reduction in Doppler-estimated pulmonary artery pressure. Adverse effects of sildenafil can include possible hypotension, cutaneous flushing, nasal congestion, or sexual adverse effects, especially in intact animals. Other vasodilator drugs tend to produce systemic effects that are similar to or greater than those on the pulmonary vasculature; therefore they are of little benefit and possibly detrimental.

Erythrocytosis can be managed by periodic phlebotomy or use of oral hydroxyurea. Ideally, the PCV is maintained at a level where the patient's signs of hyperviscosity (e.g., rear limb weakness, shortness of breath, lethargy) are minimal. A PCV of about 62% to 65% has been recommended, but this may not be optimal for all cases.

One method of performing phlebotomy is to remove 5 to 10 mL blood per kilogram of body weight. Another calculation involves removing blood volume in relation to actual and desired hematocrit as follows: Phlebotomy volume = body weight (kg) × 0.08 (percent blood volume) × 1000 mL/kg × (actual hematocrit – desired hematocrit)/(actual hematocrit). Regardless of which calculation is chosen, it is generally advisable to replace the blood with an equal volume of isotonic fluid to avoid significant hemodynamic shifts. In most patients with marked erythrocytosis, a large bore needle (>18G) must be used.

Hydroxyurea therapy (40-50 mg/kg by mouth q48h or 3×/week) can be a useful alternative to periodic phlebotomy in patients with secondary erythrocytosis. A complete blood cell count and platelet count should be monitored weekly or biweekly to start. Possible adverse effects of hydroxyurea include anorexia, vomiting, bone marrow hypoplasia causing cytopenias, alopecia, and pruritus. Depending on the patient's response, the dose can be divided q12h on treatment days, administered twice weekly, or administered at less than 40 mg/kg.

The prognosis is generally poor in animals with pulmonary hypertension and shunt reversal, although some patients do well for years with medical management. Surgical closure of a reversed shunt is generally contraindicated, because the shunt acts as a "pop-off" valve for high pulmonary and right heart pressures. The acute increase in PA pressure following shunt correction can cause RV myocardial failure and death. Shunt correction can only be considered if sildenafil therapy effectively lowers PA pressure below systemic pressure such that the shunt direction becomes left to right. There are rare reports of successful correction of reversed PDAs following sildenafil therapy.

OTHER CARDIOVASCULAR ANOMALIES

VASCULAR RING ANOMALIES

Various vascular malformations originating from the embryonic aortic arch system can occur. These can entrap the esophagus and sometimes the trachea within a vascular ring at the dorsal heart base. Persistent right aortic arch is the most common vascular ring anomaly in the dog. This developmental malformation surrounds the esophagus dorsally and to the right with the aortic arch, to the left with the ligamentum arteriosum, and ventrally with the base of the heart. Different vascular ring anomalies can occur as well. In addition, other vascular malformations such as a left cranial vena cava or PDA may accompany a vascular ring anomaly. Vascular ring anomalies are rare in cats.

The vascular ring prevents solid food from passing normally through the esophagus. Clinical signs of regurgitation and stunted growth commonly develop within 6 months of weaning. Esophageal dilation occurs cranial to the ring; food may be retained in this area. Sometimes the esophagus dilates caudal to the stricture as well, indicating that altered esophageal motility coexists.

The animal's body condition score may be normal initially, but progressive debilitation ensues. A palpably dilated cervical esophagus (containing food or gas) is evident at the thoracic inlet in some cases. Fever and respiratory signs including coughing, wheezing, and cyanosis usually signal secondary aspiration pneumonia. However, in some cases a double aortic arch can cause stridor and other respiratory signs secondary to tracheal stenosis. Vascular ring anomalies by themselves do not result in abnormal cardiac sounds.

Thoracic radiographs show a leftward tracheal deviation near the cranial heart border on DV view. Other common signs include a widened cranial mediastinum, focal narrowing and/or ventral displacement of the trachea, air or food in the cranial thoracic esophagus, and sometimes evidence of aspiration pneumonia. A barium swallow allows visualization of the esophageal stricture over the heart base and cranial esophageal dilation (with or without caudal esophageal dilation).

Surgical division of the ligamentum arteriosum (or other vessel if the anomaly is not a persistent right aortic arch) is the recommended therapy. In some cases, a retroesophageal left subclavian artery or left aortic arch is also present and must be divided to free the esophagus. Medical management

consists of frequent small, semisolid, or liquid meals eaten in an upright position. This feeding method may be necessary indefinitely. Persistent regurgitation occurs in some dogs despite successful surgery, suggesting a permanent esophageal motility disorder.

COR TRIATRIATUM

Cor triatriatum is an uncommon malformation caused by an abnormal membrane that divides either the right (dexter) or the left (sinister) atrium into two chambers. Cor triatriatum dexter occurs sporadically in dogs, often in combination with PS. Cor triatriatum sinister has been described rarely in cats; functional consequences are similar to mitral valve stenosis.

Cor triatriatum dexter results from failure of the embryonic right sinus venosus valve to regress. The caudal vena cava and coronary sinus empty into the RA caudal to the intra-atrial membrane; the tricuspid orifice is within the cranial RA "chamber." Obstruction to venous flow through the opening in the abnormal membrane elevates vascular pressure in the caudal vena cava and the structures that drain into it.

Large- to medium-size breeds of dog are most often affected. Persistent ascites that develops at an early age is the most prominent clinical sign. Exercise intolerance, lethargy, distended cutaneous abdominal veins, and sometimes diarrhea are reported as well. Neither a cardiac murmur nor jugular venous distention is a feature of this anomaly.

Thoracic radiographs indicate caudal vena cava distention without generalized cardiomegaly. The diaphragm may be displaced cranially by massive ascites. The ECG usually is normal. Echocardiography reveals the abnormal membrane and prominence of the caudal RA chamber and vena cava. Doppler studies show the flow disturbance within the RA and allow estimation of the intra-RA transmembrane pressure gradient.

Successful therapy requires enlarging the membrane orifice or excising the abnormal membrane to remove flow obstruction. A minimally invasive option is percutaneous balloon dilation of the membrane orifice. A small cutting balloon can be used to score the orifice opening before dilation with a larger balloon. Alternatively, a surgical approach using inflow occlusion, with or without hypothermia, can be used to excise the membrane or break it down using a valve dilator.

ENDOCARDIAL FIBROELASTOSIS

Diffuse fibroelastic thickening of the LV and LA endocardium, with dilation of the affected chambers, characterizes endocardial fibroelastosis. This congenital abnormality has been reported occasionally in cats, especially Burmese and Siamese. Left-sided or biventricular heart failure commonly develops early in life. A mitral regurgitation murmur may be present. Criteria for LV and LA enlargement are seen on radiographs, ECG, and echocardiogram. Evidence for reduced LV myocardial function may be present. Definitive antemortem diagnosis is difficult.

OTHER VASCULAR ANOMALIES

A number of venous anomalies have been described, but most are not clinically relevant. The persistent left cranial vena cava is a fetal venous remnant that courses lateral to the left AV groove and empties into the coronary sinus of the caudal RA. Although it causes no clinical signs, its presence may complicate surgical exposure of other structures at the left heart base. Portosystemic venous shunts are common and can lead to hepatic encephalopathy, as well as other signs. These malformations are thought to be more prevalent in the Yorkshire Terrier, Pug, Miniature and Standard Schnauzers, Maltese, Pekingese, Shih Tzu, and Lhasa Apso breeds and are discussed in Chapter 38.

Suggested Readings

General References

Beijerink NJ, Oyama MA, Bonagura JD. Congenital heart disease. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of veterinary internal medicine*. 8th ed. St Louis: Elsevier; 2017:1207–1248.

Buchanan JW. Prevalence of cardiovascular disorders. In: Fox PR, Sisson D, Moise NS, eds. *Textbook of canine and feline cardiology*. 2nd ed. Philadelphia: Saunders; 1999:457.

Oliveira P, et al. Retrospective review of congenital heart disease in 976 dogs. *J Vet Intern Med*. 2011;25:477–483.

Schrope DP. Prevalence of congenital heart disease in 76,301 mixed breed dogs and 57,025 mixed-breed cats. *J Vet Cardiol*. 2015;17:192–202.

Tidholm A, et al. Congenital heart defects in cats: a retrospective study of 162 cats (1996-2013). *J Vet Cardiol*. 2015;17(suppl 1):S215–S219.

Ventricular Outflow Obstruction

Buchanan JW. Pathogenesis of single right coronary artery and pulmonic stenosis in English bulldogs. *J Vet Intern Med*. 2001;15:101–104.

Bussadori C, et al. Balloon valvuloplasty in 30 dogs with pulmonic stenosis: effect of valve morphology and annular size on initial and 1-year outcome. *J Vet Intern Med*. 2001;15:553–558.

Estrada A, et al. Prospective evaluation of the balloon-to-annulus ratio for valvuloplasty in the treatment of pulmonic stenosis in the dog. *J Vet Intern Med*. 2006;20:862–872.

Fonfara S, et al. Balloon valvuloplasty for treatment of pulmonic stenosis in English Bulldogs with aberrant coronary artery. *J Vet Intern Med*. 2010;24:354–359.

Francis AJ, et al. Outcome in 55 dog with pulmonic stenosis that did not undergo balloon valvuloplasty or surgery. *J Small Anim Prac*. 2011;52:282–288.

Kienle RD, Thomas WP, Pion PD. The natural history of canine congenital subaortic stenosis. *J Vet Intern Med*. 1994;8:423–431.

Kleman ME, et al. How to perform combined cutting balloon and high-pressure balloon valvuloplasty for dogs with subaortic stenosis. *J Vet Cardiol*. 2012;14:351–361.

Koplitz SL, et al. Aortic ejection velocity in healthy Boxers with soft cardiac murmurs and Boxers without cardiac murmurs: 201 cases (1997-2001). *J Am Vet Med Assoc*. 2003;222:770–774.

Locatelli C, et al. Independent predictors of immediate and long-term results after pulmonary balloon valvuloplasty in dogs. *J Vet Cardiol*. 2011;13:21–30.

Meurs KM, Lehmkuhl LB, Bonagura JD. Survival times in dogs with severe subvalvular aortic stenosis treated with balloon valvuloplasty or atenolol. *J Am Vet Med Assoc*. 2005;227:420–424.

Orton EC, et al. Influence of open surgical correction on intermediate-term outcome in dogs with subvalvular aortic stenosis: 44 cases (1991-1998). *J Am Vet Med Assoc*. 2000;216:364–367.
Patterson DF, Haskins ME, Schnarr WR. Hereditary dysplasia of the pulmonary valve in Beagle dogs. *Am J Cardiol*. 1981;47:631–641.
Pyle RL, Patterson DF, Chacko S. The genetics and pathology of discrete subaortic stenosis in the Newfoundland dog. *Am Heart J*. 1976;92:324–334.
Schrope DP. Primary pulmonic infundibular stenosis in 12 cats: natural history and the effects of balloon valvuloplasty. *J Vet Cardiol*. 2008;10:33–43.
Stafford Johnson M, et al. Pulmonic stenosis in dogs: balloon dilation improves clinical outcome. *J Vet Intern Med*. 2004;18:656–662.
Stern JA, et al. A single codon insertion in PICALM is associated with development of familial subvalvular aortic stenosis in Newfoundland dogs. *Hum Genet*. 2014;133:1139–1148.

Cardiac Shunts

Birchard SJ, Bonagura JD, Fingland RB. Results of ligation of patent ductus arteriosus in dogs: 201 cases (1969-1988). *J Am Vet Med Assoc*. 1990;196:2011–2013.
Blossom JE, Bright JM, Griffiths LG. Transvenous occlusion of patent ductus arteriosus in 56 consecutive dogs. *J Vet Cardiol*. 2010;12:75–84.
Bomassi E, et al. Signalment, clinical features, echocardiographic findings, and outcome of dogs and cats with ventricular septal defects: 109 cases (1992-2013). *J Am Vet Med Assoc*. 2015;247:166–175.
Buchanan JW. Patent ductus arteriosus morphology, pathogenesis, types and treatment. *J Vet Cardiol*. 2001;3:7–16.
Buchanan JW, Patterson DF. Etiology of patent ductus arteriosus in dogs. *J Vet Intern Med*. 2003;17:167–171.
Bureau S, Monnet E, Orton EC. Evaluation of survival rate and prognostic indicators for surgical treatment of left-to-right patent ductus arteriosus in dogs: 52 cases (1995-2003). *J Am Vet Med Assoc*. 2005;227:1794–1799.
Campbell FE, et al. Immediate and late outcomes of transarterial coil occlusion of patent ductus arteriosus in dogs. *J Vet Intern Med*. 2006;20:83–96.
Chetboul V, et al. Retrospective study of 156 atrial septal defects in dogs and cats (2001-2005). *J Vet Med A Physiol Pathol Clin Med*. 2006;53:179–184.
Cote E, Ettinger SJ. Long-term clinical management of right-to-left ("reversed") patent ductus arteriosus in 3 dogs. *J Vet Intern Med*. 2001;15:39–42.
Fujii Y, et al. Transcatheter closure of congenital ventricular septal defects in 3 dogs with a detachable coil. *J Vet Intern Med*. 2004;18:911–914.
Fujii Y, et al. Prevalence of patent foramen ovale with right-to-left shunting in dogs with pulmonic stenosis. *J Vet Intern Med*. 2012;26:183–185.
Goodrich KR, et al. Retrospective comparison of surgical ligation and transarterial catheter occlusion for treatment of patent ductus arteriosus in two hundred and four dogs (1993-2003). *Vet Surg*. 2007;36:43–49.
Gordon SG, et al. Transcatheter atrial septal defect closure with the Amplatzer atrial septal occluder in 13 dogs: short- and mid-term outcome. *J Vet Intern Med*. 2009;23:995–1002.
Gordon SG, et al. Transarterial ductal occlusion using the Amplatz Canine Duct Occluder in 40 dogs. *J Vet Cardiol*. 2010;12:85–92.
Margiocco ML, Bulmer BJ, Sisson DD. Percutaneous occlusion of a muscular ventricular septal defect with an Amplatzer muscular VSD occluder. *J Vet Cardiol*. 2008;10:61–66.
Moore KW, Stepien RL. Hydroxyurea for treatment of polycythemia secondary to right-to-left shunting patent ductus arteriosus in 4 dogs. *J Vet Intern Med*. 2001;15:418–421.
Nguyenba TP, Tobias AH. Minimally invasive per-catheter patent ductus arteriosus occlusion in dogs using a prototype duct occlude. *J Vet Intern Med*. 2008;22:129–134.
Orton EC, et al. Open surgical repair of tetralogy of Fallot in dogs. *J Am Vet Med Assoc*. 2001;219:1089–1093.
Saunders AB, et al. Long-term outcome in dogs with patent ductus arteriosus: 520 cases (1994-2009). *J Vet Intern Med*. 2013;28:401–410.
Saunders AB, et al. Pulmonary embolization of vascular occlusion coils in dogs with patent ductus arteriosus. *J Vet Intern Med*. 2004;18:663–666.
Saunders AB, et al. Echocardiographic and angiocardiographic comparison of ductal dimensions in dogs with patent ductus arteriosus. *J Vet Intern Med*. 2007;21:68–75.
Schrope DP. Atrioventricular septal defects: natural history, echocardiographic, electrocardiographic, and radiographic findings in 26 cats. *J Vet Cardiol*. 2013;14:233–242.
Seibert RL, et al. Successful closure of left-to-right patent ductus arteriosus in three dogs with concurrent pulmonary hypertension. *J Vet Cardiol*. 2010;12:67–73.
Singh MK, et al. Occlusion devices and approaches in canine patent ductus arteriosus: comparison and outcomes. *J Vet Intern Med*. 2012;26:85–92.

Other Anomalies

Arai S, et al. Bioprosthesis valve replacement in dogs with congenital tricuspid valve dysplasia: technique and outcome. *J Vet Cardiol*. 2011;13:91–99.
Arndt JW, Oyama MA. Balloon valvuloplasty of congenital mitral stenosis. *J Vet Cardiol*. 2013;15:147–151.
Buchanan JW. Tracheal signs and associated vascular anomalies in dogs with persistent right aortic arch. *J Vet Intern Med*. 2004;18:510–514.
Buchanan JW. Persistent left cranial vena cava in dogs: angiocardiography, significance, and coexisting anomalies. *J Am Vet Rad*. 1963;4:1–8.
Chetboul V, et al. Epidemiological, clinical, and echocardiographic features and survival times of dogs and cats with tetralogy of Fallot: 31 cases (2003-2014). *J Am Vet Med Assoc*. 2016;249:909–917.
Famula TR, et al. Evaluation of the genetic basis of tricuspid valve dysplasia in Labrador Retrievers. *Am J Vet Res*. 2002;63:816–820.
Isakow K, Fowler D, Walsh P. Video-assisted thoracoscopic division of the ligamentum arteriosum in two dogs with persistent right aortic arch. *J Am Vet Med Assoc*. 2000;217:1333–1336.
Kornreich BG, Moise NS. Right atrioventricular valve malformation in dogs and cats: an electrocardiographic survey with emphasis on splintered QRS complexes. *J Vet Intern Med*. 1997;11:226–230.
LeBlanc N, et al. Cutting balloon catheterization for interventional treatment of cor triatriatum dexter: 2 cases. *J Vet Cardiol*. 2012;14:525–530.
Lehmkuhl LB, Ware WA, Bonagura JD. Mitral stenosis in 15 dogs. *J Vet Intern Med*. 1994;8:2–17.
Muldoon MM, Birchard SJ, Ellison GW. Long-term results of surgical correction of persistent right aortic arch in dogs: 25 cases (1980-1995). *J Am Vet Med Assoc*. 1997;210:1761–1763.
Stafford Johnson M, et al. Management of cor triatriatum dexter by balloon dilatation in three dogs. *J Small Anim Pract*. 2004;45:16–20.
Zook BC, Paasch LH. Endocardial fibroelastosis in Burmese cats. *Am J Path*. 1982;106:435–438.

CHAPTER 6

Acquired Valvular and Endocardial Disease



DEGENERATIVE ATRIOVENTRICULAR VALVE DISEASE

Chronic degenerative atrioventricular (AV) valve disease is the most common cause of heart failure in the dog; it is estimated to cause more than 70% of the cardiovascular disease recognized in this species. Almost all small-breed dogs develop some degree of valve degeneration as they age; many dogs of larger breeds do as well. Degenerative valve disease also has been called endocardiosis, mucoid or myxomatous valvular degeneration, chronic valvular fibrosis, and other names. Because clinically relevant degenerative valve disease is rare in cats, this chapter focuses on canine chronic valvular disease. The mitral valve is affected most often and to a greater degree, therefore degenerative valve disease usually is referred to as chronic (or degenerative or myxomatous) mitral valve disease (CMVD). Degenerative lesions also affect the tricuspid valve in many dogs; however, isolated tricuspid involvement is uncommon. Thickening of the aortic and pulmonic valves sometimes is observed in older animals but rarely causes more than mild insufficiency.

The preclinical phase of CMVD is prolonged. Early valve lesions are evident only on post-mortem exam. As the degenerative process continues, valve insufficiency (regurgitation) with progressively worsening mitral regurgitation (MR) and volume overloading of the adjacent atrium and ventricle eventually develop over a period of years. Although many affected dogs do develop congestive heart failure (CHF) and other complications, many others do not.

ETIOLOGY AND PATHOPHYSIOLOGY

Multiple factors are involved in the development of CMVD. Although the structural and cellular changes have been fairly well delineated, the molecular mechanisms and biochemical changes involved are less clear. Studies have shown differential expression of multiple genes, with some being upregulated and others downregulated. Affected genes appear related to cell signaling, metabolism, extracellular matrix, inflammation, cardiovascular development, basement membrane structure, and other functions. Some functions of downregulated genes relate to formation of force-resistant collagen bundles, basement membrane structure, matrix metalloproteinases involved in collagen maturation and elastic fiber formation, and sarcoplasmic reticular calcium reuptake.

Chronic mechanical stress on valve leaflet edges from repeated impact is thought to play a role in initiating the myxomatous degeneration process. Subsequent alterations in valve interstitial and endothelial cell phenotype and function are important to this process. These changes cause disruptions in normal extracellular matrix homeostatic mechanisms, leading to characteristic changes in the organization, quantity, and distribution of extracellular matrix components. The major mediator of myxomatous degeneration appears to be activated valve interstitial cells, which become transformed from their normal fibroblastic phenotype into a myofibroblastic, α-smooth muscle actin-positive staining form (αSMA). The increase in these transformed cells promotes valve matrix remodelling. Altered activity of the various catabolic extracellular matrix enzymes (such as matrix metalloproteinases, collagenases, and elastases) occurs during the process of valve degeneration, which leads to increased collagen, decreased elastin, and increasing valve stiffness. Transforming growth factor-β (TGF-β) and serotonin (5-HT) signaling also appear to be involved in CMVD pathogenesis. Localized production of TGF-β occurs in affected valves, and expression of TGF-β subtypes and their receptors is increased. Through a mechanism involving TGF-β, 5-HT induces the transformation of valve interstitial cells into their activated form. Valve endothelial cell signaling, basement membrane damage, phenotypic changes in valve endothelial cells, and increased release of vasoactive substances are involved in the pathogenesis of CMVD. Several mediators are known to increase activity of matrix metalloproteinases, including angiotensin II, endothelin, norepinephrine and other catecholamines, tumor necrosis factor (TNF)α, interleukin-1β, and possibly oxidative and mechanical stresses.

Progressive thickening of the valve spongiosa layer occurs as deposition of glycosaminoglycans (GAGs), proteoglycans,

and other components increases. In addition, the normal layered arrangement of collagen within the valve fibrosa layer becomes altered and attenuated, as GAG infiltration disrupts collagen bundles. Altered collagen fiber orientation within the valve leaflets affects mechanical strain forces during the cardiac cycle, and, in turn, influences various cellular functions. The altered collagen fibril organization results in mechanically weaker and less flexible valves. Myxomatous changes are most severe in the free edge to distal third of the valve leaflets. The leaflets thicken and lengthen as CMVD progresses. Myxomatous degeneration of the chordae reduces their tensile strength and can predispose to rupture.

Gross pathologic valve changes develop gradually with age. Early lesions consist of small nodules on the free margins of the valve. Over time these become larger, coalescing plaques that thicken and distort the valve. This myxomatous interstitial degeneration causes valvular nodular thickening and deformity, weakening the valve and its chordae tendineae. Redundant tissue between chordal attachments often bulges (prolapses) like a parachute toward the atrium. Mitral valve prolapse may be important in the pathogenesis of the disease, at least in some breeds. In severely affected regions, the valve surface also becomes damaged, and endothelial cells are lost in some areas. Despite loss of valvular endothelial integrity, however, thrombosis and endocarditis are rare complications.

Affected valves gradually begin to leak because their edges do not coapt properly. Regurgitation usually develops slowly over months to years. Pathophysiologic changes relate to volume overload on the affected side of the heart after the valve or valves become incompetent, with progressive atrial and ventricular chamber enlargement. Mean atrial pressure usually remains fairly low during this time, unless a sudden increase in regurgitant volume (e.g., ruptured chordae) occurs. Secondary atrial jet lesions and endocardial fibrosis then develop. In patients with advanced disease, partial- or even full-thickness atrial tears can form. As valve degeneration worsens, a progressively larger volume of blood moves ineffectually back and forth between the ventricle and atrium, diminishing the forward flow to the aorta. Compensatory neurohormonal mechanisms are activated and augment blood volume to meet the circulatory needs of the body (see Chapter 3); these include increased sympathetic activity and renin-angiotensin-aldosterone system (RAAS) activation. Natriuretic peptide production also increases in advanced disease.

Dilation and remodeling of the affected ventricle (and atrium) gradually occurs in response to growing end-diastolic wall stress. A multitude of changes in left ventricular (LV) gene expression have been shown, many related to upregulated proinflammatory responses, collagen degradation, and reduced interstitial matrix production. The LV remodeling process is characterized by degradation and loss of the normal collagen weave between the cardiomyocytes, thought largely due to increased production of matrix metalloproteinases and chymase from mast cells. Chymase, rather than angiotensin-converting enzyme (ACE), is the enzyme responsible for interstitial production of angiotensin II in the myocardium, which contributes to continued ventricular remodeling. The interstitial collagen loss allows myocardial fiber slippage and, along with myocardial cell elongation, hypertrophy, and changes in LV geometry, produces the typical progressive eccentric (dilation) hypertrophy pattern of chronic volume overloading. Stretching of the valve annulus as the ventricle dilates contributes to further valve regurgitation and volume overload.

The compensatory changes in heart size and blood volume allow most dogs to remain asymptomatic for a prolonged period. Left atrial (LA) enlargement may become massive before any signs of decompensation appear, and some dogs never show clinical signs of heart failure. The rate at which the regurgitation worsens, as well as the degree of atrial distensibility and ventricular contractility, influences how well the disease is tolerated. A gradual increase in atrial, pulmonary venous, and capillary hydrostatic pressures stimulates compensatory increases in pulmonary lymphatic flow. Overt pulmonary edema develops when the capacity of the pulmonary lymphatic system is exceeded. Pulmonary hypertension (PH) secondary to chronically increased LA and pulmonary venous pressure, and worsening tricuspid regurgitation (TR) can lead to right-sided CHF signs. In addition to pulmonary venous hypertension, other factors contributing to increased pulmonary vascular resistance can include hypoxic pulmonary arteriolar vasoconstriction, impaired endothelium-dependent vasodilation, and chronic neurohumoral activation.

Ventricular pump function usually is maintained fairly well until late in the disease, even in the face of severe congestive signs. Nevertheless, studies of isolated myocardial cells from dogs with subclinical MR show reduced contractility, abnormal Ca^{++} kinetics, and evidence of oxidative stress. Progressive myocardial dysfunction exacerbates ventricular dilation and valve regurgitation and therefore can worsen CHF. Assessment of LV contractility in animals with MR is complicated by the fact that the commonly used clinical indices (echocardiographic fractional shortening or ejection fraction) overestimate contractility because they are obtained during ejection and are therefore affected by the reduced ventricular afterload caused by MR. Estimation of the end-systolic volume index (ESVI) and some other echo/Doppler indices also can be helpful in assessing LV systolic and diastolic function (see p. 25).

Chronic valvular disease also is associated with intramural coronary arteriosclerosis, microscopic intramural myocardial infarctions, and focal myocardial fibrosis. The extent to which these changes cause clinical myocardial dysfunction is not clear because senior dogs without valvular disease also have similar vascular lesions.

COMPLICATING FACTORS

Although CMVD usually progresses slowly, certain complicating events can precipitate acute clinical signs in dogs with previously compensated disease (Box 6.1). For example,

BOX 6.1

Potential Complications of Chronic Mitral Valve Disease

Causes of Acutely Worsened Pulmonary Edema

- Arrhythmias
  - Frequent atrial premature complexes
  - Paroxysmal atrial/supraventricular tachycardia
  - Atrial fibrillation
  - Frequent ventricular tachyarrhythmias
- Ruptured chordae tendineae
- Iatrogenic volume overload
  - Excessive volumes of IV fluids or blood
  - High-sodium fluids
- Erratic or improper medication administration
- Insufficient medication for stage of disease
- Increased cardiac workload
  - Physical exertion
  - Anemia
  - Infections/sepsis
  - Hypertension
  - Disease of other organ systems (e.g., pulmonary, renal, liver, endocrine)
  - Hot, humid environment
  - Excessively cold environment
  - Other environmental stresses
  - High salt intake
  - Myocardial degeneration and poor contractility

Causes of Reduced Cardiac Output or Weakness

- Arrhythmias (see previously)
- Ruptured chordae tendineae
- Cough-syncope
- Pulmonary hypertension
- Secondary right-sided heart failure
- Left atrial tear
  - Intrapericardial bleeding
  - Cardiac tamponade
- Myocardial degeneration and poor contractility
- Hypertension
- Anemia or other systemic disease

tachyarrhythmias may be severe enough to cause decompensated CHF, syncope, or both. Frequent atrial premature contractions, paroxysmal atrial tachycardia, or atrial fibrillation can reduce ventricular filling time and cardiac output, increase myocardial oxygen needs, and worsen pulmonary congestion and edema. Ventricular tachyarrhythmias also occur but are less common.

Acute rupture of diseased chordae tendineae acutely increases regurgitant volume and can quickly precipitate fulminant pulmonary edema and signs of low cardiac output in previously asymptomatic or compensated dogs. Ruptured minor chordae tendineae can be an incidental finding in some dogs. Marked LA enlargement itself might contribute to left mainstem bronchus compression or collapse, and stimulate persistent coughing even in the absence of CHF. Concurrent airway inflammatory disease and bronchomalacia are common in small-breed dogs with chronic MR.

Massive left (or right) atrial distention can result in partial- or full-thickness tearing. Atrial wall rupture can cause acute cardiac tamponade or an acquired atrial septal defect. There appears to be a higher prevalence of this complication in male Cocker Spaniels, Dachshunds, and possibly Miniature Poodles. In Cavalier King Charles Spaniels, the prevalence seems to be similar between females and males. Severe valve disease, marked atrial enlargement, atrial jet lesions, and ruptured first-order chordae tendineae are common findings in these cases.

CLINICAL FEATURES

Middle-aged and older small to mid-size breeds are most often affected; a strong hereditary basis is thought to exist, and disease prevalence and severity increase with age. The majority of small-breed dogs older than 10 years of age are affected. Common breeds include Cavalier King Charles Spaniels, Toy and Miniature Poodles, Miniature Schnauzers, Chihuahuas, Pomeranians, Fox Terriers, Cocker Spaniels, Pekingese, Dachshunds, Boston Terriers, Miniature Pinschers, and Whippets. An especially high prevalence and early onset of CMVD occurs in Cavalier King Charles Spaniels, in which the disease is suspected to be a complex autosomal polygenic trait with variable penetrance. The overall prevalence of MR murmurs and degenerative valve disease appears similar in male and female dogs, but males have earlier onset and faster disease progression. Some large-breed dogs are also affected, although the degree of valve thickening and prolapse tends to be less pronounced than in small-breed dogs. German Shepherd Dogs may be overrepresented. Larger-breed dogs also are prone to dilated cardiomyopathy (DCM, which may coexist) or are more susceptible to myocardial dysfunction secondary to chronic volume overload.

Many dogs with CMVD have no clinical signs, even with fairly advanced disease. In those that do, early signs of CHF usually include reduced exercise tolerance, and tachypnea or cough with exertion. Because a persistent increase in baseline respiratory rate (RR) often signals the onset of pulmonary interstitial edema before other signs develop, owner monitoring of resting (sleeping) RR is useful even in dogs with early evidence of disease (see Chapter 3, p. 74). Coughing might occur at night and in the early morning, as well as with activity. However, the genesis of coughing in many dogs with CMVD could relate more to concurrent chronic airway disease, rather than CHF itself. A study of dogs with CMVD showed CHF (as assessed by radiographic evidence of pulmonary edema) was not significantly associated with coughing; however, an abnormal airway pattern as well as enlarged LA size were. A persistent cough without progressive increase in RR and effort usually is associated with airway disease, rather than CHF. The cough caused by airway compression or collapse often is described as dry or "honking." Severe pulmonary edema causes obvious respiratory distress, often with a soft, moist cough. Signs of severe pulmonary edema can develop gradually or acutely. Intermittent episodes of symptomatic pulmonary edema interspersed with periods of

compensated heart failure occurring over months to years are also common.

Episodes of transient weakness or acute collapse (syncope) are more common in dogs with advanced disease. These could occur from tachyarrhythmias, an acute vasovagal response, PH, or an atrial tear. Coughing spells can precipitate syncope, as can exercise or excitement. Signs of right-sided CHF usually are associated with severe TR, PH, or both. These include abdominal distension (ascites, hepatomegaly) and respiratory distress from pleural effusion. Gastrointestinal (GI) signs could accompany splanchnic congestion. Only rarely does noticeable peripheral tissue edema develop in dogs with CMVD.

The typical auscultatory finding is a holosystolic murmur heard best in the area of the left apex (left fourth to sixth intercostal space). The murmur can radiate in any direction. Mild regurgitation can be inaudible or cause a murmur only in early systole (protosystolic). Exercise and excitement often increase the intensity of soft MR murmurs. Louder murmurs have been associated with more advanced disease; in dogs with massive regurgitation and severe heart failure, however, the murmur can be soft or even inaudible. Occasionally, the murmur sounds like a musical tone or whoop. Some dogs with early MVD have an audible mid- to late-systolic click, with or without a soft murmur. In dogs with advanced disease and myocardial failure, an S_3 gallop might be audible at the left apex. TR typically causes a holosystolic murmur best heard at the right apex. Features that aid in differentiating a TR murmur from radiation of an MR murmur to the right chest wall include jugular vein pulsations, a precordial thrill over the right apex, and a different quality to the murmur heard over the tricuspid region.

Pulmonary sounds can be normal or abnormal. Accentuated, harsh breath sounds and end-inspiratory crackles (especially in ventral lung fields) develop as pulmonary edema worsens. Fulminant pulmonary edema causes widespread inspiratory, as well as expiratory, crackles and wheezes. Some dogs with chronic MR have abnormal lung sounds caused by underlying pulmonary or airway disease rather than CHF. Although not a pathognomonic finding, dogs with CHF often have sinus tachycardia, whereas marked sinus arrhythmia is common in those with chronic pulmonary disease. Pleural effusion may cause diminished pulmonary sounds ventrally.

Other physical examination findings may be normal or noncontributory. Heart rate and rhythm generally are normal, although sinus tachycardia is more typical as CHF develops. Arrhythmias are more likely to occur with advanced disease. Peripheral capillary perfusion and arterial pulse strength usually are good, although pulse deficits might be present in dogs with tachyarrhythmias. A palpable precordial thrill accompanies loud (grade 5-6/6) murmurs. Jugular vein distention and pulsations are not expected in dogs with MR alone. In animals with TR, especially PH, jugular pulses occur during ventricular systole; these are more evident after exercise or in association with excitement. Jugular venous distention results from elevated right heart filling pressures. Jugular pulsations and distention are more evident with cranial abdominal compression (positive hepatojugular reflux). Ascites or hepatomegaly may be evident in dogs with right-sided CHF.

Concurrent diseases that could be confused with decompensated CHF from CMVD include tracheal collapse, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary neoplasia, pneumonia, pharyngitis, heartworm disease, DCM in larger breeds, and infective endocarditis (which is rare with CMVD).

DIAGNOSIS

CLINICOPATHOLOGIC FINDINGS

Routine clinical laboratory tests often are normal or reflect changes consistent with CHF or concurrent extracardiac disease. Elevations in natriuretic peptide concentrations tend to reflect increasing disease severity. Dogs with high levels (e.g., NT-proBNP ≥ 1500 pmol/L) are more likely to have CHF (or develop it sooner) and have a worse prognosis. Elevations in circulating cardiac troponin I (cTnI) also occur in moderate to severe CMVD and increase with severity of clinical signs. This could be a marker for myocardial fibrosis in chronic heart disease.

RADIOGRAPHY

Thoracic radiographs are normal in dogs with early (stage B1) CMVD. As MR severity increases, progressive LA and then LV enlargement develops (stage B2), usually over a period of years (Fig. 6.1). Dorsal elevation of the carina and, as LA size increases, dorsal main bronchus displacement occur. Severe LA enlargement can cause the appearance of carina and left mainstem bronchus compression (Fig. 6.1, *C*). Fluoroscopy might demonstrate dynamic airway collapse (of the left main bronchus or other regions) during coughing or even quiet breathing because concurrent airway disease is common in these cases. Extreme dilation of the LA can result over time, even without clinical heart failure. The vertebral heart score (VHS) increases with the growing volume overload. In coughing dogs with CMVD, a VHS ≤ 11.4 v suggests a noncardiac cause; dogs with cardiac or mixed-origin cough tend to have higher VHS. The rate of change in VHS, as well as the echocardiographic dimensions of LA and LV in both diastole and systole, becomes greatest at the onset of CHF. The increase in cardiac size occurs most rapidly within the 12 months preceding CHF onset. Variable right heart enlargement occurs in association with chronic TR, but this may be masked by left heart and pulmonary changes associated with concurrent MVD.

Pulmonary venous congestion can be an early sign of left-sided congestive failure. However, visibly distended pulmonary veins are not always appreciable. Interstitial edema occurs with the onset of left-sided CHF. Radiographic findings associated with early pulmonary edema can appear similar to those caused by chronic airway or pulmonary disease. With CHF, progressive interstitial and alveolar

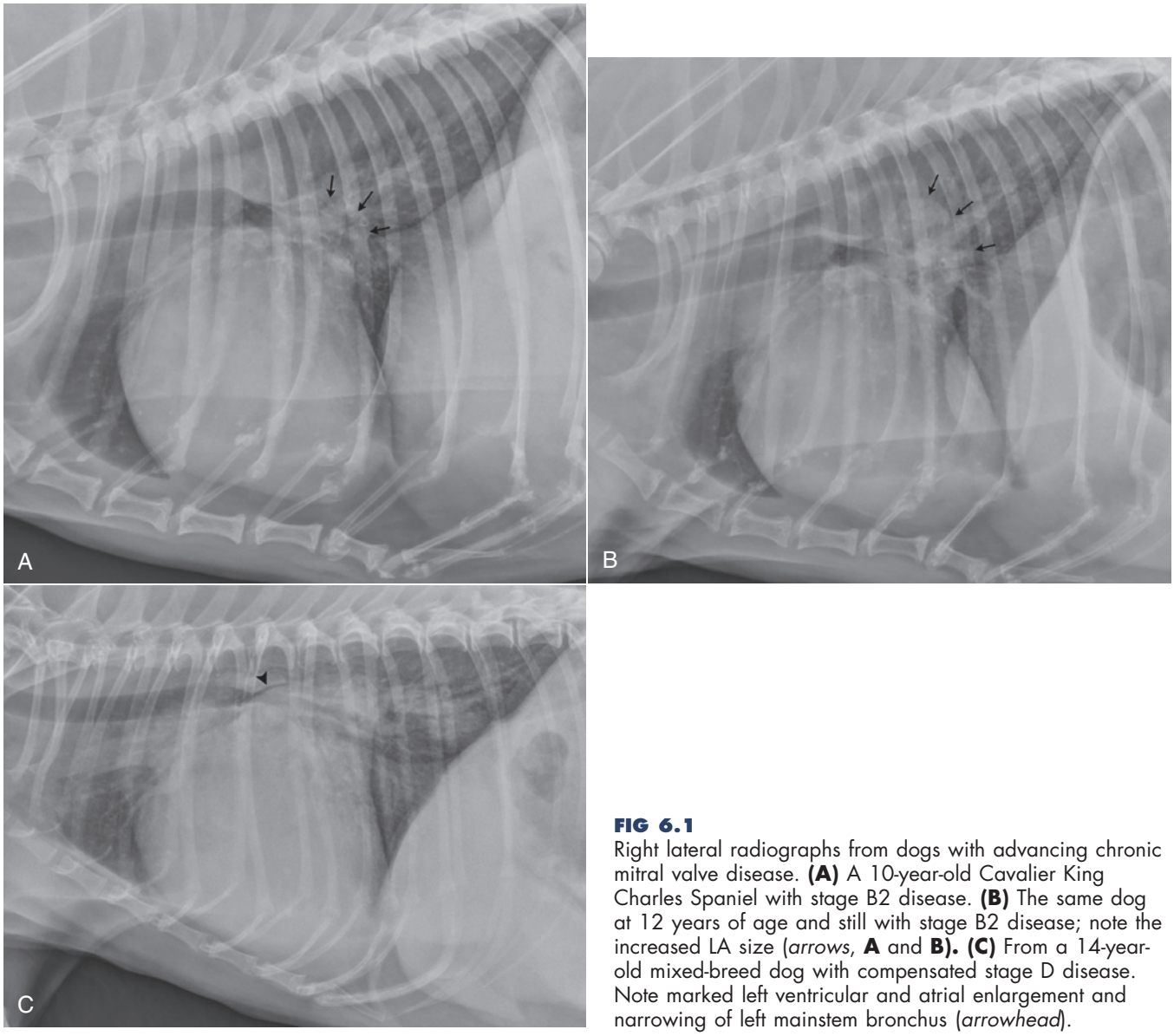


FIG 6.1
Right lateral radiographs from dogs with advancing chronic mitral valve disease. **(A)** A 10-year-old Cavalier King Charles Spaniel with stage B2 disease. **(B)** The same dog at 12 years of age and still with stage B2 disease; note the increased LA size (*arrows*, **A** and **B**). **(C)** From a 14-year-old mixed-breed dog with compensated stage D disease. Note marked left ventricular and atrial enlargement and narrowing of left mainstem bronchus (*arrowhead*).

pulmonary edema follow. Although cardiogenic pulmonary edema in dogs typically has a hilar, dorsocaudal, and bilaterally symmetric pattern, an asymmetric distribution is seen in many dogs; this might relate to may relate to the angulation of the MR jet. The presence and severity of pulmonary edema do not necessarily correlate with the degree of cardiomegaly. Acute, severe MR (for example, from rupture of chordae tendineae) can cause severe edema with minimal LA enlargement. Conversely, slowly worsening MR can produce massive LA enlargement with no evidence of CHF. Early signs of right-sided heart failure include caudal vena cava distention, pleural fissure lines, and hepatomegaly. Overt pleural effusion and ascites occur with advanced failure.

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) might suggest LA or biatrial enlargement and LV dilation (see p. 45), although the tracing is often normal. Echocardiography is a much more sensitive tool for detecting chamber enlargement. An RV enlargement pattern is occasionally seen in dogs with severe TR. Arrhythmias, especially sinus tachycardia, supraventricular premature complexes, paroxysmal or sustained supraventricular tachycardias, ventricular premature complexes, and atrial fibrillation are common in dogs with advanced disease. These arrhythmias can be associated with decompensated CHF, weakness, or syncope.

ECHOCARDIOGRAPHY

Echocardiography shows valve structural changes and chamber enlargement secondary to valve insufficiency, and it allows ventricular function estimation. Color flow Doppler imaging shows the direction and extent of disturbed flow in the atrium. In early CMVD, only mild mitral leaflet thickening, with or without a small MR jet, and normal chamber size are typical. As the disease progresses, the affected valve

cusps become thicker. Mild mitral prolapse is seen early in some dogs. Mitral prolapse usually involves the anterior leaflet or both leaflets. Its severity tends to increase with worsening disease (Fig. 6.2). Sometimes, a ruptured chorda tendineae or flail leaflet tip is seen during systole (Fig. 6.2, C). Color flow Doppler imaging allows semiquantitative assessment of MR severity, based on the width of the regurgitant jet at its origin along the closed valve, as well as how much of the atrial area is affected by the disturbed flow pattern (Fig. 6.3). More quantitative calculation of MR severity can be obtained by the proximal isovelocity surface area (PISA) method (see Suggested Readings list), although there are multiple potential inaccuracies and it is not often done clinically.

The degree of atrial and ventricular dilation increases as the volume overload secondary to worsening valve regurgitation increases. Large LA size and LA/aortic root (Ao) ratio are associated with worse prognosis. Increased LV end diastolic dimension (LVIDd) also has been associated with negative outcome. A ratio of LVIDd/Ao diameter ≥3 was identified as an independent risk factor for first onset CHF. As the LV dilates from the increasing volume overload, it becomes more spherical in shape. This LV enlargement and geometric change are associated with increased risk for CHF and may contribute to impaired pump function. As the LV becomes more spherical, the increased mitral annulus size leads to even greater MR and risk of decompensation to CHF.

RV and RA dilation develop with TR and PH; RV chamber dilation is more prominent than RV wall hypertrophy with PH secondary to CMVD. Paradoxical septal motion can occur with marked RV volume overload and interferes with FS assessment. Spectral Doppler interrogation of TR peak velocity is the easiest way to estimate presence and severity of PH (see Chapter 2, p. 30). Where a measurable TR jet is not present, other echo parameters can suggest PH, including pulmonary annulus dilation, PR jet velocity, right pulmonary artery distensibility index, decreased PA acceleration time to deceleration time (AT/DT), increased (corrected for body weight) RVIDd, and increased LA:Ao. See Chapter 10 and Suggested Readings for additional information.

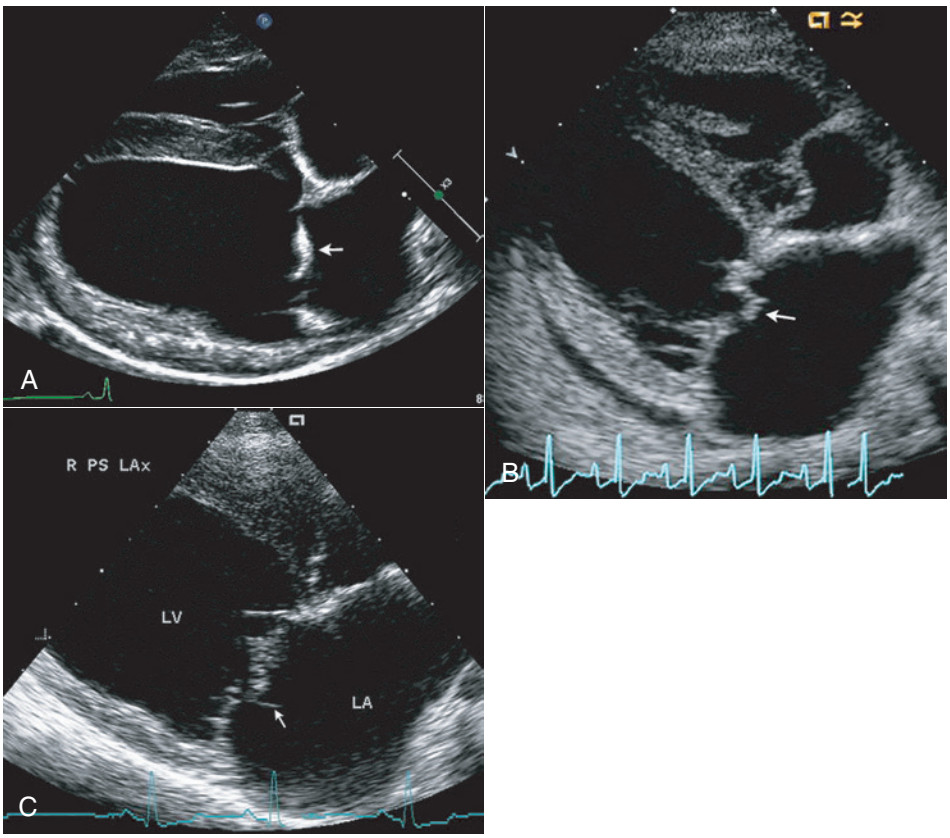


FIG 6.2
(A) Thick, mildly prolapsing mitral valve *(arrow)* is seen from the right long-axis view in a mixed-breed dog with early (stage B1) chronic mitral valve disease. **(B)** Pronounced prolapse of the anterior mitral leaflet *(arrow)* and left atrial enlargement in a 10-year-old Miniature Schnauzer with severe degenerative mitral valve disease (stage C). The tricuspid valve also is thickened, and there is a small amount of pericardial effusion. **(C)** Chorda tendineae rupture is evident by the flail segment *(arrow)* seen in the enlarged left atrium of a 12-year-old English Pointer.

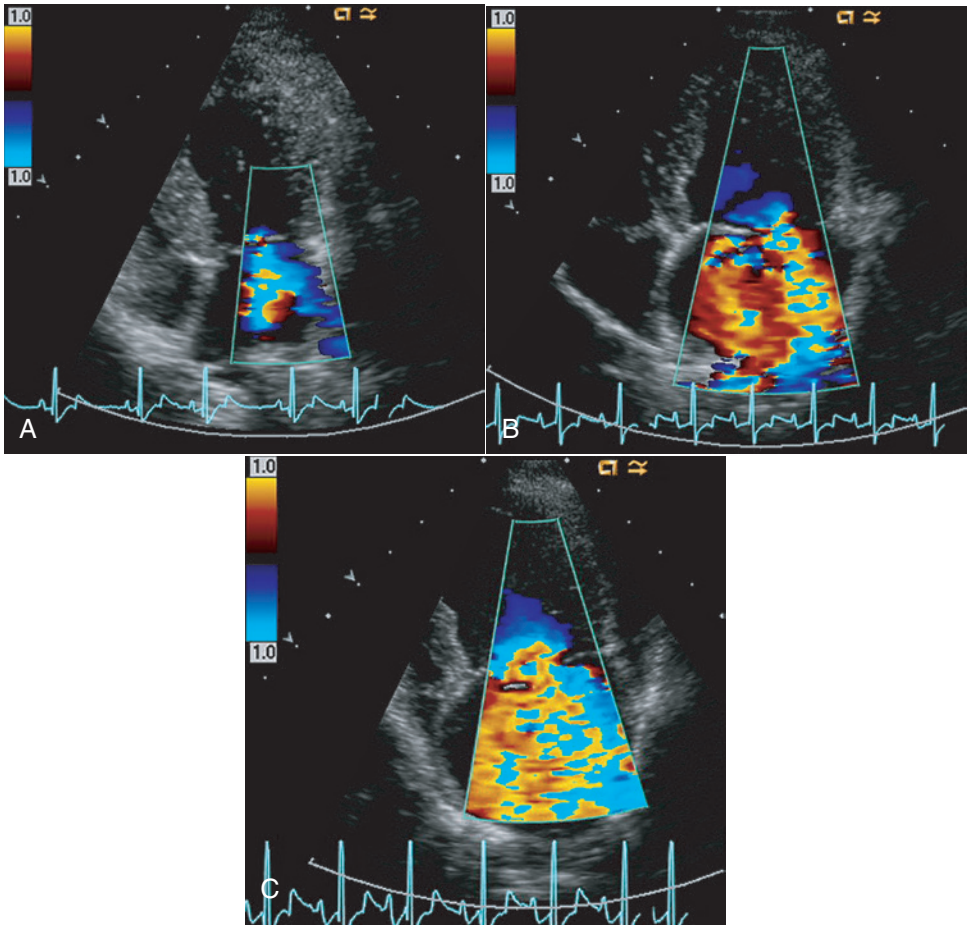


FIG 6.3
Varying degrees of MR severity in three dogs with chronic mitral valve disease, seen with color flow Doppler imaging from the left apical 4-chamber view (the LV is at top of each image, LA at bottom). **(A)** Mild MR in a 10-year-old Miniature Schnauzer. **(B)** Moderately severe MR in a different, older Miniature Schnauzer. **(C)** Severe MR, from the same dog as in Fig. 6.2, *B*. Comparing **(A)** with **(C)**, note the increasing width of the flow disturbance at its origin at the mitral valve, the greater color mixing (representing turbulent flow) and intensity within the left atrium, and also the prominent left atrial enlargement in **(B)** and **(C)**. *Note:* Color is visible only within the sector outlined by the green line. *LA,* Left atrium; *LV,* left ventricle; *MR,* mitral regurgitation.

LV wall and septal motion usually appear quite vigorous with moderate to severe MR, because in most cases overall pump function is well preserved until late in the disease. Small to no EPSS and a high FS are seen (Fig. 6.4). Although diastolic LV dimension increases with MR, when contractility is good, systolic dimension remains normal. An increasing LV systolic dimension implies impaired myocardial contractility; this can occur even before CHF develops. Declining systolic function can be identified on serial echocardiography exams; however, changes in ventricular loading associated with CMVD can interfere. For example, shortening and ejection fractions generally are increased with severe MR, even in the presence of CHF and declining myocardial contractility. The ESVI normalizes LV end systolic volume to body surface area. This index has been used to estimate myocardial systolic function in patients with valve insufficiency because it is minimally influenced by preload changes. ESVI derived from long-axis two-dimensional (2-D) images optimized for maximal LV size, using the method of discs, is considered more accurate than volume estimation derived from a single M-mode LV dimension measurement. Spectral Doppler interrogation of MR jet acceleration rate also can be used to estimate LV contractility (dP/dtmax), and MR peak velocity can be used to estimate the systolic pressure gradient between LA and LV, although an eccentric jet angle and mitral prolapse can impair accuracy.

Pericardial fluid (blood), with or without signs of cardiac tamponade (see Chapter 9), can be evident if a full thickness LA tear has occurred. Mild pericardial effusion (transudate) also can develop with right-sided congestive failure. Pericardial effusion secondary to CHF generally does not cause tamponade.

Spectral Doppler imaging of mitral inflow velocity and isovolumic relaxation time (IVRT), and tissue Doppler

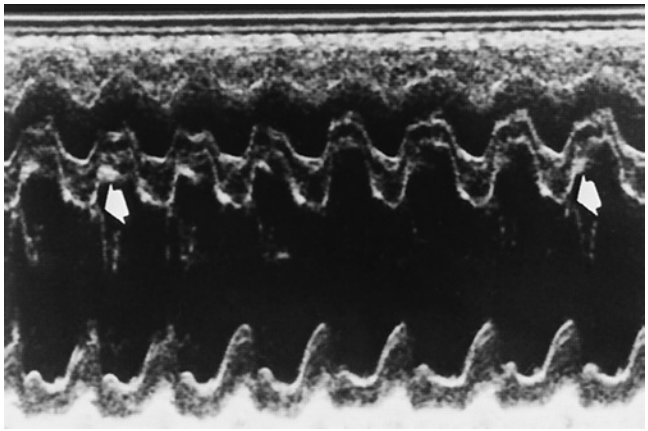


FIG 6.4
M-mode echocardiogram from a male Maltese with advanced mitral valve regurgitation and congestive heart failure. Note vigorous septal and left ventricular posterior wall motion (fractional shortening = 50%) and lack of mitral valve E point–septal separation *(arrows)*.

(TDI) measurement of lateral or septal annulus velocity help characterize LV diastolic function and LV filling pressure. Discrimination of disease-induced mild diastolic dysfunction is difficult, because many older dogs have the delayed relaxation pattern of mitral inflow (E/A<1). However, pseudonormal and restrictive inflow patterns are common in dogs with advanced CMVD, especially those with CHF. Mitral E velocities well over 1 m/s are common with advanced CMVD. However, mitral inflow pattern by itself is not a sensitive correlate for identifying high LA pressure and pulmonary edema. Nor is the ratio of early LV inflow to annular tissue velocity ratio, E/Ea (also expressed as E/E' and E/Em), useful for predicting LA filling pressure (or CHF) in dogs with CMVD. However, the early mitral inflow velocity to IVRT ratio (E:IVRT) is more useful in identifying elevated LA (LV filling) pressure in dogs with MR. This index combines peak mitral E velocity (determined mainly by LV filling pressure and relaxation) and IVRT (dependent mostly on LV relaxation). An E:IVRT >2.5 has been proposed as a cut-off value for predicting CHF in dogs with CMVD.

Treatment and Prognosis

Goals of preclinical (stage B) CMVD management are to delay the onset of CHF, and to identify and treat the early signs of decompensation before fulminant pulmonary edema develops. For dogs that already have developed CHF (stage C), therapy is aimed at controlling signs of congestion, enhancing forward blood flow, reducing regurgitant volume, and diminishing excessive NH activation. Ultimately, the goal is to provide good quality of life while extending survival time. Box 6.2 outlines treatment guidelines for CMVD based on level of disease progression.

PRECLINICAL (STAGE B) CVMD

It is important to assess the severity of MR and cardiac remodelling. This helps determine risk for CHF and guide recommendations for monitoring, management, and reevaluation. Thoracic radiographs and NT-proBNP are useful for this. However, especially as the disease advances, echocardiography becomes more important to assess LA and LV size, ventricular function, and other factors.

STAGE B1

Thoracic radiographs, blood pressure (BP) measurement, and plasma NT-proBNP or echocardiography generally are recommended yearly to monitor dogs with stage B1 disease; although semiannual rechecks for large-breed dogs with advancing CMVD are considered prudent because of their tendency to develop reduced myocardial function sooner. Routine preventative healthcare should be continued, including heartworm disease prophylaxis, vaccinations, dental prophylaxis, etc. Concurrent medical problems should be identified and managed as appropriate. Owner education about the disease process and early signs of heart failure is important.

Clients should be taught how to assess their pet's resting (ideally, sleeping) RR to establish that individual's normal baseline, and, as the disease advances, to help screen for possible early signs of decompensation (see Chapter 3, p. 73 and Box 3.2, p. 74). No specific cardiac therapy currently is recommended for dogs in stage B1. For dogs with elevated BP, an ACE inhibitor (ACEI) is recommended to maintain normal arterial pressure and cardiac afterload. Normal exercise and activity, as well as a normal diet, can be maintained at this stage although avoiding high-salt foods and treats is recommended. Extremely obese dogs could benefit from weight reduction during this preclinical stage; however, a mildly overweight state is not considered problematic and could be helpful later if chronic CHF therapy becomes necessary.

STAGE B2

Dogs with measurable left heart enlargement but without ever having developed clinical signs of CHF are in stage B2 CMVD. Monitoring and routine healthcare recommendations for these dogs are similar to those for stage B1, except recheck frequency is increased to every 6 to 9 months, or sometimes more often for markedly advanced disease. In addition to a thorough physical examination and BP check, thoracic radiographs and echocardiogram or NT-proBNP are done to monitor progression; echocardiography provides more specific information about cardiac enlargement and function. Screening for concurrent medical problems also is advised. Home monitoring, as described for stage B1 dogs, should be continued with greater attention.

Pimobendan (Vetmedin) at the standard label dose currently is recommended for dogs with stage B2 CMVD. Pimobendan has been shown to delay the onset of CHF (by a median of 15 months) and prolong survival without

BOX 6.2

Treatment Guidelines for Chronic Mitral Valve Disease

Stage B1 (Asymptomatic, No or Minimal Cardiac Enlargement)

Client education (about disease process and early heart failure signs)
Routine health maintenance
- Blood pressure measurement
- Baseline chest radiographs, ±echocardiogram or NT-proBNP, and yearly rechecks
- Maintain normal body weight/condition
- Regular exercise, as tolerated
- Heartworm testing and prophylaxis in endemic areas

Manage other medical problems (including mild/moderate hypertension!)
Avoid high-salt foods
Have client begin monitoring RRR to establish normal baseline for that animal (see Box 3.2, p. 74)

Stage B2 (Asymptomatic, Progressive Cardiac Enlargement Evident)

Client education (see stage B1)
Routine health maintenance
- Blood pressure measurement
- Chest radiographs, echocardiogram, or NT-proBNP yearly (or every 6 months, if advanced disease or large-breed dog)
- Maintain normal body weight/condition
- Regular mild to moderate activity, as tolerated
- Avoid excessively strenuous activity
- Heartworm testing and prophylaxis in endemic areas

Manage other medical problems (if arterial blood pressure elevated, institute ACEI therapy)
Avoid high-salt foods; consider introducing moderately salt-restricted diet now
**New recommendation: institute pimobendan therapy (0.2-0.3 mg/kg q12h) in stage B2
Have client continue monitoring RRR periodically to help detect onset of early CHF signs (see Box 3.2, p. 74)

Stage C (Chronic/Outpatient Care; No Current CHF Signs [Stage C1] or Mild to Moderate CHF Signs [Stage C2])*

Considerations as previously noted
Furosemide, as needed
Pimobendan
ACEI
Spironolactone
Antiarrhythmic therapy, if necessary (see Chapter 4)
If CHF signs: complete exercise restriction until after signs fully resolve
If no current CHF signs: regular mild (to moderate) activity, as tolerated; avoid strenuous exercise
Moderate dietary salt restriction
Continue home monitoring of RRR to help detect early signs of CHF decompensation (see Box 3.2, p. 74)

Stage C (Acute/Hospitalized Care Needed; Severe CHF Signs [Stage C3])*

Supplemental O_2
Cage rest and minimal patient handling
Furosemide (more aggressive doses, parenteral)
Pimobendan (continue or add as soon as PO administration possible; or use IV, if available)
Vasodilator therapy (consider intravenous [IV] nitroprusside or (IV or PO) hydralazine, ± topical nitroglycerin
±Sedation, as needed
Antiarrhythmic therapy, if necessary
See Box 3.1 for other recommendations
Thoracocentesis, if moderate- to large-volume pleural effusion

Stage D (Chronic Recurrent or Refractory Heart Failure) Strategies for in-Hospital or Outpatient Care as Needed)*

Ensure that standard therapies for stage C are being given at optimal doses and intervals, including furosemide, ACEI (q12h), pimobendan, spironolactone (see Chapter 3, p. 74)
Rule out systemic arterial hypertension, arrhythmias, anemia, and other complications
Increase furosemide dose/frequency as needed (check renal function and electrolyte status); may be able to decrease somewhat in several days after signs resolve
Enforced rest until after signs abate
Additional afterload reduction (such as amlodipine [or hydralazine]); monitor blood pressure
Other strategies to consider:
- Increase pimobendan dosage (up to q8h frequency, +/or up to 0.4-0.5 mg/dose)
- Switch from furosemide to torsemide (initial dose at 1/10-1/12 of total daily furosemide dose, divided)
- ± Add a thiazide diuretic (if not using torsemide) – use low dose, monitor renal function and electrolytes closely!
- ± Add digoxin, if not currently prescribed; monitor serum concentration

Antiarrhythmic therapy, if indicated (see Chapter 4)
If pulmonary hypertension with signs of R-CHF or collapse, add sildenafil (1-3 mg/kg q8-12h PO)
Add (or increase dose of) second diuretic (e.g., spironolactone, hydrochlorothiazide)
Thoracocentesis (or abdominocentesis) as needed
Consider bronchodilator trial or cough suppressant for persistent dry cough
Further restrict dietary salt intake; verify that drinking water is low in sodium

*See Tables 3.2 and 3.3 and Box 3.1, pp. 60, 62, and 64, for further details and doses.

increasing adverse events compared to placebo in dogs with stage B2 CMVD. Current evidence suggests that initiating ACEI therapy at stage B2 does not significantly delay CHF onset in most dogs. Nevertheless, some controversy remains and, especially for dogs with advanced CMVD and severe left heart enlargement, an ACEI might provide some benefit toward delaying CHF. In any case, for dogs with systemic hypertension, ACE inhibition is recommended as first-line therapy to moderate BP. Regular (mild to moderate) exercise should be maintained as tolerated. Strenuous exercise that provokes shortness of breath or excessive fatigue is to be avoided. Gradual transition to a diet moderately reduced in salt, but also well balanced and with adequate protein content, is recommended. Although some experimental studies found a possible myocardial protective effect from β-blocker therapy, clinical β-blocker therapy trials in dogs with stage B2 MVD have not delayed CHF onset. Therefore routine β-blocker use is not recommended.

CHF ONSET IN CMVD (STAGE C)

The onset of congestive signs appears gradually in some dogs, but in others fulminant pulmonary edema or episodes of syncope can develop rapidly. Therapy should be guided by clinical status and whether any complicating factors are present. Medical therapy is the mainstay for dogs that have experienced decompensated CHF. Although surgical valve repair or replacement is sometimes an option and might be available at some referral centers, treatment for most dogs is solely medical. Clinical compensation (no congestive signs) for months to years can be possible with appropriate therapy, although frequent reevaluation and medication adjustment become necessary as the disease progresses. Intermittent episodes of decompensation (congestive signs) are common in dogs on long-term heart failure therapy; often these can be successfully managed.

Furosemide, pimobendan, and an ACEI comprise the standard, so-called "triple therapy" for dogs that have developed CHF. However, spironolactone often is added to these three other medications for chronic CHF, so perhaps "quadruple therapy" is a more apt description. Pimobendan usually is well tolerated and, when compared directly to an ACEI, has greater benefit for long-term heart failure management. Generally, an ACEI and pimobendan are used together for CHF management, although whether their benefits are additive is unclear. Pimobendan and ACEIs both can reduce LA pressure. Spironolactone may reduce the risk of cardiac death or euthanasia because of CHF in dogs with CMVD. Some dogs can develop serum electrolyte disturbances or azotemia while on spironolactone, so checking for these 1 to 2 weeks after initiating therapy and periodically thereafter is recommended. If for some reason pimobendan cannot be used, digoxin could be added instead, especially in advanced disease or for management of atrial tachyarrhythmias. Conservative doses are used and serum concentrations measured to avoid toxicity (see Chapter 3, p. 70, and Table 3.3).

No exercise should be allowed until signs of CHF fully resolve. During chronic, compensated disease, however, mild to moderate regular activity can be beneficial. Strenuous exercise is best avoided. At-home monitoring is important because decompensation can occur unexpectedly. A persistent increase in resting respiratory rate (RRR) can signal early decompensation with pulmonary edema. If decompensated CHF develops, therapy is intensified or adjusted as needed while searching for any complicating factors that may need to be addressed. Box 6.2 lists strategies for modifying or intensifying CHF therapy. Dogs with a persistent dry cough from primary airway disease or mainstem bronchus compression, and no pulmonary edema, might require antitussive therapy (e.g., hydrocodone bitartrate [0.25 mg/kg PO q4-12h] or butorphanol [0.5 mg/kg PO q6-12h]).

MILD TO MODERATE SIGNS OF CHF

Early signs of decompensation usually include persistent increases in RRR at home, shortness of breath, increased respiratory effort or excessive panting, or decreased willingness to exercise. A new or increased cough also might be noted. The history and physical examination, thoracic radiographs, NT-proBNP, and/or echocardiography can help the clinician differentiate CHF from other causes. BP measurement and routine laboratory tests can be useful for identifying other complications.

The individual patient's clinical signs and response to therapy guide the aggressiveness of CHF therapy. Furosemide is instituted when clinical signs and radiographic evidence of pulmonary edema first appear. Higher and more frequent doses are indicated for more severe edema. When the signs of failure are controlled, the dose and frequency of furosemide gradually are reduced to find the lowest effective levels for long-term therapy in that patient. Although furosemide alone might be prescribed initially as a therapeutic trial in some cases (see later in this chapter), for chronic heart failure treatment furosemide monotherapy is not recommended and does not meet standard of care.

Mild clinical signs with pulmonary venous congestion and/or only mild pulmonary edema on radiographs often responds well to PO furosemide (e.g., 1-2 mg/kg q12h), an ACEI given q24h, and pimobendan at standard dose (see Table 3.3, p. 64). A diet moderately reduced in salt is recommended. If the client can restrict activity at home, the patient might be more comfortable there. No exercise should be allowed until the next reevaluation, usually in 5 to 7 days unless problems arise sooner. Then, if all CHF signs have resolved, mild (to moderate) activity can be slowly reintroduced. Recheck exams should assess clinical status, BP, renal function, and serum electrolytes; depending on clinical findings and case progression, repeat thoracic radiographs, ECG, NT-proBNP, and echocardiogram might be appropriate as well.

Some dogs show signs suggesting early CHF; without clear radiographic evidence for pulmonary edema, however,

making the diagnosis is unclear. The presence of pulmonary lobar venous distension suggests that CHF is imminent, however this is not always seen. When it is unclear if respiratory signs are caused by heart failure or a noncardiac cause, an initial furosemide trial (e.g., 1-2 mg/kg PO q8-12h) for 2 to 3 days can be helpful. Plasma NT-proBNP measurement also can be useful. Some clinicians add an ACEI during the therapeutic trial for suspected CHF. Cardiogenic pulmonary edema usually responds rapidly, so if CHF was the cause, the owner should see rapid improvement in RR and effort as well as reduced (cardiogenic) cough. In these cases, triple therapy is instituted along with recommendation for moderate dietary salt restriction. Depending on the individual case, it may be possible to reduce the dose of furosemide somewhat, using RRR monitoring as a guide. On the other hand, coughing or other respiratory signs that persist despite furosemide trial makes a diagnosis of CHF unlikely. Nevertheless, confusion is still possible in some cases because a cough from airway irritation may resolve spontaneously, or furosemide may have a mild antiinflammatory or antitussive effect.

MODERATE TO SEVERE SIGNS OF CHF

Fulminant pulmonary edema with shortness of breath at rest is a true emergency. Aggressive therapy, but with gentle handling, is crucial in these fragile patients. Cage rest, supplemental oxygen, high-dose (e.g., 2-4 mg/kg q1-4h initially) parenteral furosemide, and vasodilator therapy are indicated (see Box 3.1, p. 62). Intravenous (IV) nitroprusside or hydralazine (PO or IV) can be used for acute therapy for rapid arteriolar vasodilating effect. BP must be closely monitored. A low dose is used in animals already receiving an ACEI. Amlodipine is another alternative, although onset of action is slower. Amlodipine can significantly decrease LA pressure and MR regurgitant jet severity compared to ACEI, however up to four days are needed for full effect. Topical nitroglycerin can be used in combination with an arteriolar dilator in an attempt to reduce pulmonary venous pressure by direct venodilation. Pimobendan dosing is begun (or continued) as soon as possible.

Heart rate and rhythm should be monitored. For the control of supraventricular tachyarrhythmias, diltiazem or a β-blocker (see Table 4.2, p. 90) can be used instead of or in addition to digoxin. Although several days are needed to achieve therapeutic digoxin serum concentration with oral maintenance doses, IV digoxin is not recommended. Therapy for ventricular tachyarrhythmias is warranted in occasional cases. For dogs with CMVD that require BP support or when myocardial function is poor, other more potent inotropic agents (e.g., dobutamine or dopamine) can be given IV (see Box 3.1, p. 62).

Mild sedation is used to reduce anxiety (e.g., butorphanol; see Box 3.1, p. 62). Patient handling should be minimized, and radiographs and other diagnostic procedures postponed until the respiratory status is more stable. A bronchodilator (e.g., theophylline, aminophylline) sometimes is used when bronchospasm induced by severe pulmonary edema is suspected; although the efficacy of this is unclear, these agents may help support respiratory muscle function. Bronchodilators can potentially increase the risk for tachyarrhythmias, though. In dogs with moderate- to large-volume pleural effusion, thoracocentesis should be done as expeditiously as possible to improve pulmonary function; ascites severe enough to impede respiration also should be drained. Close monitoring for the patient's response to therapy and any adverse effects (e.g., hypotension, azotemia, electrolyte abnormalities, arrhythmias, drug toxicity, and so on) is important for optimizing care (see Chapter 3, p. 65 for additional information). Mild to moderate azotemia is common after aggressive diuretic therapy. Slow oral "self-rehydration" is effective for most patients. Because it can exacerbate congestive signs, parenteral fluid therapy is avoided whenever possible (see Chapter 3, p. 65, section of monitoring and follow-up after acute CHF treatment).

TRANSITION TO HOME CARE

After the patient is stabilized, medications are adjusted over the next several days to weeks to determine the best regimen for long-term treatment. Furosemide is titrated to the lowest dose and longest interval that controls signs of congestion. RRR monitoring over time helps guide this (see p. 74). An ACEI is recommended for chronic therapy if another vasodilator was used initially. The ACEI can be dosed once daily to start as the patient is weaned off the other (arteriolar) vasodilator over a couple days. The ACEI can be increased to q12h dosing over the next several days to a week. Client education about the purpose and potential adverse effects of prescribed medications, RRR monitoring, diet, activity restrictions, follow-up schedule, and other recommendations is important.

MONITORING HEART FAILURE THERAPY

Continued monitoring is important, especially for renal function, serum electrolyte concentrations, BP, and recurrent congestive signs. Intermittent arrhythmias can trigger decompensated congestive failure, as well as episodes of transient weakness or syncope. Cough-induced syncope, atrial rupture, or other causes of reduced cardiac output also can occur. Despite periodic recurrence of CHF signs, with proper management many dogs with CMVD enjoy a good quality of life for several months to years after signs of failure first appear. Dogs with recently diagnosed or decompensated CHF should be rechecked more frequently (every few days to every week or so) until their condition is stable; those with chronic heart failure that is well controlled can be reevaluated less often but usually at least three to four times per year.

COMMON COMPLICATIONS

END-STAGE/REFRACTORY (STAGE D) HEART FAILURE

Recurrent acute CHF should be treated in-hospital as described previously (see Box 3.1, p. 62). Pleural and abdominal effusions are drained as needed to maintain patient

comfort. Other strategies for intensifying home therapy are discussed in Chapter 3, p. 74.

PULMONARY HYPERTENSION

The development and severity of PH associated with high pulmonary venous pressure (so-called *postcapillary PH*) increases with advancing CMVD severity. It is most common in dogs with stage C disease. Usually, PH associated with CMVD is of mild to moderate severity, although a minority of dogs with CMVD has severe PH. Although PH seen with CMVD usually is related to chronic pulmonary venous hypertension, increased precapillary vascular resistance from hypoxia-induced pulmonary arteriolar vasoconstriction can occur with pulmonary edema or concurrent pulmonary disease. Reactive pulmonary vascular remodeling can contribute to PH, especially in dogs with severe disease. Moderate and severe PH increases right heart strain, promotes RV dilation (and hypertrophy), and contributes to tricuspid annulus dilation and worsening TR. Dogs with CVMD and moderate to severe PH are likely to have worse outcomes.

Dogs with mild to moderate PH can be asymptomatic or have some degree of exercise intolerance or other clinical signs consistent with CMVD. Especially with severe PH, clinical signs can include cough, respiratory difficulty, R-CHF signs (ascites, pleural effusion), lethargy, weakness, syncope, prerenal azotemia, and cyanosis. Concurrent arrhythmias can exacerbate these signs. On auscultation, the animal's systolic murmur might be louder over the tricuspid region, with or without a loud or split S_2 sound. Pulmonary crackles can relate either to pulmonary edema or concurrent chronic lung disease in these dogs. The diagnosis of PH is generally made by echocardiography, although radiographs can be suggestive (see Chapters 2 and 10, pp. 30 and 191).

Management of CVMD with PH first centers on standard CHF therapy to reduce pulmonary venous pressure by controlling pulmonary edema and improving forward cardiac output. Pimobendan, besides supporting myocardial function and systemic vasodilation, also has some pulmonary vasodilating effect via phosphodiesterase (PDE)-3 inhibition. Additional therapy with a PDE-5 inhibitor (such as sildenafil) generally is reserved for dogs with PH that have persistent signs of R-CHF or syncope. Sildenafil (1-3 mg/kg q8h) usually is started at a lower dose q(8-)12h then titrated upward over several days to a week based on clinical response. Concurrent administration of an L-arginine supplement (100 mg/kg q8h PO) is thought to enhance sildenafil's efficacy, because this amino acid is a substrate for nitric oxide production. Doppler (TR maximum velocity) and other echo observations can help assess the effect of sildenafil treatment, although a decrease in TR Vmax or smaller RV is not always documented despite clinical improvement. Systemic BP should be monitored, especially in patients receiving another vasodilator along with an ACEI, even though sildenafil primarily affects the pulmonary vasculature. Occasionally, dogs with severe PH and advanced CMVD can develop worsened pulmonary edema after initial sildenafil treatment, especially at higher doses; rapid reduction in pulmonary vascular resistance with an increase in pulmonary blood flow is thought to be the cause in these cases. Therefore close monitoring for increasing RRR, cough, and other respiratory signs is warranted when beginning sildenafil therapy. An increase in dose and/or frequency of pimobendan administration is another strategy that could enhance pulmonary vasodilation.

ARRHYTHMIAS

The onset or worsening of paroxysmal or sustained tachyarrhythmias can precipitate weakness, syncope, and congestive signs in a previously stable patient. The arrhythmia may be evident on physical examination and further identified on resting ECG; however, ambulatory ECG monitoring may be needed for definitive diagnosis and to guide antiarrhythmic therapy. Conversely, an intermittent bradyarrhythmia may underlie episodic weakness in syncope in some dogs. See Chapter 4 for management.

RUPTURED CHORDAE TENDINEAE

Affected animals tend to be older, male small-breed dogs, although chordal rupture also occurs in females. Rupture of a primary (marginal) chorda tendineae often provokes acute pulmonary edema, and prognosis can be poor in such cases. Rupture of a minor (second- or third-order) chorda sometimes is an incidental finding on echocardiogram or at necropsy. Factors that influence the clinical outcome include the size and location of the ruptured chord, the degree of valve regurgitation, LA compliance, and LV function.

LA RUPTURE

Older, male Miniature Poodles, Cocker Spaniels, Cavalier King Charles Spaniels (CKCS), Dachshunds, and Shetland Sheepdogs are thought to have higher prevalence of LA tearing, but mixed breed and other dogs also are affected. Full-thickness tearing of the LA wall is an uncommon but devastating complication of CMVD. Acute intrapericardial bleeding generally causes rapid onset of cardiac tamponade (see Chapter 9) and often is fatal. Acute weakness or collapse is typical; other signs could include cough, dyspnea, and respiratory or cardiac arrest. Most of these dogs have advanced CMVD, with severe LA enlargement, atrial jet lesions, and often ruptured first-order chordae tendineae. Pericardial effusion, usually with tamponade, is seen on echocardiography in almost all cases. There may be clots in the fluid. Echocardiography also may show an intraluminal thrombus attached to the LA wall, with either a partial or full thickness tear. In rare cases, an LA tear occurs in the interatrial septum rather than the lateral LA wall.

In dogs with tamponade, a cautious attempt at pericardiocentesis might relieve the tamponade, although the decrease in intrapericardial pressure could trigger further bleeding, especially if a clot seal is disturbed. Prognosis generally is poor in these cases, even with aggressive supportive care and immediate surgical attempt to close the rupture. However, if

the intrapericardial bleed is modest and the dog appears relatively stable, conservative management might be successful. This involves cage rest, BP support, continued CHF therapy, and removal of a small volume of pericardial fluid only if required for signs of tamponade. Over time, the rupture could seal and pericardial blood would be reabsorbed. For dogs with echo evidence of an intraluminal thrombus in the LA, there is presumably increased risk for arterial thromboembolism (ATE). However, it is unclear whether the benefit of antiplatelet therapy to reduce ATE potentially outweighs the risk of worsening intrapericardial bleeding, if a full thickness tear is present or develops. Dogs that survive are prone to another LA tear.

CHRONIC AIRWAY DISEASE

Chronic bronchitis and collapsing trachea are common in older small breed dogs. Associated signs are sometimes difficult to differentiate from CHF signs. At home, RRR monitoring, changes in exercise tolerance and activity level, and thoracic radiographs are helpful in this regard. For dogs with a new or worsening cough, especially a dry honking cough, that maintain normal RRR at home, empiric therapy (e.g., antibiotic trial, bronchodilator, and finally antiinflammatory doses of glucocorticoid) or further diagnostic testing can be offered (e.g., radiographs with airway fluoroscopy, tracheal wash or bronchoscopy with bronchoalveolar lavage, and culture of airway secretions). For persistent dry cough in the absence of pulmonary edema, a cough suppressant (e.g., hydrocodone or butorphanol) can be helpful. This may only be needed intermittently when the dog is having a "bad day" of coughing. It is important that the owner continue to monitor RRR and be alert to possible episodes of recurrent pulmonary edema.

ABNORMAL BLOOD PRESSURE

Systemic hypertension, although not caused by CMVD, can complicate its treatment. Because hypertension can exacerbate MR and cardiac workload, BP should be checked at each visit. If elevated, and if ACEI dose is already maximized, an arteriolar vasodilator (e.g., amlodipine) is added. Care should be taken to verify that the high BP readings are not just related to excitement.

Conversely, hypotension can occur with excessive dosing of an arteriolar vasodilator, dehydration, persistent arrhythmias, and/or poor contractility. Although uncommon, LA rupture with cardiac tamponade causes acute and profound hypotension

RENAL DYSFUNCTION

Impaired renal function is common in older dogs with CMVD; it can be difficult to manage when there are increasing congestive signs. The lowest effective doses of furosemide are used. Optimizing forward cardiac output also helps preserve renal perfusion. BP should be monitored, and high levels managed as possible. An arteriolar vasodilator (e.g., amlodipine) added to standard therapy can help improve forward cardiac output and renal perfusion as long as hypotension is avoided. If spironolactone or another diuretic is also being used, it should be reduced or discontinued, depending on the level and progression of azotemia. Likewise, some cases can tolerate a slight decrease in furosemide dose without precipitating pulmonary edema; however, close monitoring (RRR and other signs) is required. Alternatively, the dose or frequency of ACEI could be decreased. Increasing pimobendan to q8h dosing also might help by improving renal perfusion. It is important to verify that the patient does not have a treatable underlying disease that may be affecting renal function, such as ascending urinary tract infection. Mild azotemia can be acceptable as long as the patient feels good and is eating well. Electrolytes should be monitored. If the azotemic patient is receiving digoxin, serum concentrations should be monitored more often to avoid toxicity. The digoxin dose may need to be reduced or discontinued.

Prognosis

The prognosis for dogs with CMVD can be quite variable. Most dogs remain in a preclinical stage for years, and some never develop CHF. The median survival time for dogs with more advanced (stage B2) disease could be slightly more than 2 years. Although some suggest that median survival times in dogs with moderate CHF might range from about 1 to 3 years, the therapy used, complications that develop, or even breed may influence this. However, for dogs with advanced CHF, survival times between 6 to 9 months are probably more likely. Yet some dogs with advanced stage C disease do well for many months, or even a couple of years, with appropriate therapy. Despite periodic episodes of CHF decompensation or other complications, quality of life can be good most of the time. Nevertheless, some dogs die or are euthanized during the first onset of CHF. Estimates of cardiac death from CMVD have ranged from around 40% to almost 70% of cases. Nevertheless, management strategies for CHF are becoming more effective in controlling clinical signs and increasing survival time. Factors that have been associated with disease progression or worse prognosis include older age, male gender, more severe valve lesions and degree of valve leaflet prolapse or MR, ruptured chordae, severe LA and LV enlargement, reduced LV systolic function, and elevated natriuretic peptide levels.

Risk factors for first onset CHF are mainly related to increased heart size and associated high circulating NT-proBNP concentration. One study identified NT-proBNP concentrations ≥1500 pmol/L, end-diastolic LV dimension indexed to aortic root diameter (LVIDd:Ao) ≥3, and VHS >12 v as independent risk factors for first onset CHF in stage B dogs with CMVD, with failure likely to occur within the subsequent 3 to 6 months. The rate at which heart size increases has been observed to accelerate within the 6 to 12 months before clinical CHF onset.

Prognostic indicators of reduced survival after CHF onset also relate to left heart enlargement, and high circulating NT-proBNP and cardiac troponin I concentrations, although a decrease in circulating NT-proBNP concentration after CHF therapy is thought to be a positive sign. LA

enlargement may be the strongest echocardiographic predictor of reduced survival. However, evidence for reduced LV contractility or moderate to severe PH also suggests worse prognosis.

INFECTIVE ENDOCARDITIS

Infection of the cardiac valves and other endocardial tissue is relatively uncommon; however, it causes severe systemic as well as cardiac consequences. Infective endocarditis occurs more often in dogs than in cats. It can be difficult to diagnose, especially before severe valve damage has occurred. CHF is a common sequela; however, other consequences include thromboembolic (TE) events, multiorgan infection and abscessation, immune-mediated polyarthritis and glomerulonephritis, arrhythmias, and sometimes sudden death. Because of the widely disparate manifestations, endocarditis has been called the "great imitator."

Etiology and Pathophysiology

Multiple factors play a role in the development of infective endocarditis, including endothelial damage, disturbed blood flow, hemostatic and immune responses, bacteremia, and bacterial virulence. Bacteremia, either persistent or transient, is necessary for endocardial infection to occur. The likelihood of a cardiac infection becoming established is increased when organisms are highly virulent or the bacterial load is heavy. Recurrent bacteremia may occur with infections of the skin, mouth, urinary tract, prostate, lungs, or other organs. Dentistry procedures are known to cause a transient bacteremia, although rarely is endocarditis a consequence. Other procedures presumed to cause transient bacteremia in some cases include endoscopy, urethral catheterization, anal surgery, and other so-called "dirty" procedures. Sometimes the predisposing cause of infective endocarditis is never identified.

The aortic and mitral valves are affected most often. The endocardial surface of the valve is infected directly from the blood flowing past it. Endothelial damage, with platelet and fibrin aggregation, probably serves as a nidus for circulating bacterial colonization in most cases. Highly virulent organisms or a heavy bacterial load increase the risk of cardiac infection. Virulent bacteria can invade normal valves, but previously damaged valves are at greater risk, especially with persistent bacteremia. Such damage may result from mechanical trauma (such as jet lesions from turbulent blood flow or catheter-induced endocardial injury). For example, dogs with subaortic stenosis are at greater risk for aortic valve endocarditis because the high velocity systolic jet can damage the endothelium on the underside of the aortic valve. However, there is no clear evidence linking CMVD with a higher risk for infective endocarditis of the mitral valve.

The most common organisms identified in dogs with endocarditis have been *Staphylococcus* spp., *Streptococcus* spp., and *Escherichia coli.* Various *Bartonella* species, especially *B. vinsonii* subsp. *berkhoffii* and *B. henselae,* have been increasingly identified in dogs as well as cats with endocarditis. *Bartonella* is an important cause of culture-negative endocarditis in some geographic areas, where it could be responsible for 20% to 30% of cases. Dogs infected with *Bartonella* may harbor more than one species and also may be coinfected with *Ehrlichia, Babesia,* and/or *Rickettsia* spp. Yet in dogs with endocarditis from other more common bacteria, coinfection with *Bartonella* appears to be rare. Besides endocarditis, other consequences of *Bartonella* infection include myocarditis, polyarthritis, meningoencephalitis, and granulomatous inflammation in lymph nodes and other tissues. Endocarditis-causing *Bartonella* spp. appear to preferentially affect the aortic valve, although the mitral valve occasionally is involved. *Bartonella* infection appears less likely to cause fever and is often associated with worse survival. Other organisms less frequently isolated from infected valves in dogs include *Corynebacterium (Arcanobacterium)* spp., *Pasteurella* spp., *Pseudomonas aeruginosa, Erysipelothrix rhusiopathiae (E. tonsillaris),* and others, including anaerobic *Propionibacterium* and *Fusobacterium* spp. Rarely, fungal organisms (usually associated with a foreign body) are involved. There are only rare reports of endocarditis in cats; in addition to *Bartonella* spp., *Streptococcus* spp., *Staphylococcus* spp., *E. coli*, *Pseudomonas*, and anaerobic bacteria have been identified in this species.

Endothelial disruption stimulates platelet activation and a local coagulation response, with resulting aggregate of fibrin, platelets, red blood cells, and leukocytes. Circulating bacteria adhere to and colonize this initially sterile clot. Bacterial clumping caused by the action of an agglutinating antibody can facilitate attachment to the valves; some colonizing bacteria secrete enzymes that damage valve tissue. Ulceration of the valve endothelium and subendothelial collagen exposure stimulate platelet aggregation and coagulation cascade activation, leading to the formation of vegetative lesions. These vegetations consist mainly of aggregated platelets, fibrin, blood cells, and bacteria. Newer vegetations are friable, but with time the lesions become fibrous and may calcify. As additional fibrin is deposited over bacterial colonies, they become protected from normal host defenses and many antibiotics. Some organisms, including *S. aureus* and *Bartonella* spp., are internalized by endothelial cells, conferring more protection from the immune system. Although vegetations usually involve the valve leaflets, lesions may extend to the chordae tendineae, sinuses of Valsalva, mural endocardium, or adjacent myocardium. Vegetations cause valve deformity, including perforations or tearing of the leaflet(s), and result in valve insufficiency. Rarely, large vegetations may cause the valve to become stenotic. *Streptococcus* spp. appears to more commonly affect the mitral valve. *Bartonella* spp. infects the aortic valve most often, causing somewhat different lesions of fibrosis, mineralization, endothelial proliferation, and neovascularization.

Endothelial damage and mechanical valve trauma also can cause nonbacterial thrombotic endocarditis. This is a sterile accumulation of platelets and fibrin on the valve

surface. Nonseptic (so-called "bland") emboli can break off from such vegetations and cause infarctions elsewhere. Subsequent bacteremia can cause a secondary infective endocarditis too.

Valve damage generally causes progressively worsening valve regurgitation with secondary volume overload. Signs of CHF can develop acutely or gradually, depending on the extent and progression of valve damage, and whether both mitral and aortic valves or other predisposing factors are involved. LV diastolic and LA pressures can rise relatively quickly, leading to rapid onset of pulmonary edema. Aortic endocarditis, especially, is likely to cause acute CHF and fulminant pulmonary edema. Left heart dilation can be minimal when disease progression is rapid or multiple valves are involved. In the few cases where vegetative lesions also cause valve stenosis, cardiac workload and risk of CHF are further increased.

Cardiac function can be compromised by myocardial injury resulting from coronary arterial embolization causing myocardial infarction and abscess formation, or from direct extension of the infection into the myocardium. Reduced contractility and atrial or ventricular tachyarrhythmias often result. Aortic valve endocarditis lesions may extend into the AV node and cause partial or complete AV block. Arrhythmias can cause weakness, syncope, and sudden death or contribute to the development of CHF.

Fragments of vegetative lesions often break loose. Embolization of other body sites can cause infarction or metastatic infection, which results in diverse clinical signs. Larger and more mobile vegetations (based on echocardiographic appearance) are associated with a higher incidence of embolic events in people and, presumably, also in animals. Emboli can be septic or bland (noninfective). Septic arthritis, diskospondylitis, urinary tract infections, and renal and splenic infarctions are common in affected animals. Local abscess formation resulting from septic thromboemboli contributes to recurrent bacteremia and fever. Hypertrophic osteopathy has also been associated with bacterial endocarditis. Circulating immune complexes and cell-mediated responses contribute to the disease syndrome. Sterile polyarthritis, glomerulonephritis, vasculitis, and other forms of immune-mediated organ damage are common.

Clinical Features

The prevalence of bacterial endocarditis is low in dogs (estimates range widely from 0.05% to over 6%) and even lower in cats. Most reports suggest larger (>15 kg) dogs are at greater risk, although middle-aged medium-breed dogs sometimes are affected. German Shepherd Dogs and possibly Boxers, Golden Retrievers, and Labrador Retrievers might be overrepresented. Male dogs are affected more commonly than females.

Either the aortic or the mitral valve is involved in virtually all cases; the prevalence of mitral endocarditis may be slightly greater than that of aortic endocarditis. Both valves are affected in some cases. Subaortic stenosis is a known risk factor for aortic valve endocarditis. Although some animals with endocarditis have evidence of past or concurrent infection, a clear history of predisposing factors often is absent. Possible relationship between severe periodontal disease and risk of endocarditis is unclear; small breeds of dog, which often are affected with severe periodontal disease and CMVD, have a low prevalence of endocarditis. Neutropenic and otherwise immunocompromised animals may be at greater risk for endocarditis.

The combination of fever, lameness, and a cardiac murmur (especially if new, altered in quality, or diastolic in timing) should strongly raise suspicion of infective endocarditis. Nevertheless, the clinical signs of endocarditis are variable and relate to the underlying infection, immune-mediated effects, TE events, and progressive valvular or myocardial dysfunction. The presenting signs can result from left-sided CHF or arrhythmias; however, cardiac signs often are overshadowed by signs of systemic infarction, infection, immune-mediated disease (including polyarthritis), or a combination of these. Nonspecific signs of lameness or stiffness (possibly shifting from one limb to another), lethargy, trembling, recurrent fever, weight loss, inappetence, vomiting, diarrhea, and weakness may be the predominant complaints. A majority of cases with bacterial endocarditis are febrile or have waxing/waning temperature spikes, although some are normothermic (especially those with *Bartonella* endocarditis). Palpable joint effusion may be present. A cardiac murmur is heard in most dogs with endocarditis, although an audible murmur can be absent if the endocarditis lesions have caused only minimal or no valve regurgitation. Murmur characteristics depend on the valve involved. Ventricular tachyarrhythmias are common, but supraventricular tachyarrhythmias or AV block (especially with aortic valve infection) also occur. Infective endocarditis often mimics immune-mediated disease. Dogs with endocarditis are commonly evaluated for a "fever of unknown origin." Some of the consequences of infectious endocarditis are outlined in Box 6.3.

Signs of CHF in an unexpected clinical setting or in an animal with a murmur of recent onset may herald infective valve damage, especially if other suggestive signs are present. However, a "new" murmur can be a manifestation of noninfective acquired disease (e.g., CMVD, cardiomyopathy), a previously undiagnosed congenital disease, or physiologic alterations (e.g., fever, anemia). Conversely, endocarditis may develop in an animal known to have a murmur caused by another cardiac disease. Although a change in murmur quality or intensity over a short time frame may indicate active valve damage, physiologic causes of murmur variation are common. The onset of a diastolic murmur at the left heart base is suspicious for aortic valve endocarditis, especially if fever or other signs are present.

Diagnosis

It can be difficult to establish a definitive antemortem diagnosis. Presumptive diagnosis of infective endocarditis is made based on two or more positive blood cultures (or positive *Bartonella* testing; see Chapter 94), in addition to either

BOX 6.3

Potential Sequelae of Infective Endocarditis

Heart

Valve insufficiency or stenosis
- Murmur
- Congestive heart failure

Coronary embolization (aortic valve*)
- Myocardial infarction
- Myocardial abscess
- Myocarditis
- Decreased contractility (segmental or global)
- Arrhythmias

Myocarditis (direct invasion by microorganisms)
- Arrhythmias
- AV conduction abnormalities (aortic valve*)
- Decreased contractility

Pericarditis (direct invasion by microorganisms)
- Pericardial effusion
- Cardiac tamponade (?)

Kidney

Infarction
- Reduced renal function

Abscess formation and pyelonephritis
- Reduced renal function
- Urinary tract infection
- Renal pain

Glomerulonephritis (immune mediated)
- Proteinuria
- Reduced renal function

Musculoskeletal

Septic arthritis
- Joint swelling and pain
- Lameness

Immune-mediated polyarthritis
- Shifting-leg lameness
- Joint swelling and pain

Septic osteomyelitis
- Bone pain
- Lameness

Myositis
- Muscle pain

Hypertrophic pulmonary osteopathy

Brain and Meninges

Abscesses
- Associated neurologic signs

Encephalitis and meningitis
- Associated neurologic signs

Vascular System in General

Vasculitis
- Thrombosis
- Petechiae and small hemorrhages (e.g., eye, skin)

Obstruction
- Ischemia of tissues served, with associated signs

Lung

Pulmonary emboli (tricuspid or pulmonic valves, rare*)
Pneumonia (tricuspid or pulmonic valves, rare*)

Nonspecific

Sepsis
Fever
Anorexia
Malaise and depression
Shaking
Vague pain
Inflammatory leukogram
Mild anemia
±Positive antinuclear antibody test
±Positive blood cultures

*Diseased valve most commonly associated with abnormality.

echocardiographic evidence of vegetations or valve destruction. Endocarditis is likely even when blood culture results are negative or intermittently positive if there is echocardiographic evidence of vegetations or valve destruction along with a combination of other criteria (Box 6.4).

Clinical laboratory findings in all species usually reflect the presence of inflammation. Neutrophilia with toxic neutrophils or a left shift is typical of acute endocarditis; mature neutrophilia with or without monocytosis develops with time. Variable thrombocytopenia (mild to marked) occurs in more than half of affected dogs, as does mild nonregenerative anemia. In dogs diagnosed with bartonellosis, thrombocytopenia, eosinophilia, and monocytosis have been reported. Evidence for disseminated intravascular coagulation may be present in association with endocarditis. Common biochemical findings in dogs include hypoalbuminemia, elevated liver enzymes, azotemia, acidosis, and hyperglobulinemia. Urinalysis often shows hematuria, proteinuria, and pyuria. Because the kidneys are a possible source of primary and secondary bacterial infection, culturing the urine is also recommended. Urine protein/creatinine ratio is useful in cases with proteinuria; a high ratio can signal increased risk of TE from hypercoagulability related to urinary loss of plasma antithrombin. Rheumatoid factor and antinuclear antibody tests may be positive in dogs with subacute or chronic bacterial endocarditis.

Blood cultures should be done, although they are negative in about 40% to 70% of cases. Negative culture results do not rule out infective endocarditis, especially with chronic endocarditis, recent antibiotic therapy, intermittent bacteremia, or infection by fastidious or slow growing organisms. Ideally,

BOX 6.4

Criteria for Diagnosis of Infective Endocarditis*

Definite Endocarditis by Pathologic Criteria

Pathologic (postmortem) lesions of active endocarditis with evidence of microorganisms in vegetation (or embolus) or intracardiac abscess

Definite Endocarditis by Clinical Criteria

Two major criteria (below), or
One major and two to three minor criteria, or
Five minor criteria

Possible Endocarditis

Findings consistent with infectious endocarditis that fall short of "definite" but not "rejected"

Rejected Diagnosis of Endocarditis

Firm alternative diagnosis for clinical manifestations
Resolution of manifestations of infective endocarditis with 4 or fewer days of antibiotic therapy
No pathologic evidence of infective endocarditis at surgery or necropsy

Major Criteria

Positive blood cultures
- Typical microorganism for infective endocarditis from two separate blood cultures
- Persistently positive blood cultures for organism consistent with endocarditis (samples drawn >12 hours apart, or three or more cultures drawn ≥1 hour apart)

Evidence of endocardial involvement
- Positive echocardiogram for infective endocarditis (oscillating mass on heart valve or supportive structure or in path of regurgitant jet, or evidence of cardiac abscess)
- New valvular regurgitation, especially if more than mild aortic regurgitation; increase or change in preexisting murmur is not sufficient evidence

Minor Criteria

Subaortic stenosis or other predisposing cardiac condition (see p. 132)
Fever
Thromboembolic disease, including major arterial emboli, septic infarcts
Immune-mediated disease, including glomerulonephritis, polyarthritis, or positive antinuclear antibody or rheumatoid factor tests
Echocardiogram consistent with infective endocarditis, but not meeting major criteria above
High seroreactivity (e.g., titer ≥1 : 1024) or positive PCR test for *Bartonella* spp.†
Medium to large dog (>15 kg)†
Positive blood culture not meeting major criterion, as previously mentioned
(Rare in dogs and cats: repeated nonsterile IV drug administration)

*Adapted from modified Duke criteria for endocarditis.
†Proposed minor criterion for endocarditis in dogs.

three to four blood samples of at least 10 mL are collected aseptically over 24 hours for bacterial culture, with more than an hour elapsing between collections. Sampling during a fever spike or, if antibiotic therapy has already been given, at the time of drug trough concentration may increase diagnostic yield. A shorter sampling period of 3 to 4 hours could be used for critical patients before beginning empiric antibiotic therapy. Different venipuncture sites should be used for each sample. Blood collection from an indwelling IV catheter is not recommended. Both aerobic and anaerobic cultures have been recommended, although the value of routine anaerobic culture is questionable. Prolonged incubation (3-4 weeks) is recommended, because some bacteria are slow growing.

Bartonella spp are an important cause of culture-negative endocarditis in some regions. These organisms are especially difficult to identify on blood cultures. Use of specialized culture conditions and an enriched insect cell culture medium (Bartonella α Proteobacteria growth medium; BAPGM) or heart infusion agar may increase the likelihood of growing these organisms. Blood can be aseptically collected in plastic ethylene diamine tetraacetic acid (EDTA) tubes then frozen at -70° C until plated. Molecular testing using polymerase chain reaction (PCR) amplification of specific *Bartonella* gene segments is an important diagnostic tool. However, PCR amplification directly from blood or other body fluid samples often does not identify *Bartonella* DNA because of low circulating bacterial levels or intermittent bacteremia, and bacterial sequestration within endothelial cells and vegetative lesions. Positive results are more likely in immunosuppressed patients. A combined technique using preenrichment culture of aseptically collected blood (or body fluid or surgical tissue samples) in BAPGM followed by a high-sensitivity PCR assay can increase diagnostic yield and is commercially available (Galaxy Diagnostics Inc.; www.galaxydx.com). Aseptic handling of samples is important to avoid contamination. Serologic testing (including immunofluorescent antibody [IFA] or enzyme-linked immunosorbent assay [ELISA] tests) also can help, although *Bartonella* infection can cause variable seroreactivity. Some cases develop high titers to *Bartonella* spp., but others (~half of dogs) are not seroreactive. The particular *Bartonella*

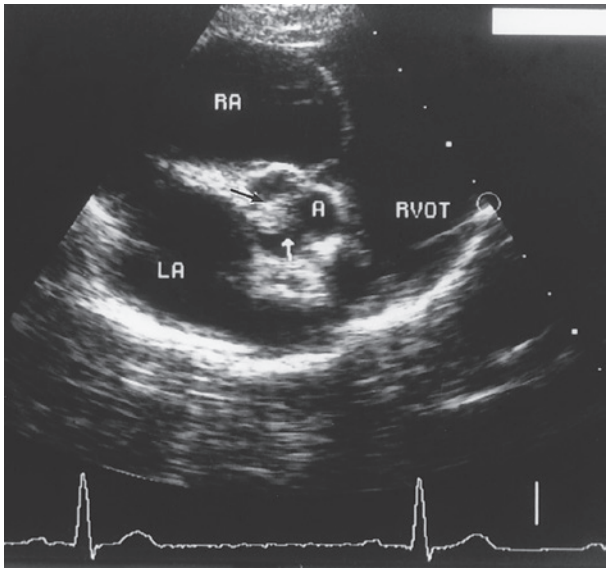


FIG 6.5
Right parasternal short-axis echocardiographic image at the aortic valve-left atrial level in a 2-year-old male Vizsla with congenital subaortic stenosis and pulmonic stenosis. Note the aortic valve vegetation *(arrows)* caused by infective endocarditis. *A,* Aorta; *LA,* left atrium; *RA,* right atrium; *RVOT,* right ventricular outflow tract.

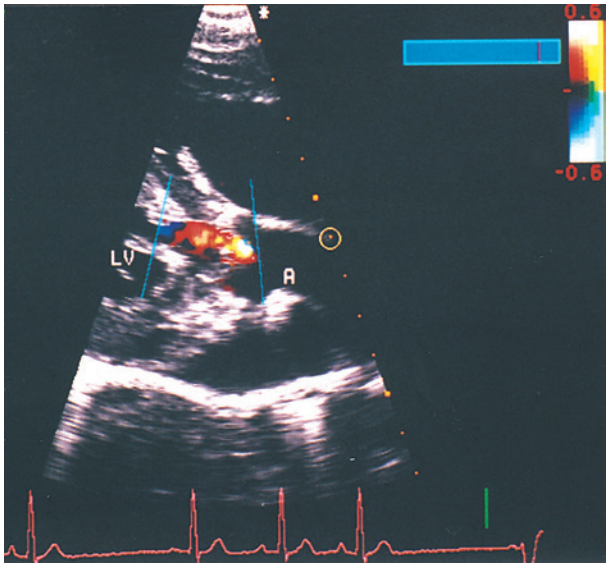


FIG 6.6
Right parasternal long axis, color flow Doppler image taken during diastole from the same dog as in Fig. 6.5. The "flame-like" jet of aortic regurgitation extends from the closed aortic valve into the left ventricular outflow tract. *A,* Aorta; *LV,* left ventricle.

species involved may influence seroreactivity. Seroreactivity (e.g., titer ≥1 : 64) to *B. vinsonii* subsp. *berkhoffii* in a dog with clinical signs of disease is evidence for exposure and likely an active *Bartonella* infection. However, follow-up culture or PCR documentation of infection is recommended. Dogs with a positive *Bartonella* antibody titer may also be positive for other tick-borne diseases such as *Anaplasma phagocytophilum*, *Ehrlichia canis*, or *Rickettsia rickettsi*, so screening for other tick-borne disease is advised.

Radiographic findings might be normal when valve damage is minimal. In cases with acute, severe valve regurgitation leading to CHF, pulmonary venous congestion and edema can occur with minimal or no cardiac chamber enlargement. Other cases have evidence of cardiomegaly, with or without pulmonary edema, or other organ involvement (such as diskospondylitis). Hypertrophic pulmonary osteopathy of the long bones, along with pulmonary infiltrates, has occurred rarely in dogs with endocarditis.

Echocardiography is especially supportive if oscillating vegetative lesions and abnormal valve motion can be identified (Fig. 6.5). The visualization of lesions depends on their size, location, and image resolution quality. Because false-negative and false-positive "lesions" may be found, cautious interpretation of images is important. Mild valve thickening and/or enhanced echogenicity can occur with early valve damage. Degenerative mitral valve disease can look similar in some cases, especially those with markedly thickened and knobby mitral leaflets; however, CMVD causes smooth valve thickening and also is more likely to occur in small-breed dogs. Nevertheless, differentiation of mitral vegetations from degenerative thickening can be impossible, especially in the early stages. Vegetative lesions appear as irregular dense masses that can be rough or shaggy, or have long flailing tendrils. Increased echogenicity of more chronic lesions can result from dystrophic calcification. As valve destruction progresses, ruptured chordae, flail leaflet tips, and other abnormal valve motion can be seen. Aortic regurgitation can cause fluttering of the anterior mitral valve leaflet during diastole as the regurgitant jet makes contact with this leaflet. Secondary effects of valve dysfunction include chamber enlargement from volume overload, as well as progressive myocardial dysfunction and arrhythmias. Spontaneous contrast within the left heart chambers is observed occasionally, probably related to hyperfibrogenemia and increased erythrocyte sedimentation. Doppler studies illustrate the flow disturbances (Fig. 6.6). The ECG can be normal or show premature ectopic complexes or tachycardia, conduction disturbances, or evidence of myocardial ischemia.

Treatment and Prognosis

Aggressive therapy with bactericidal antibiotics capable of penetrating fibrin and supportive care are indicated for infective endocarditis. Ideally, drug choice is guided by culture and in vitro susceptibility test results. However, to avoid treatment delay, broad-spectrum combination therapy usually is begun immediately after obtaining blood and urine culture samples (and blood for potential *Bartonella* testing). Therapy can be altered, if necessary, based on culture results. Culture-negative cases should be continued on the broad-spectrum regimen. Testing for *Bartonella* is advised in dogs

and cats with culture-negative endocarditis. Initial, empiric broad-spectrum combination therapy for infective endocarditis usually includes a β-lactam antibiotic such as a synthetic penicillin derivative (e.g., ampicillin [22-40 mg/kg IV q6-8h], or ticarcillin/clavulanate [50 mg/kg IV q6h]) or a cephalosporin (e.g., cefazolin [22-33 mg/kg IV q8h], or ceftriaxone [20 mg/kg IV q12h]), with either an aminoglycoside (amikacin [7-10 mg/kg IV q12h; or 20 mg/kg q24h], with fluid support) or a fluoroquinolone (enrofloxacin [5-10 mg/kg IV q12h]). The former provides a gram-positive spectrum and the latter, gram-negative. Clindamycin or metronidazole provides added anaerobic coverage. Antibiotics are best administered via IV for the first week or two to obtain higher and more predictable blood concentrations. Oral therapy can be used thereafter for the sake of practicality, assuming clinical and laboratory abnormalities are improved. Empirical options for continued oral therapy include either amoxicillin/clavulanate (20-25 mg/kg PO q8h) or cephalexin (25-30 mg/kg PO q8h), in combination with enrofloxacin (2.5-5 mg/kg PO q12h). For multiple-drug resistant bacteria requiring therapy with imipenem, SC administration following an initial 1- to 2-week course of IV administration has been recommended. In general, antimicrobial therapy is continued for at least 6 weeks, although therapy for 8 weeks is often recommended. However, aminoglycosides are discontinued after 7 to 10 days or sooner if renal toxicity develops. Close monitoring of the urine sediment is indicated to detect early aminoglycoside nephrotoxicity. Fluid therapy is given concurrently because of the concern for aminoglycoside nephrotoxicity. Furosemide should not be given during aminoglycoside treatment because it can exacerbate nephrotoxicity. Therefore aminoglycoside use is generally contraindicated in patients with CHF or underlying renal disease.

It is important to seek confirmation of suspected *Bartonella* endocarditis infection (see p. 135, discussed earlier) because treatment may require extremely long-term antibiotic therapy (e.g., for up to 3 months), using at least two antimicrobial drugs with different modes of action, in an attempt to eliminate the organism. Nevertheless, the most effective strategy for eliminating *Bartonella* in dogs and cats currently remains unproven. In vitro testing and reported antibiotic minimal inhibitory concentration (MIC) do not reflect efficacy against *Bartonella* in the host animal. Bacterial persistence can lead to recurrent clinical infection, especially with immunosuppression or concurrent disease process. Although previous recommendations have included use of azithromycin, this drug is no longer recommended as first-line therapy for *Bartonella* because of the rapid development of resistance to it.

For dogs with *Bartonella* endocarditis (or myocarditis), initial therapy with amikacin (15-30 mg/kg q24h IV, IM, or SC) for 7 to 10 days, combined with doxycycline ([5-]10 mg/kg q12h PO) has been recommended. Renal function must be closely monitored when using an aminoglycoside; this agent should not be used in certain patients (see previous discussion). After amikacin is discontinued, an oral fluoroquinolone is added. Currently recommended oral therapy for *Bartonella* infection includes doxycycline (5-10 mg/kg q12h PO; or minocycline at 10 mg/kg q12h PO), combined with enrofloxacin (5-20 mg/kg q24h PO) or pradofloxacin (5-10 mg/kg q24[-12]h PO; not approved for dogs in the United States) for 28 to 42 days (at least). In clinically stable *Bartonella* patients where initial IV therapy is not used, the recommendation has been made to start oral treatment with one drug (e.g., doxycycline at 5 mg/kg q12h), followed in 5 to 7 days with the addition of the second drug. However, this may not be possible in patients with endocarditis or myocarditis because of illness severity. This recommendation is based on the observation that, when both antibiotics are begun simultaneously for *Bartonella* infection, a reaction can occur within 4 to 7 days (or longer) which may include lethargy, fever, and vomiting (Jarisch-Herxheimer–like reaction). It is thought that the reaction, which can last a few days, relates to acute bacterial injury or death and host cytokine release. Unless the patient's clinical status continues to deteriorate from this reaction, the PO antibiotic strategy should be continued as planned and supportive care given as appropriate. The addition of antiinflammatory doses of a glucocorticoid may be helpful for patients experiencing this reaction; however, the glucocorticoid should be discontinued after a few days as those signs abate.

For cats with cardiac *Bartonella* infection, initial therapy with amikacin (10-14 mg/kg q24h IV, IM, or SC) for 7 to 10 days, combined with doxycycline ([5-]10 mg/kg q12h PO) has been recommended. Aminoglycoside precautions for patient selection and renal function monitoring are as for dogs (see previous discussion). When the amikacin is discontinued, oral pradofloxacin (5-10 mg/kg q24[-12]h PO) can be added. Currently recommended oral therapy for *Bartonella* infection includes doxycycline (5-10 mg/kg q12h PO; or minocycline at 8.8 mg/kg q12h PO), combined with pradofloxacin (5-10 mg/kg q24[-12]h PO) for 28 to 42 days (at least). Because higher doses and longer treatment duration generally are needed for treating *Bartonella* infection, and because cats are at risk for retinotoxicity when enrofloxacin is used at doses >5 mg/kg/day, this agent is no longer recommended for *Bartonella* infections in cats. Jarisch-Herxheimer–like reactions (see previous discussion) also can occur in cats.

Supportive care includes management for CHF (see Chapter 3) and arrhythmias (see Chapter 4), if present. Complications related to the primary source of infection, embolic events, or immune responses are addressed to the extent possible. Attention to hydration status, nutritional support, and general nursing care is also important. BP and renal function should be monitored, along with other parameters as indicated for the individual patient. Hypertension should be vigorously controlled (see Chapter 11). Even when BP is normal, modest additional afterload reduction with an arteriolar vasodilator can help support cardiac function, especially with advancing aortic or mitral valve regurgitation. Corticosteroids generally are contraindicated. The

effectiveness of aspirin in reducing vegetative lesion growth and incidence of embolic events is questionable.

For animals with positive blood (or urine) cultures, repeated cultures 1 to 2 weeks after starting antibiotic therapy and also 1 to 2 weeks after completion of antibiotic therapy are recommended. Patients with a positive Bartonella antibody titer can be retested in 4 weeks after starting antibiotic therapy to verify that titers are decreasing. Persistently elevated titers suggest that antibiotic strategy should be changed. Animals testing positive for *Bartonella* via serologic and BAPGM enrichment blood culture techniques before beginning antibiotic therapy should have these tests repeated at 2 and 6 weeks after therapy has been discontinued to evaluate treatment efficacy. Other tests or monitoring may be indicated depending on the type and severity of concurrent disease and secondary complications in the individual patient. Recheck echocardiograms during (for example, at 2 and 8 weeks after starting therapy) and a few weeks following the treatment period are indicated to monitor changes in vegetation size, valve function, chamber dimensions, and LV function. Even if antibiotic therapy is successful in resolving the infection, progressive cardiac enlargement and myocardial dysfunction are common because of residual valve damage and insufficiency. So continued cardiac monitoring is recommended. Radiographs, complete blood count (CBC) and serum biochemistry tests, and other tests are repeated as indicated for the individual patient.

Prognosis

Long-term prognosis generally is guarded to poor. Some dogs die within days to weeks; others that survive the acute stages are likely to die later from progressive CHF. Echocardiographic evidence of vegetations (especially of the aortic valve) and volume overload suggests a poor prognosis. Other negative prognostic indicators include *Bartonella* or gram-negative infections, renal or cardiac complications that respond poorly to treatment, septic embolization, and thrombocytopenia. Glucocorticoid therapy and inadequate antibiotic therapy can contribute to a poor outcome. Aggressive therapy may be successful if valve dysfunction is not severe and large vegetations are absent. CHF is the most common cause of death, although sepsis, systemic embolization, arrhythmias, or renal failure may be the proximate cause.

Antibiotic Prophylaxis

The use of prophylactic antibiotics is controversial. Experience in people suggests that most cases of infective endocarditis are not preventable. The risk of endocarditis from a specific (e.g., dental) procedure in humans is low compared with the cumulative risk associated with normal daily activities. However, in view of the increased occurrence of endocarditis with certain cardiovascular malformations (especially SAS), antimicrobial prophylaxis usually is recommended for these animals before dental or other "dirty" procedures (those involving the oral cavity or intestinal or urogenital systems). Antimicrobial prophylaxis also is advised for animals with an implanted pacemaker or other device, or with a history of endocarditis; it should be considered in immunocompromised animals as well. Recommendations have included high-dose ampicillin, amoxicillin, or a cephalosporin 1 hour before and 6 hours after oral or upper respiratory procedures; clindamycin before dental procedures; ampicillin with an aminoglycoside (given IV) one half hour before and 8 hours after GI or urogenital procedures; and ticarcillin or a first-generation cephalosporin (IV) 1 hour before and 6 hours after a procedure.

Suggested Readings

Degenerative AV Valve Disease

Atkins C, et al. Guidelines for the diagnosis and treatment of canine chronic valvular heart disease (ACVIM Consensus Statement). *J Vet Intern Med*. 2009;23:1142–1150.

Atkins CE, Haggstrom J. Pharmacologic management of myxomatous mitral valve disease in dogs. *J Vet Cardiol*. 2012;14:165–184.

Atkins CE, et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency. *J Am Vet Med Assoc*. 2007;231:1061–1069.

Atkinson KJ, et al. Evaluation of pimobendan and N-terminal pro-brain natriuretic peptide in the treatment of pulmonary hypertension secondary to degenerative mitral valve disease in dogs. *J Vet Intern Med*. 2009;23:1190–1196.

Aupperle H, Disatian A. Pathology, protein expression and signalling in myxomatous mitral valve degeneration: comparison of dogs and humans. *J Vet Cardiol*. 2012;14:59–71.

Bernay F, et al. Efficacy of spironolactone on survival in dogs with naturally occurring mitral regurgitation caused by myxomatous mitral valve disease. *J Vet Intern Med*. 2010;24:331–341.

Birkegard AC, et al. Breeding restrictions decrease the prevalence of myxomatous mitral valve disease in Cavalier King Charles Spaniels over an 8- to 10-year period. *J Vet Intern Med*. 2016;30:63–68.

Borgarelli M, et al. Prevalence and prognostic importance of pulmonary hypertension in dogs with myxomatous mitral valve disease. *J Vet Intern Med*. 2015;29:569–574.

Borgarelli M, Buchanan JW. Historical review, epidemiology and natural history of degenerative mitral valve disease. *J Vet Cardiol*. 2012;14:93–101.

Borgarelli M, et al. Survival characteristics and prognostic variables of dogs with preclinical chronic degenerative mitral valve disease attributable to myxomatous valve disease. *J Vet Intern Med*. 2012;26:69–75.

Boswood A, et al. Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: the EPIC study—a randomized clinical trial. *J Vet Intern Med*. 2016;30:1765–1779.

Chetboul V, et al. Association of plasma N-terminal Pro-B-type natriuretic peptide concentration with mitral regurgitation severity and outcome in dogs with asymptomatic degenerative mitral valve disease. *J Vet Intern Med*. 2009;23:984–994.

Chetboul V, Tissier R. Echocardiographic assessment of canine degenerative mitral valve disease. *J Vet Cardiol*. 2012;14:127–148.

Diana A, et al. Radiographic features of cardiogenic pulmonary edema in dogs with mitral regurgitation: 61 cases (1998-2007). *J Am Vet Med Assoc*. 2009;235:1058–1063.

Dillon AR, et al. Left ventricular remodeling in preclinical experimental mitral regurgitation of dogs. *J Vet Cardiol*. 2012;14:73–92.
Eriksson AS, et al. Increased NT-proANP predicts risk of congestive heart failure in Cavalier King Charles Spaniels with mitral regurgitation caused by myxomatous valve disease. *J Vet Cardiol*. 2014;16:141–154.
Falk T, et al. Cardiac troponin-I concentration, myocardial arteriosclerosis, and fibrosis in dogs with congestive heart failure because of myxomatous mitral valve disease. *J Vet Intern Med*. 2013;27:500–506.
Ferasin L, et al. Risk factors for coughing in dogs with naturally acquired myxomatous mitral valve disease. *J Vet Intern Med*. 2013;27:286–292.
Fox PR. Pathology of myxomatous mitral valve disease in the dog. *J Vet Cardiol*. 2012;14:103–126.
Gordon SG, et al. Retrospective review of carvedilol administration in 38 dogs with preclinical chronic valvular heart disease. *J Vet Cardiol*. 2012;14:243–252.
Gouni V, et al. Quantification of mitral valve regurgitation in dogs with degenerative mitral valve disease by use of the proximal isovelocity surface area method. *J Am Vet Med Assoc*. 2007;231: 399–406.
Guglielmini C, et al. Use of the vertebral heart score in coughing dogs with chronic degenerative mitral valve disease. *J Vet Med Sci*. 2009;71:9–13.
Haggstrom J, et al. Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study. *J Vet Intern Med*. 2008;22:1124–1135.
Hezzell MJ, et al. The combined prognostic potential of serum high-sensitivity cardiac troponin I and N-terminal pro-B-type natriuretic peptide concentrations in dogs with degenerative mitral valve disease. *J Vet Intern Med*. 2012;26:302–311.
Hezzell MJ, et al. Selected echocardiographic variables change more rapidly in dogs that die from myxomatous mitral valve disease. *J Vet Cardiol*. 2012;14:269–279.
Kellihan HB, Stepien RL. Pulmonary hypertension in canine degenerative mitral valve disease. *J Vet Cardiol*. 2012;14:149–164.
Kim JH, Park HM. Usefulness of conventional and tissue Doppler echocardiography to predict congestive heart failure in dogs with myxomatous mitral valve disease. *J Vet Intern Med*. 2015;29: 132–140.
Lake-Bakaar GA, et al. Effect of pimobendan on the incidence of arrhythmias in small breed dogs with myxomatous mitral valve degeneration. *J Vet Cardiol*. 2015;17:120–128.
Lefebvre HP, et al. Safety of spironolactone in dogs with chronic heart failure because of degenerative valvular disease: a population-based, longitudinal study. *J Vet Intern Med*. 2013;27:1083–1091.
Ljungvall I, et al. Cardiac troponin I is associated with severity of myxomatous mitral valve disease, age, and C-reactive protein in dogs. *J Vet Intern Med*. 2010;24:153–159.
Lombard CW, Jons O, Bussadori CM. Clinical efficacy of pimobendan versus benazepril for the treatment of acquired atrioventricular valvular disease in dogs. *J Am Anim Hosp Assoc*. 2006;42:249–261.
López-Alvarez J, et al. Clinical severity score system in dogs with degenerative mitral valve disease. *J Vet Intern Med*. 2015;29: 575–581.
Lord PF, et al. Radiographic heart size and its rate of increase as tests for onset of congestive heart failure in Cavalier King Charles Spaniels with mitral valve regurgitation. *J Vet Intern Med*. 2011;25:1312–1319.
Moesgaard SG, et al. Flow-mediated vasodilation measurements in Cavalier King Charles Spaniels with increasing severity of myxomatous mitral valve disease. *J Vet Intern Med*. 2012;26:61–68.
Moonarmart W, et al. N-terminal pro B-type natriuretic peptide and left ventricular diameter independently predict mortality in dogs with mitral valve disease. *J Small Anim Pract*. 2010;51:84–96.
Muzzi RA, et al. Regurgitant jet area by Doppler color flow mapping: quantitative assessment of mitral regurgitation severity in dogs. *J Vet Cardiol*. 2003;5:33–38.
Ohad DG, et al. Sleeping and resting respiratory rates in dogs with subclinical heart disease. *J Am Vet Med Assoc*. 2013;243:839–843.
Oui H, et al. Measurements of the pulmonary vasculature on thoracic radiographs in healthy dogs compared to dogs with mitral regurgitation. *Vet Radiol Ultrasound*. 2015;56:251–256.
Oyama MA. Neurohormonal activation in canine degenerative mitral valve disease: implications on pathophysiology and treatment. *J Small Anim Pract*. 2009;50:3–11.
Polizopoulou ZS, et al. Serial analysis of serum cardiac troponin I changes and correlation with clinical findings in 46 dogs with mitral valve disease. *Vet Clin Pathol*. 2014;43:218–225.
Reineke EL, Burkett DE, Drobatz KJ. Left atrial rupture in dogs: 14 cases (1990-2005). *J Vet Emerg Crit Care*. 2008;18:158–164.
Reynolds CA, et al. Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: the PREDICT cohort study. *J Vet Cardiol*. 2012;14:193–202.
Sargent J, et al. Echocardiographic predictors of survival in dogs with myxomatous mitral valve disease. *J Vet Cardiol*. 2015;17: 1–12.
Schober KE, et al. Effects of treatment on respiratory rate, serum natriuretic peptide concentration, and Doppler echocardiographic indices of left ventricular filling pressure in dogs with congestive heart failure secondary to degenerative mitral valve disease and dilated cardiomyopathy. *J Am Vet Med Assoc*. 2011;239:468–479.
Schober KE, et al. Detection of congestive heart failure in dogs by Doppler echocardiography. *J Vet Intern Med*. 2010;24:1358–1368.
Serres F, et al. Chordae tendineae rupture in dogs with degenerative mitral valve disease: prevalence, survival, and prognostic factors (114 cases, 2001-2006). *J Vet Intern Med*. 2007;21:258–264.
Singh MK, et al. Bronchomalacia in dogs with myxomatous mitral valve degeneration. *J Vet Intern Med*. 2012;26:312–319.
Tarnow I, et al. Predictive value of natriuretic peptides in dogs with mitral valve disease. *Vet J*. 2009;180:195–201.
Uechi M. Mitral valve repair in dogs. *J Vet Cardiol*. 2012;14:185–192.

Infective Endocarditis

Breitschwerdt EB. Bartonellosis of the cat and dog. *Plumb's Therapeutics Brief*. 2015;18–23.
Breitschwerdt EB, et al. Bartonellosis: an emerging infectious disease of zoonotic importance to animals and human beings. *J Vet Emerg Crit Care*. 2010;20:8–30.
Calvert CA, Thomason JD. Cardiovascular infections. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 4th ed. St Louis: Elsevier; 2012:912–936.
Glickman LT, et al. Evaluation of the risk of endocarditis and other cardiovascular events on the basis of the severity of periodontal disease in dogs. *J Am Vet Med Assoc*. 2009;234:486–494.
MacDonald K. Infective endocarditis in dogs: diagnosis and therapy. *Vet Clin North Am Small Anim Pract*. 2010;40:665–684.
MacDonald KA. Infective endocarditis. In: Bonagura JD, Twedt DC, eds. *Kirk's current veterinary therapy XV*. St Louis: Elsevier; 2014:e291–e299.

Meurs KM, et al. Comparison of polymerase chain reaction with bacterial 16s primers to blood culture to identify bacteremia in dogs with suspected bacterial endocarditis. *J Vet Intern Med*. 2011;25:959–962.

Ohad DG, et al. Molecular detection of Bartonella henselae and Bartonella koehlerae from aortic valves of Boxer dogs with infective endocarditis. *Vet Microbiol*. 2010;141:182–185.

Peddle G, Sleeper MM. Canine bacterial endocarditis: a review. *J Am Anim Hosp Assoc*. 2007;43:258–263.

Peddle GD, et al. Association of periodontal disease, oral procedures, and other clinical findings with bacterial endocarditis in dogs. *J Am Vet Med Assoc*. 2009;234:100–107.

Pennisi MG, et al. Bartonella species infection in cats: ABCD guidelines on prevention and management. *J Feline Med Surg*. 2013;15:563–569.

Pesavento PA, et al. Pathology of *Bartonella* endocarditis in six dogs. *Vet Pathol*. 2005;42:370–373.

Semedo-Lemsaddek T, Tavares M, SaoBraz B. Enterococcal infective endocarditis following periodontal disease in dogs. *PLoS ONE*. 2016;11:e0146860.

Sykes JE, et al. Clinicopathologic findings and outcome in dogs with infective endocarditis: 71 cases (1992-2005). *J Am Vet Med Assoc*. 2006;228:1735–1747.

Sykes JE, et al. Evaluation of the relationship between causative organisms and clinical characteristics of infective endocarditis in dogs: 71 cases (1992-2005). *J Am Vet Med Assoc*. 2006;228:1723–1734.

CHAPTER 7

Myocardial Diseases of the Dog



Heart muscle disease that leads to contractile dysfunction and cardiac chamber enlargement is an important cause of heart failure in dogs. Idiopathic or primary dilated cardiomyopathy (DCM) is most common and mainly affects the larger breeds. Arrhythmogenic right ventricular cardiomyopathy (ARVC), previously known as Boxer cardiomyopathy, is an important myocardial disease in Boxers but uncommon in other breeds. Secondary and infective myocardial diseases (see p. 150) occur less often. Hypertrophic cardiomyopathy (HCM) is recognized infrequently in dogs (see p. 152).

DILATED CARDIOMYOPATHY

Etiology and Pathophysiology

DCM is a disease characterized by poor myocardial contractility, with or without arrhythmias. Although considered idiopathic, DCM as an entity probably represents the end stage of different pathologic processes or metabolic defects involving myocardial cells or the intercellular matrix rather than a single disease. A genetic basis is thought to exist for many cases of idiopathic DCM, especially in breeds with a high prevalence or a familial occurrence of the disease. Large and giant breeds are most commonly affected, including Doberman Pinschers, Great Danes, Saint Bernards, Scottish Deerhounds, Irish Wolfhounds, Labrador Retrievers, Newfoundlands, Afghan Hounds, and Dalmatians. Some smaller breeds such as Cocker Spaniels can also be affected. The disease is rarely seen in dogs that weigh less than 12 kg. Doberman Pinschers appear to have the highest prevalence of DCM with an autosomal dominant pattern of inheritance. A causative genetic mutation on chromosome 14 has been associated with DCM in Doberman Pinschers; the affected protein codes for a mitochondrial protein associated with regulation of cardiac glucose metabolism, and mutation is associated with poor systolic function. Testing for the mutation is commercially available (North Carolina State University Veterinary Cardiac Genetics Laboratory; https://cvm.ncsu.edu/genetics/); however, penetrance of this mutation is only approximately 67%, and some Dobermans with DCM are homozygous-negative for this mutation. Multiple other mutations associated with DCM likely exist in Dobermans and other breeds. In at least some Great Danes, DCM appears to be an X-linked recessive trait. DCM in Irish Wolfhounds appears to be familial, with an autosomal recessive inheritance with sex-specific alleles. The familial DCM affecting young Portuguese Water Dogs has an autosomal recessive inheritance pattern and is rapidly fatal in puppies that are homozygous for the mutation.

Various biochemical defects, nutritional deficiencies, toxins, immunologic mechanisms, and infectious agents may be involved in the pathogenesis of DCM in different cases. Impaired intracellular energy homeostasis and decreased myocardial adenosine triphosphate (ATP) concentrations have been found in myocardial biochemical studies of affected Doberman Pinschers. Abnormal gene expression related to cardiac ryanodine receptor regulation and intracardiac Ca^{++} release has been reported in Great Danes with DCM. Idiopathic DCM has also been associated with prior viral infections in people. However, on the basis of polymerase chain reaction (PCR) analysis of myocardial samples from a small number of dogs with DCM, viral agents do not seem to be commonly associated with DCM in this species.

Decreased ventricular contractility (systolic dysfunction) is the major functional defect in dogs with DCM. Progressive cardiac chamber dilation (eccentric hypertrophy and remodeling) develops as systolic pump function and cardiac output worsen, and compensatory mechanisms become activated. Poor cardiac output can cause weakness, syncope, and ultimately cardiogenic shock. Increased diastolic stiffness also contributes to the development of high end-diastolic pressures, venous congestion, and congestive heart failure (CHF). Cardiac enlargement and papillary muscle dysfunction often cause poor systolic apposition of mitral and tricuspid leaflets, leading to mild to moderate valve insufficiency.

As cardiac output decreases, sympathetic, hormonal, and renal compensatory mechanisms become activated. These mechanisms increase heart rate, peripheral vascular

resistance, and volume retention (see Chapter 3). Chronic neurohormonal activation is thought to contribute to progressive myocardial damage, as well as to CHF. Coronary perfusion can be compromised by poor forward blood flow and increased ventricular diastolic pressure; myocardial ischemia further impairs myocardial function and predisposes to development of arrhythmias. Signs of low-output heart failure and left-sided, right-sided, or biventricular CHF (see Chapter 3) are common in dogs with DCM.

Atrial fibrillation (AF) often develops in dogs with DCM, particularly giant-breed dogs and dogs with severe left atrial (LA) enlargement. Approximately 30% of Doberman Pinschers and more than 80% of giant breed dogs with DCM have concurrent AF. In Irish Wolfhounds, AF may precede echocardiographic changes. Atrial contraction contributes importantly to ventricular filling, especially at faster heart rates. The loss of the "atrial kick" associated with AF reduces cardiac output and can cause acute clinical decompensation. Persistent tachycardia associated with AF probably also accelerates disease progression. Ventricular tachyarrhythmias are common as well and can cause syncope and sudden death. In Doberman Pinschers, serial Holter recordings have documented the appearance of ventricular premature complexes (VPCs) months to more than a year before early echocardiographic abnormalities of DCM were identified. Once left ventricular (LV) function begins to deteriorate, the frequency of tachyarrhythmias increases. Excitement-induced bradyarrhythmias have also been associated with low-output signs in Doberman Pinschers.

Dilation of all cardiac chambers is typical in dogs with DCM, although LA and LV enlargement usually predominate. The ventricular wall thickness may appear decreased compared with the lumen size. Flattened, atrophic papillary muscles and endocardial thickening also occur. Concurrent degenerative changes of the AV valves are generally only mild to moderate, if present at all. Histopathologic findings include scattered areas of myocardial necrosis, degeneration, and fibrosis, especially in the left ventricle (LV). Narrowed (attenuated) myocardial cells with a wavy appearance may be a common finding. Inflammatory cell infiltrates, myocardial hypertrophy, and fatty infiltration (mainly in Doberman Pinschers and Boxers with ARVC) are inconsistent features.

Clinical Findings

The prevalence of DCM increases with age, although most dogs with CHF are 4 to 10 years old. Among Doberman Pinschers, prevalence of DCM approaches 50% in dogs greater than 8 years of age. Male Doberman Pinschers generally show signs at an earlier age than females and are more likely to experience CHF.

DCM appears to develop slowly, with a prolonged preclinical (occult) stage that may evolve over several years before clinical signs become evident. Further cardiac evaluation is indicated for dogs with a history of reduced exercise tolerance, weakness, or syncope or in those in which an arrhythmia, murmur, or gallop sound is detected on routine physical examination. Occult DCM is often recognized through use of screening echocardiography and Holter monitoring, more commonly performed in breeding or show dogs. Some giant-breed dogs with mild to moderate LV dysfunction are relatively asymptomatic, even in the presence of AF.

Clinical signs of DCM may seem to develop rapidly, especially in sedentary dogs in which early signs may not be noticed. Sudden death before CHF signs develop is relatively common. Presenting complaints include any or all of the following: weakness, lethargy, tachypnea or dyspnea, exercise intolerance, cough (sometimes described as "gagging"), anorexia, abdominal distention (ascites), and syncope. Loss of muscle mass (cardiac cachexia), accentuated along the dorsal midline, may be severe in advanced cases.

Physical examination findings vary with the degree of cardiac decompensation. Some dogs with occult disease have normal physical examination findings. Others have a soft murmur of mitral or tricuspid regurgitation or an arrhythmia. Dogs with advanced disease and poor cardiac output have increased sympathetic tone and peripheral vasoconstriction, with pale mucous membranes and slowed capillary refill time. The femoral arterial pulse and precordial impulse often are weak and rapid. Uncontrolled AF and frequent VPCs cause an irregular and usually rapid heart rhythm, with frequent pulse deficits and variable pulse strength (see Fig. 4.1). Signs of left- and/or right-sided CHF include tachypnea, increased breath sounds, pulmonary crackles, jugular venous distention or pulsations, pleural effusion or ascites, and/or hepatosplenomegaly. Heart sounds may be muffled because of pleural effusion or poor cardiac contractility. An audible third heart sound (S_3 gallop) is a classic finding, although it may be obscured by an irregular heart rhythm. Soft to moderate-intensity systolic murmurs of mitral and/or tricuspid regurgitation are common.

RADIOGRAPHY

Diagnosis

The stage of disease, chest conformation, and hydration status influence the radiographic findings. Dogs with early occult disease are likely to be radiographically normal. Generalized cardiomegaly (predominately left heart enlargement) is evident in those with advanced DCM (Fig. 7.1). In Doberman Pinschers and other deep-chested breeds, the heart might appear minimally enlarged, except for the left atrium (LA). In other dogs, generalized cardiomegaly can be severe and can mimic the globoid cardiac silhouette typical of large pericardial effusions. Distended pulmonary veins and pulmonary interstitial or alveolar opacities accompany left-sided CHF with pulmonary edema. The distribution of pulmonary edema infiltrates in DCM often is diffuse (see Fig. 7.1). Pleural effusion, caudal vena cava distention, hepatomegaly, and ascites usually accompany right-sided CHF. Biventricular CHF is common.

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) findings in dogs with DCM also are variable. Sinus rhythm usually is the underlying

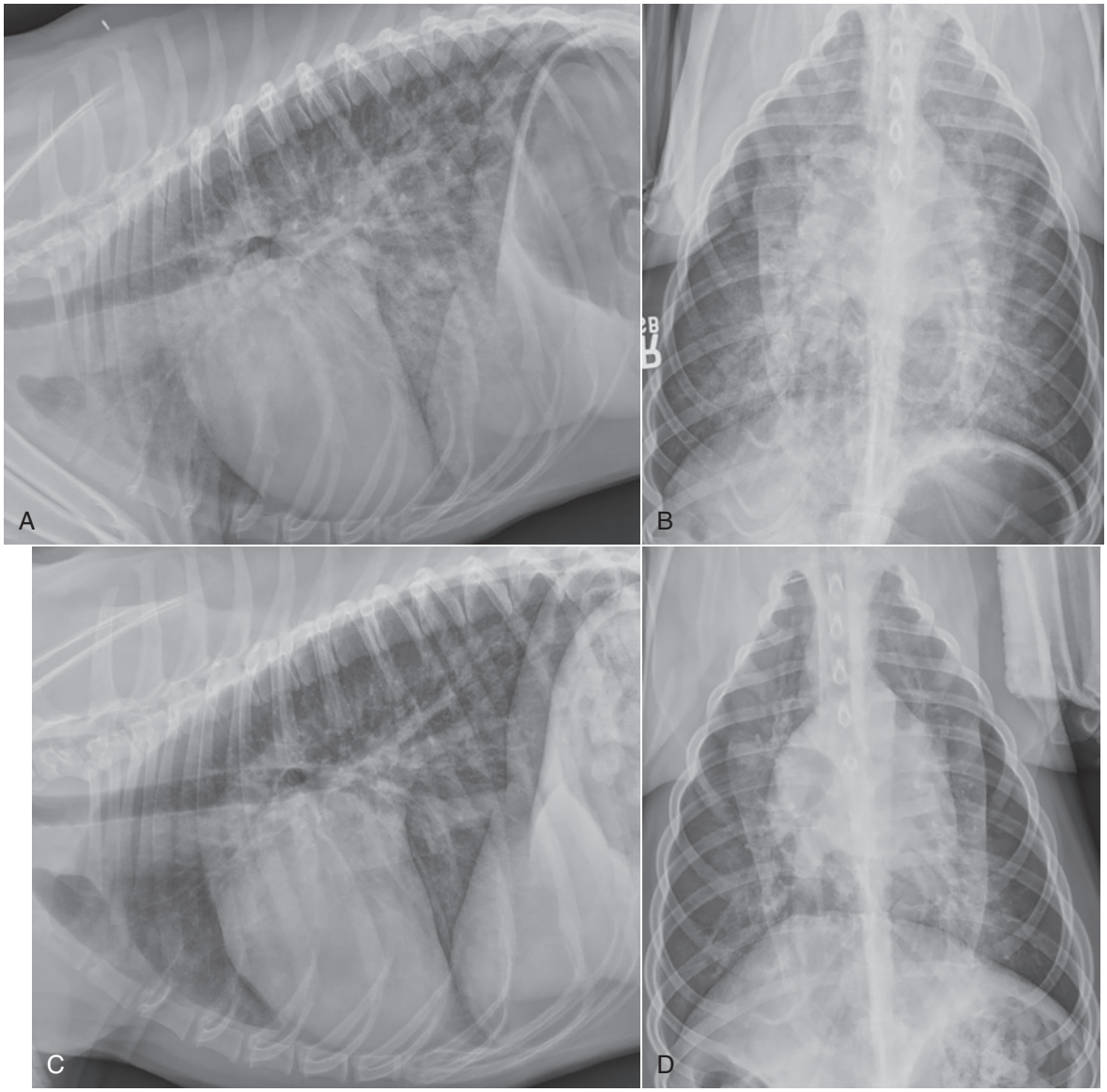


FIG 7.1
Radiographic example of dilated cardiomyopathy with congestive heart failure (and subsequent resolution) in a 5-year-old male Doberman Pinscher. Lateral **(A)** and dorsoventral **(B)** views showing left ventricular and left atrial enlargement, pulmonary venous distension, and moderate diffuse pulmonary edema, consistent with left-sided congestive heart failure. Following medical therapy for congestive heart failure, thoracic lateral **(C)** and dorsoventral **(D)** radiographs of the same patient show resolution of pulmonary edema, with persistent cardiomegaly.

rhythm, although AF is common, especially in Irish Wolfhounds and other giant breeds (see Fig. 2.30). Ventricular tachyarrhythmias, including multiform VPCs, ventricular couplets and triplets, or paroxysmal or sustained ventricular tachycardia are also common, particularly in Doberman Pinschers. Presence of VPCs during a 5-minute ECG is a specific (although insensitive) indicator of frequent VPCs on Holter monitor; even a single VPC noted in a Doberman is highly suggestive of occult DCM. The QRS complexes can be tall (consistent with LV dilation), normal in size, or small. Myocardial disease often causes a widened QRS complex with a slowed R-wave descent and slurred ST segment. A bundle-branch block pattern or other intraventricular conduction disturbance might be observed. The P waves in dogs with sinus rhythm frequently are widened and notched, suggesting LA enlargement.

Twenty-four-hour Holter monitoring is useful for documenting the presence and frequency of ventricular ectopy and can be used as a screening tool for DCM in Doberman Pinschers (see p. 48). The presence of more than 50 VPCs/day or any couplets or triplets is thought to predict future overt DCM in Doberman Pinschers. Some dogs with fewer

than 50 VPCs/day on initial evaluation also develop DCM after several years. The frequency and complexity of ventricular tachyarrhythmias appear to be negatively correlated with fractional shortening; sustained ventricular tachycardia has been associated with increased risk of sudden death. Variability in the number of VPCs between repeated Holter recordings in the same dog can be high (up to 85%). If available, the technique of signal-averaged electrocardiography can reveal the presence of ventricular late potentials, which could suggest an increased risk for sudden death in Doberman Pinschers with occult DCM.

ECHOCARDIOGRAPHY

Echocardiography is used to definitively diagnose DCM (and differentiate from pericardial effusion or chronic mitral valve disease), assess severity of systolic dysfunction, and document degree of cardiac chamber enlargement. Dilated cardiac chambers and poor ventricular systolic wall motion are characteristic findings in dogs with DCM (Fig. 7.2). In severe cases only, minimal wall motion is evident. Left heart enlargement predominates, although all chambers are usually affected to some degree. Echocardiographic indices of LV systolic function are decreased, including fractional shortening, fractional area change, and ejection fraction. LV systolic (as well as diastolic) dimension is increased compared with normal ranges for the breed; the LV appears more spherical, and mitral valve E point–septal separation is increased. LV free-wall and septal thicknesses are normal to decreased. The calculated end-systolic volume index (see p. 25) typically is greater than 80 mL/m^2 in dogs with overt DCM (<30 mL/m^2 is considered normal). Evidence for abnormal diastolic function also can be found in dogs with advanced disease. Mild to moderate centrally directed AV valve regurgitation usually is seen with Doppler echocardiography (Fig. 7.3).

Echocardiography is used to screen for occult myocardial disease also. Screening is complicated by the fact that apparently healthy Doberman Pinschers, Greyhounds, and some other athletic dogs can have slightly reduced fractional shortening compared with what is generally considered normal for most breeds. For asymptomatic Doberman Pinschers, the following echocardiographic criteria suggest occult DCM with a high risk for overt disease within 2 to 3 years: LVIDs greater than 4.6 cm (in dogs ≤42 kg) or greater than 5.0 cm (in dogs >42 kg), LVIDs greater than 3.8 cm, mitral valve E point–septal separation greater than 0.9 cm, or VPCs during initial examination (*LVID,* left ventricular internal diameter; *d,* diastole; *s,* systole).

Clinicopathologic Findings

Circulating concentrations of the natriuretic peptides (B-type natriuretic peptide [BNP] and atrial natriuretic peptide [ANP]) and cardiac troponin are elevated in Doberman Pinschers with occult DCM, and levels of these biomarkers rise as disease progresses and CHF develops. Among these biomarkers, NT-proBNP appears to have the best sensitivity and specificity for detecting occult DCM, particularly when echocardiographic abnormalities are present. However, NT-proBNP has wide biologic variability in normal dogs and is relatively insensitive for detecting occult DCM when ventricular arrhythmias precede echocardiographic changes. Thus the gold standard screening regimen for detecting occult DCM in individual dogs is combined Holter monitoring and echocardiography. In high-volume screening situations, a combination of Holter monitoring and NT-proBNP testing could be considered. Genetic screening is recommended in Doberman Pinschers intended for breeding.

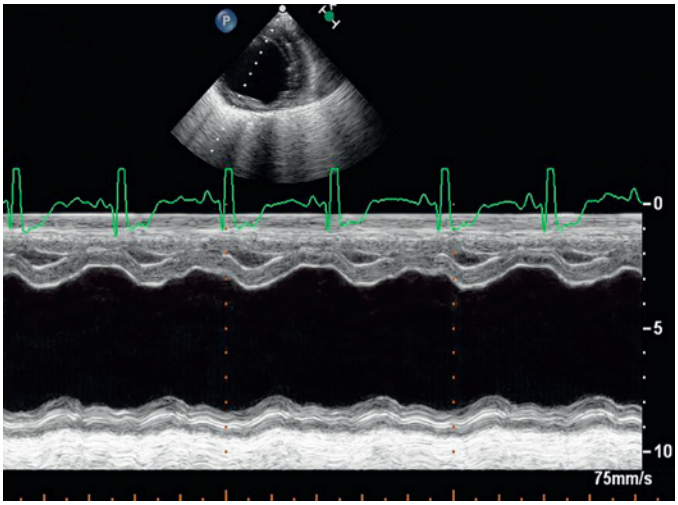


FIG 7.2
M-mode echocardiogram from a Doberman Pinscher with dilated cardiomyopathy at the level of the left ventricular papillary muscles. Note attenuated wall motion (fractional shortening ~18%) and the increased left ventricular dimensions in both diastole and systole.

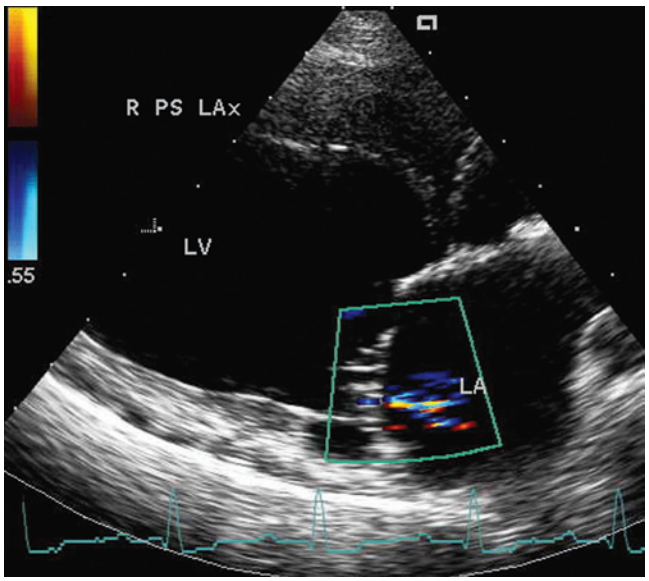


FIG 7.3
Mild mitral regurgitation is indicated by a relatively small area of disturbed flow in this systolic frame from a Standard Poodle with dilated cardiomyopathy. Note the LA and LV dilation. Right parasternal long axis view, optimized for the left ventricular inflow tract. *LA,* Left atrium; *LV,* left ventricle.

Other clinicopathologic findings are noncontributory in most cases, although prerenal azotemia from poor renal perfusion or mildly increased liver enzyme activities from passive hepatic congestion often occur in advanced disease. Severe CHF can be associated with hypoproteinemia, hyponatremia, and hyperkalemia. Hypothyroidism, with associated hypercholesterolemia, occurs in some dogs with DCM. Others have a low serum T_4 hormone concentration without hypothyroidism (euthyroid sick syndrome); normal thyroid-stimulating hormone (TSH) and free T_4 concentrations are common. Increased circulating neurohormones (e.g., norepinephrine, aldosterone, endothelin, in addition to the natriuretic peptides) occur mainly in DCM dogs with overt CHF.

STAGE B (OCCULT) DILATED CARDIOMYOPATHY

Treatment

Pimobendan has been shown to delay progression to CHF or sudden death in Doberman Pinschers with echocardiographic evidence of occult DCM. In a randomized, blinded, placebo-controlled study, pimobendan prolonged the preclinical period by approximately 9 months compared with placebo. It is unclear whether pimobendan would also be beneficial in Doberman Pinschers with ventricular arrhythmias only (before echocardiographic changes). Pimobendan also has been shown to delay progression to CHF or sudden death in Irish Wolfhounds with AF and/or echocardiographic evidence of occult DCM. Compared with benazepril or digoxin, pimobendan delayed the preclinical period in Irish Wolfhounds by approximately 2 years. It remains unknown whether the benefits of pimobendan in occult disease extend to other dog breeds commonly affected by DCM.

An angiotensin-converting enzyme inhibitor (ACEI) also is generally recommended for dogs with LV dilation or reduced LV systolic function. Preliminary evidence in Doberman Pinschers suggests this may delay the onset of CHF. Other therapy aimed at modulating early neurohormonal responses and ventricular remodeling processes have theoretical appeal, but their clinical usefulness is not clear. In particular, certain β-blockers have proven beneficial in humans with cardiomyopathy, but clinical trials demonstrating benefit in canine DCM are lacking. Carvedilol, a combined β-blocker and α-blocker with antioxidant properties, has largely fallen out of favor due to limited and unpredictable oral bioavailability in dogs.

The decision to use antiarrhythmic drug therapy in dogs with ventricular tachyarrhythmias is influenced by arrhythmia frequency and complexity seen on Holter recording, as well as presence or absence of clinical signs (episodic weakness, syncope). Various antiarrhythmic agents have been used, but the most effective regimen(s) and when to institute therapy remain unclear. A regimen that decreases arrhythmia frequency and severity and increases ventricular fibrillation threshold is desirable to decrease clinical signs and reduce risk of sudden death. Common first-line ventricular antiarrhythmic medications used in DCM include sotalol and/or mexiletine. Amiodarone or procainamide sometimes are used in refractory cases (see Chapter 4).

STAGE C (CLINICALLY EVIDENT) DILATED CARDIOMYOPATHY

Therapy is aimed at improving the patient's quality of life and prolonging survival to the extent possible by controlling signs of CHF, optimizing cardiac output, and managing arrhythmias. Pimobendan, an ACEI, and furosemide (dosed as needed) are used for most dogs (Box 7.1). Spironolactone is advocated as well. Antiarrhythmic drugs are used based on individual need.

Acute therapy

Dogs with acute CHF are treated as outlined in Box 3.1, with parenteral furosemide, supplemental oxygen, inotropic support, cautious use of a vasodilator, and other medications according to individual patient needs. Thoracocentesis is indicated if pleural effusion is suspected or identified.

Dogs with poor myocardial contractility, persistent hypotension, or fulminant CHF can benefit from additional inotropic support provided by intravenous (IV) infusion of dobutamine (or dopamine) for 1 to 3 days. Long-term use of strong positive inotropic drugs is thought to have detrimental effects on the myocardium. During infusion of these drugs, the patient must be observed closely for worsening tachycardia or arrhythmias (especially VPCs). If ventricular arrhythmias develop, the drug is discontinued or infused at up to half the original rate. In dogs with AF, catecholamine infusion is likely to increase the ventricular response rate because of enhanced AV conduction.

Rapid AF is treated with drugs to slow ventricular response rate. Diltiazem and digoxin are options for rate control in this setting; although both are available in IV and oral formulations, IV digoxin is avoided in most circumstances. Diltiazem is more effective at lowering heart rate, but its negative inotropic properties can further compromise systolic function in patients with advanced DCM; if the dog is not already receiving pimobendan, this drug should be administered as soon as possible. Digoxin is less potent for rate reduction, with slower onset of action, but has the benefit of being a mild positive inotrope. For long-term rate control, a combination of oral diltiazem and oral digoxin is preferred. Strategies for acute rate control include (see p. 84): (1) diltiazem loading (either PO or with small IV boluses, if necessary followed by cautious continuous rate infusion [CRI]), with transition to oral maintenance diltiazem and addition of oral digoxin; or (2) digoxin loading (PO loading with double the oral maintenance dose, or possibly cautious IV loading using small boluses hourly over 4 hours), with subsequent initiation of oral maintenance digoxin and addition of oral diltiazem. During an acute episode of CHF, the goal is to reduce ventricular response rate to 150 to 160 beats per minute to maximize cardiac output; more aggressive rate reduction is counterproductive and can lead to worsened cardiogenic shock.

BOX 7.1

Treatment Outline for Dogs With Dilated Cardiomyopathy

Occult CM (Stage B)

Client education (about disease process and early heart failure signs)
Routine health maintenance
Manage other medical problems
Pimobendan
ACE inhibitor
±Consider β-blocker titration (e.g., atenolol or metoprolol)
Antiarrhythmic therapy, if indicated (e.g., sotalol or mexiletine for ventricular tachyarrhythmias; digoxin and diltiazem combination therapy for atrial fibrillation; see Chapter 4)
Avoid high-salt foods; consider moderately salt-restricted diet
Monitor for early signs of CHF (e.g., resting respiratory rate [see p. 74], activity level)

Mild to Moderate Signs of CHF (Stage C, Chronic/Outpatient Care)*

Furosemide, dose as needed
Pimobendan
ACE inhibitor
Spironolactone
Antiarrhythmic therapy, if indicated (e.g., sotalol or mexiletine for ventricular tachyarrhythmias; digoxin and diltiazem combination therapy for atrial fibrillation; see Chapter 4)
Client education and manage concurrent problems, as previously mentioned
Complete exercise restriction until after signs abate
Moderate dietary salt restriction
Consider dietary supplement (fish oil, ±taurine or carnitine, if indicated)
Monitor resting respiratory rate (see p. 74) ±heart rate at home

Severe CHF Signs (Stage C, Acute/Hospitalized Care)*

Supplemental O_2
Cage rest and minimal patient handling
Furosemide (more aggressive doses, parenteral)
Pimobendan (continue or add as soon as oral administration possible)
Consider dobutamine, especially if persistent hypotension (see Box 3.1, p. 62)
Antiarrhythmic therapy, if necessary (e.g., lidocaine for ventricular tachycardia, PO loading or IV diltiazem (or digoxin) for uncontrolled AF, see text and Table 4.2, p. 90)
Consider cautious use of a vasodilator (nitroprusside, hydralazine, or amlodipine) for adjunct afterload reduction, if necessary, and if blood pressure is not low; beware hypotension
Thoracocentesis, if moderate- to large-volume pleural effusion

Chronic Recurrent or Refractory Heart Failure Strategies (Stage D)*

Ensure that therapies for stage C are being given at optimal doses and intervals, including furosemide, pimobendan, ACE inhibitor, spironolactone
Rule out complicating factors: arrhythmias, renal or other metabolic abnormalities, systemic arterial hypertension, anemia, and other complications
Increase furosemide dose/frequency as needed (and as renal function allows)
Increase pimobendan dose frequency to q8h and/or increase dose
Consider adding digoxin for additional inotropic support
Add (or increase dose of) adjunctive diuretics (e.g., spironolactone, hydrochlorothiazide); monitor renal function and electrolytes closely
Consider additional afterload reduction (e.g., amlodipine or hydralazine); monitor blood pressure closely
Strictly curtail exercise
Further restrict dietary salt intake
Thoracocentesis (or abdominocentesis) as needed
Hospitalize as needed for acute CHF therapy (see Box 3.1)
Manage arrhythmias, if present (see Chapter 4)

ACE, Angiotensin-converting enzyme; *AF,* atrial fibrillation; *CHF,* congestive heart failure; *IV,* intravenous.
*See text, Chapter 3, Tables 3.2 and 3.3 and Box 3.1 for further details and doses.

Clinical status in dogs with DCM can deteriorate rapidly, so close patient monitoring is important. Respiratory rate and character, lung sounds, pulse quality, heart rate and rhythm, peripheral perfusion, rectal temperature, body weight, renal function, mentation, pulse oximetry, and blood pressure should be monitored. Because ventricular contractility is abysmal in many dogs with severe DCM, these patients have little cardiac reserve; diuretic and vasodilator therapy can lead to hypotension and even cardiogenic shock.

Long-term therapy

Pimobendan (Vetmedin, Boehringer Ingelheim Vetmedica) is the oral positive inotrope of choice for long-term management of DCM and CHF. Pimobendan is a phosphodiesterase III inhibitor that increases contractility through a Ca^{++}-sensitizing effect; the drug also has vasodilator and other beneficial effects. Pimobendan improves clinical signs and survival in dogs with DCM and CHF. Starting dose is 0.2 to 0.3 mg/kg PO q12h. In progressive or refractory cases, pimobendan dose can be uptitrated to 0.5 mg/kg PO q8h. This higher dose recommendation is outside of the FDA approved labeling for pimobendan, and such off-label use should be explained to and approved by the client.

Furosemide is used at the lowest effective oral dosage for long-term therapy (see Table 3.3). Hypokalemia and other

electrolyte and acid-base abnormalities are common sequelae. Hypokalemia is often treated with addition of the potassium-sparing diuretic spironolactone, although dietary potassium supplementation can also be considered if needed.

An ACEI should be used in the chronic treatment of DCM and may attenuate progressive ventricular dilation and secondary mitral regurgitation. ACEIs have a positive effect on survival in patients with myocardial failure. These drugs minimize clinical signs and increase exercise tolerance. Enalapril or benazepril are used most commonly, but other ACEIs have similar effects.

Spironolactone is thought to be useful because of its aldosterone-antagonist properties as well as potential mild diuretic effects. Aldosterone is known to promote cardiovascular fibrosis and abnormal remodeling and, as such, contributes to the progression of cardiac disease. Spironolactone is therefore advocated as adjunctive therapy in combination with an ACEI, furosemide, and pimobendan for chronic DCM therapy.

For dogs with AF, a combination of oral diltiazem and oral digoxin is advocated for long-term control of ventricular response rate (see Table 4.2). Digoxin is a weak positive inotrope with neurohormonal modulating and antiarrhythmic effects. Although pimobendan has largely replaced digoxin for oral inotropic support, digoxin still is indicated for heart rate control in AF and can be given in conjunction with pimobendan. The recommended oral maintenance dose of digoxin is 0.003 to 0.005 mg/kg PO q12h, or approximately 0.125 mg total dose, PO, q12h for typical Dobermans (~40 kg). Toxicity is uncommon at these low doses, but monitoring is still recommended due to the narrow therapeutic index of this drug. Serum digoxin concentration should be measured 7 to 10 days after digoxin therapy is initiated or the dose is changed; serum samples should be drawn 6 to 8 hours after the last oral dose (see p. 70). Diltiazem is a cardiac-specific calcium-channel blocker that is very effective at slowing AV nodal conduction and thus decreasing heart rate in AF. Because of its negative inotropic effect, a low initial dose and gradual dosage titration to effect or a maximum recommended level is advised. Diltiazem is available in several dose formulations; typically, an extended-release formulation allowing twice daily dosing (Dilitazem ER/XR, Dilacor) is used for chronic administration.

Heart rate control in dogs with AF is important, but specific goals for rate control have yet to be firmly established. A maximum ventricular rate of 140 beats/min in the hospital (i.e., stressful) setting is the recommended target; lower heart rates (e.g., ≈100 beats/min or less) are expected at home. Because heart rate assessment by auscultation or chest palpation in dogs with AF often is highly inaccurate, an ECG recording is recommended. Femoral pulses should never be used to assess heart rate in the presence of AF. At-home rate assessment with Holter monitors or smartphone-based ECG applications may assist with dose adjustment.

Additional afterload reduction with amlodipine or hydralazine (see Table 3.3) could be useful as adjunct therapy for dogs with refractory CHF, although arterial blood pressure should be carefully monitored in such animals. Any vasodilator must be used cautiously in dogs with a low cardiac reserve because of the increased potential for hypotension. Hydralazine is more likely to precipitate hypotension and therefore reflex tachycardia and further neurohormonal activation. Therapy is initiated at a low dose; if this is well tolerated (monitored with blood pressure measurement), the next dose is increased to a low maintenance level. Signs of worsening tachycardia, weakened pulses, or lethargy can indicate the presence of hypotension.

A number of other therapies might be useful in certain dogs with DCM, although additional studies are necessary to define optimal recommendations. These include omega-3 fatty acids, L-carnitine (in dogs with low myocardial carnitine concentrations), taurine (in dogs with low plasma concentrations), long-term β-blocker therapy, or possibly others (see Chapter 3, p. 72). Advanced therapeutics, including gene transfer and stem cell transplantation, are under experimental investigation but are not currently recommended in clinical settings. Biventricular pacing to better synchronize ventricular contraction has improved clinical status in people with myocardial dysfunction, but there is little clinical experience with resynchronization therapy in dogs with DCM.

Monitoring

Owner education regarding the purpose, dosage, and adverse effects of each drug used is important. Monitoring the dog's resting respiratory (and heart) rate at home helps in assessing how well the CHF is controlled (see Chapter 3, p. 73). The time frame for reevaluation visits depends on the patient's status. Recheck visits once or twice a week may be necessary initially. Dogs with stable heart failure can be rechecked every 2 or 3 months. Current medications, diet, and any owner concerns should be reviewed. Patient activity level, appetite, and attitude, along with renal values and electrolytes, heart rate and rhythm, thoracic imaging to assess pulmonary edema or pleural effusion, blood pressure, body weight, and other appropriate factors should be evaluated and therapy adjusted as needed.

Prognosis

The prognosis for dogs with DCM is generally guarded. In Doberman Pinschers, occult disease tends to develop at 3 to 6 years of age, with ventricular arrhythmias preceding echocardiographic changes. Onset of CHF generally occurs within 2 to 3 years, although addition of pimobendan delays disease progression. Sudden death occurs in about 20% to 40% of affected Doberman Pinschers and may occur in the occult stage before CHF is present. Doberman Pinschers and Great Danes appear to have a worse prognosis than other breeds, with younger age of onset and more rapid progression of disease. Certain breeds, including Irish Wolfhounds and Cocker Spaniels, have more protracted preclinical periods and may live for years with mild to moderate LV systolic dysfunction. Prognosis following an episode of CHF is poor. Median survival time with treatment is in the realm of 4 to 6 months. Negative prognostic indicators include presence of pleural effusion, severity of LV

systolic dysfunction, presence of ventricular tachycardia or atrial fibrillation, and higher values of cardiac biomarkers. In individual cases, however, it is reasonable to assess the animal's response to initial treatment before pronouncing an unequivocally dismal prognosis. Overall prognosis for DCM, in both preclinical stages and in CHF, is improved with use of pimobendan.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

ARVC is the most common acquired heart disease of Boxer dogs. This inherited primary myocardial disease shares many similar features to those of ARVC in people. Histologic changes in the myocardium are more extensive than other canine cardiomyopathies and are characterized by fatty or fibrofatty infiltration, usually most severe in the right ventricle (RV) free wall. Atrophy of myofibers and myocardial fibrosis are also common. Focal areas of myocytolysis, necrosis, hemorrhage, and mononuclear cell infiltration may be seen. Ultrastructural abnormalities, including reduced numbers of myocardial gap junctions and desmosomes, are apparent throughout the myocardium (including the atria), suggesting that the disease process is not confined to the RV.

ARVC in Boxers is familial with an autosomal dominant inheritance pattern. A mutation in the striatin gene on chromosome 17, which encodes for a protein involved in cell-to-cell adhesion, has been associated with Boxer ARVC. Boxers with at least one copy of the striatin mutation are 40 times more likely to develop ARVC than homozygous negative dogs. Overall genetic penetrance of this mutation is approximately 80%, with nearly 100% of homozygous positive dogs affected. Yet the fact that this mutation is not present in all Boxers with ARVC and is present in some without ARVC suggests that it may collocate with, rather than being, the causative mutation. However, as in people, there may be a number of gene mutations associated with ARVC in different bloodlines. Genetic testing for the striatin gene mutation is available (North Carolina State University Veterinary Cardiac Genetics Laboratory; https://cvm.ncsu.edu/genetics/).

Clinical manifestations of ARVC can appear in three forms, although these are thought to represent the same underlying disease. Dogs with the occult form have ventricular arrhythmias without clinical signs. Dogs with overt ARVC have syncope or weakness associated with paroxysmal or sustained ventricular tachycardia, usually despite normal heart size and LV function. Approximately 10% of affected Boxers have a form of ARVC where ventricular tachyarrhythmias are accompanied by a DCM phenotype, with poor myocardial function that progresses to CHF, unless sudden death occurs first. Myocardial changes in the DCM phenotype typically involve both the LV and RV, and left-sided CHF is most common. Some dogs with normal LV systolic function at the time of ARVC diagnosis progress to develop the DCM phenotype later in life. Dogs that are homozygous-positive for the striatin mutation appear more likely to develop the DCM phenotype, although some heterozygous dogs also manifest this more severe form of ARVC.

Clinical Findings

Signs may appear at any age, but the median age at diagnosis is 6 years. Syncope is the most common clinical complaint. Ventricular tachyarrhythmias underlie most instances of syncope in Boxers with ARVC. However, another potential cause for syncope in young adult Boxers is neurocardiogenic (reflex-mediated) syncope, where a sudden surge in sympathetic activity triggers reflex vagal stimulation and inappropriate bradycardia and hypotension. Neurocardiogenic syncope can occur in normal Boxers and in Boxers with ARVC, and can potentially be exacerbated by use of sotalol or (other) β-blocker therapy.

The physical examination could be normal, although a soft left basilar systolic murmur is common in Boxers, whether ARVC is present or not. In many Boxers, this is a breed-related physiologic murmur related to aortic annular hypoplasia relative to body size, or it may be associated with underlying subaortic stenosis. In some dogs, a cardiac arrhythmia with pulse deficits is found on physical examination; in others, the resting heart rhythm is normal. When CHF occurs in dogs with DCM phenotype, left-sided signs are more common than ascites or other signs of right-sided heart failure; a mitral insufficiency murmur can be present in these cases as well.

Diagnosis

Radiographic findings are variable. Boxers with ARVC and normal myocardial function have no visible abnormalities. Those with DCM phenotype and CHF generally show evidence of cardiomegaly and pulmonary edema. Echocardiographic findings also vary between disease manifestations. Most Boxers with ARVC have normal cardiac size and function; dogs with DCM phenotype show reduced fractional shortening and chamber dilation, similar to other dogs with DCM.

The characteristic ECG finding is ventricular ectopy. VPCs occur singly, in pairs, in short runs, or as sustained ventricular tachycardia. Most ectopic ventricular complexes originate in the RV and thus appear upright in leads II and aVF (Fig. 7.4). However, some Boxers have multiform VPCs. Usually an underlying sinus rhythm exists; AF is less common. Supraventricular tachycardia, conduction abnormalities, and evidence of chamber enlargement also are sometimes seen on ECG, particularly in patients with the DCM phenotype.

Twenty-four-hour Holter monitoring is used to quantify the frequency and complexity of ventricular tachyarrhythmias and as a screening tool for Boxer ARVC. It also is recommended to evaluate the efficacy (and any proarrhythmic adverse effects) of antiarrhythmic drug therapy. Frequent VPCs and/or complex ventricular arrhythmias are characteristic findings in affected dogs. Absolute criteria for separating normal from abnormal Boxers are not entirely

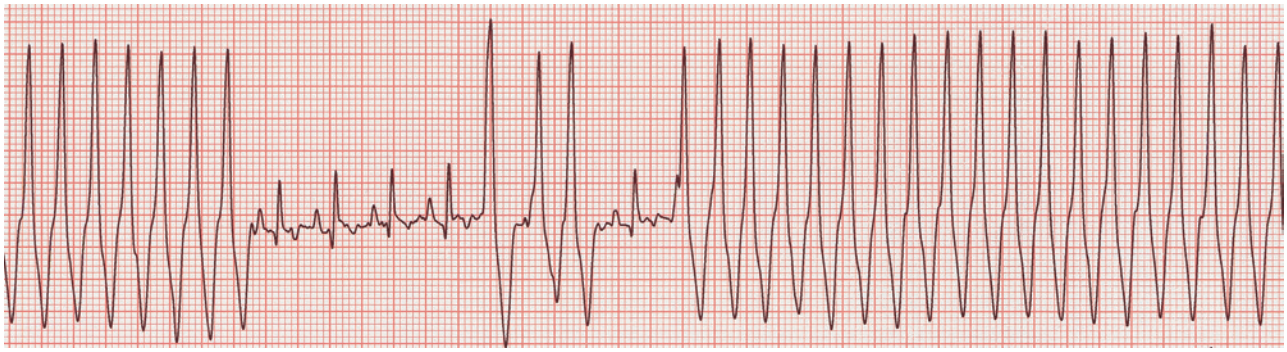


FIG 7.4
Paroxysmal ventricular tachycardia at a rate of almost 300 beats/min in a Boxer with arrhythmogenic right ventricular cardiomyopathy. Note the typical upright (left bundle branch block–like) appearance of the ventricular ectopic complexes in the caudal leads. Lead II, 25 mm/sec.

clear. However, Animal Registry of Certified Health guidelines (ARCH, http://www.archcertify.org/) suggest the following classifications: fewer than 50 single monomorphic VPCs/24-hour period is interpreted as normal; between 50 and 300 single monomorphic VPCs/24-hour period is equivocal (ARVC cannot be definitively diagnosed or excluded); and greater than 300 VPCs/24-hour period, or periods of couplets, triplets, or runs of ventricular tachycardia (VT), is abnormal and consistent with a diagnosis of ARVC. Frequent VPCs or episodes of ventricular tachycardia signal an increased risk for syncope and sudden death. The occurrence of ventricular arrhythmias appears to be widely distributed throughout the day, and there can be enormous variability (up to 85%) in the number of VPCs between repeated Holter recordings in the same dog. Longitudinal studies of Boxer dogs show that the onset of ventricular arrhythmias in ARVC is relatively abrupt, with a sudden increase in VPC number from <50 VPCs/24 hour in the year preceding ARVC diagnosis to an average of ~1200 VPCs/24 hour at time of diagnosis. The biomarkers cardiac troponin I and NT-proBNP do not reliably discriminate between normal and affected dogs, except possibly in dogs with DCM phenotype.

Annual Holter recordings are recommended beginning at age 2 to 3 years to screen for development and monitor progression of ARVC in Boxer dogs. Once Holter criteria for ARVC are met, annual echocardiography is also recommended to screen for development of DCM phenotype. Genetic testing for the striatin mutation is highly recommended for animals considered for breeding and may also provide prognostic information about an individual dog (particularly the likelihood of developing the DCM phenotype). Homozygous-positive dogs should not be bred, and heterozygous-positive dogs should be bred only to dogs negative for the striatin mutation. Dogs meeting Holter diagnostic criteria for ARVC (greater than 300 VPCs/24 hour or dogs with complex ventricular ectopy) also should not be bred, regardless of genotype.

Treatment

Antiarrhythmic treatment is indicated for Boxers with clinical signs from tachyarrhythmias (i.e., syncope). Asymptomatic dogs with Holter findings of greater than 1000 single VPCs/24 hour, ventricular tachycardia, or close coupling of VPCs to the preceding QRS on Holter monitoring are usually given antiarrhythmic therapy as well. However, the best regimen(s) and when to institute therapy are still not clear. Sotalol and mexiletine have each shown efficacy in reducing VPC frequency and complexity. Either of these drugs is generally considered acceptable first-line therapy for dogs with ARVC, and combination therapy is common. Other drugs that can be used or added in refractory cases include amiodarone, procainamide, or other β-blockers such as atenolol (see Chapter 4). The addition of an omega-3 fatty acid supplement might also reduce VPC frequency. Magnesium supplementation (usually in the form of magnesium oxide) is used occasionally.

The goals of antiarrhythmic drug therapy are to decrease number and complexity of VPCs, reduce frequency of syncope, and, ideally, reduce risk of sudden death. Holter monitoring is used to monitor efficacy of antiarrhythmic therapy; given biologic variability in daily VPC number in dogs with ARVC, a reduction in VPCs of at least 85% generally is needed to conclude adequate antiarrhythmic effect. Unfortunately, sudden death remains possible even with apparently good control of arrhythmias.

Therapy for dogs with DCM phenotype is similar to that described for dogs with idiopathic DCM. Pimobendan and ACEI are typically prescribed once LV systolic dysfunction is documented, although benefit of these drugs has not been evaluated in this specific setting. Once CHF occurs, furosemide and spironolactone are added. Antiarrhythmics are prescribed or continued as previously discussed; caution should be used with sotalol in the setting of DCM phenotype and acute CHF, because the mild β-blocking effects of this drug may exacerbate LV systolic dysfunction. Myocardial carnitine deficiency has been documented in some Boxers

with DCM phenotype and CHF. Some of these dogs have responded to oral L-carnitine supplementation.

Prognosis

The prognosis for Boxers with ARVC and normal systolic function is good with antiarrhythmic treatment. A longitudinal study showed no difference in life span between Boxers with and without ARVC (median survival time in both groups was between 10 and 11 years). In contrast, prognosis for Boxers with the DCM phenotype form of ARVC is guarded. Most dogs with DCM phenotype progress to CHF, and survival after onset of CHF is generally less than 6 months. Unfortunately, sudden death remains the most common cause of death in dogs with ARVC, regardless of LV systolic function, and antiarrhythmic treatment may ameliorate but does not eliminate this risk.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN DOGS OF OTHER BREEDS

A form of cardiomyopathy that mainly affects the RV has been observed rarely in English Bulldogs and other breeds. It appears similar to ARVC described in people and cats. Pathologic changes are characterized by widespread fibrous and fatty tissue replacement in the RV myocardium. Marked right heart dilation is typical. In certain geographic areas, trypanosomiasis is a possible differential diagnosis. Clinical manifestations are largely related to right-sided CHF and severe ventricular tachyarrhythmias; sudden death is a potential outcome.

SECONDARY MYOCARDIAL DISEASE

Poor myocardial function can result from a variety of identifiable insults and nutritional deficiencies. Myocardial infections (see p. 153), inflammation, trauma (see p. 155), ischemia, neoplastic infiltration, and metabolic abnormalities can impair normal contractile function. Hyperthermia, irradiation, electric shock, certain drugs, and other insults can also damage the myocardium. Some substances are known cardiac toxins.

MYOCARDIAL TOXINS

Doxorubicin

The antineoplastic drug doxorubicin induces both acute and chronic cardiotoxicity. Release of histamine with secondary catecholamine release appears to underlie acute toxicity, which is idiosyncratic and leads to transient ventricular or supraventricular arrhythmias during drug administration. Chronic cardiotoxicity appears to be mediated by DNA intercalation, inhibition of topoisomerase II, and free-radical production. The resulting myocardial damage is characterized histologically by vacuolization and degeneration of cardiomyocytes. Chronically, cellular toxicity leads to LV dilation and decreased LV systolic function, mimicking idiopathic DCM. Left-sided CHF is the eventual clinical outcome. Cardiac conduction defects (infranodal AV block and bundle branch block), as well as ventricular and supraventricular tachyarrhythmias, can also develop with chronic toxicity. ECG changes do not necessarily precede CHF.

Chronic doxorubicin-induced cardiotoxicity is directly related to the cumulative dose of doxorubicin administered. Echocardiographic changes and CHF are generally seen at cumulative doses of greater than 150 mg/m^2, although ECG changes can be seen at doses as low as 90 mg/m^2. Cardiotoxicity becomes particularly likely when cumulative dose of doxorubicin exceeds 240 mg/m^2. In dogs that have normal pretreatment cardiac function, clinical cardiotoxicity causing CHF is uncommon, occurring in an estimated 2% to 5% of treated dogs. Depending on the underlying neoplastic process (e.g., hemangiosarcoma), dogs may not live long enough to experience chronic toxicity from doxorubicin treatment. Although predicting whether and when clinical cardiotoxicity will occur is difficult, dogs with underlying cardiac abnormalities and those of breeds with a higher prevalence of idiopathic myocardial disease (e.g., Dobermans, Great Danes, Boxers) are thought to be at higher risk.

Echocardiography and ECG are used to diagnose doxorubicin cardiotoxocity. Increases in circulating cardiac troponin concentrations can also be seen. However, no screening modalities (biomarkers or imaging) have proven effective in predicting future cardiotoxicity. Whether and how frequently to screen dogs for cardiotoxicity during treatment depends on multiple factors, including breed, presence of preexisting heart disease, underlying neoplastic disease, and relative risk aversion of the oncologist and owner.

Various strategies have been employed in an attempt to decrease risk of cardiotoxicity with doxorubicin administration. In humans, giving doxorubicin as a prolonged continuous infusion (at least 6 hours) decreases drug toxicity; there is some evidence that in dogs, administering the drug diluted (0.5 mg/mL) over 1 hour may similarly decrease risk. Concurrent administration of the iron chelator dexrazoxane (Zinecard) prevents doxorubicin-induced lipid peroxidation and might also decrease risk of toxicity. However, application to veterinary medicine is somewhat limited due to expense of this drug. Other attempts have involved use of pegylated liposome-encapsulated doxorubicin or concurrent administration of antioxidants such as carvedilol or vitamin E and selenium.

Other toxins

Ethyl alcohol, especially if given IV for the treatment of ethylene glycol intoxication, can cause severe myocardial depression and death; slow administration of a diluted (≤20%) solution is advised. Other cardiac toxins include plant toxins (e.g., *Taxus,* foxglove, black locust, buttercups, lily-of-the-valley, gossypol); anesthetic drugs; catecholamines (including the feed additive ractopamine); and ionophores such as monensin. Other potential cardiac toxins recognized in humans include heavy metals (e.g., arsenic, lead, mercury); antineoplastic drugs (cyclophosphamide, 5-fluorouracil, interleukin-2, α-interferon); other drugs (e.g., thyroid hormone, cocaine, amphetamines, lithium);

and biologic toxins (wasp or scorpion stings, snake venom, spider bites).

METABOLIC AND NUTRITIONAL DEFICIENCY

L-carnitine

L-carnitine is an essential component of the mitochondrial membrane transport system for fatty acids, which are the heart's most important energy source. It also transports potentially toxic metabolites out of the mitochondria in the form of carnitine esters. L-carnitine-linked defects in myocardial metabolism have been found in some dogs with DCM. Rather than simple L-carnitine deficiency, one or more underlying genetic or acquired metabolic defects are suspected. There may be an association between DCM and carnitine deficiency in some families of Boxers, Doberman Pinschers, Great Danes, Irish Wolfhounds, Newfoundlands, and Cocker Spaniels. L-carnitine is mainly present in foods of animal origin. DCM has developed in some dogs fed strict vegetarian diets.

Plasma carnitine concentration is not a sensitive indicator of myocardial carnitine deficiency. Most dogs with myocardial carnitine deficiency, diagnosed via endomyocardial biopsy, have had normal or high plasma carnitine concentrations. Furthermore, the response to oral carnitine supplementation is inconsistent. Subjective improvement may occur, but few dogs have echocardiographic evidence of improved function. Dogs that do respond show clinical improvement within the first month of supplementation; there may be some degree of improvement in echo parameters after 2 to 3 months. L-carnitine supplementation does not suppress preexisting arrhythmias or prevent sudden death. See p. 73 for supplementation guidelines.

Taurine

Although most dogs with DCM are not taurine deficient, low plasma taurine concentration has been documented in some and appears particularly common in certain breeds. Low taurine, and sometimes carnitine, concentrations occur in Cocker Spaniels with DCM. Oral supplementation of these amino acids can improve LV size and function, as well as reduce the need for heart failure medications in this breed. Low taurine concentrations have also been found in some Newfoundlands, Golden Retrievers, Labrador Retrievers, Saint Bernards, and other dogs with DCM. Some such dogs have been fed low-protein lamb meal and rice, or vegetarian diets; others have been consuming diets with adequate taurine content. In particular, DCM has been identified in Dalmatians fed protein-restricted diets for prevention of breed-related urate urolithiasis.

Assessment of plasma or whole blood taurine concentration should be considered in "atypical" breeds affected with DCM or any dog with concern for nutritional deficiency based on diet history. Plasma taurine concentrations less than 40 nmol/mL and blood taurine concentrations less than 150 nmol/mL are generally considered deficient. Specific collection and submission guidelines should be obtained from the laboratory used. If taurine deficiency is documented, a trial of supplemental taurine for 3 to 4 months is recommended (see p. 73 for supplementation guidelines). However, the effect of taurine supplementation on disease progression is unclear. Taurine-deficient dogs may show echocardiographic improvement after supplementation; however, some degree of cardiac abnormality often persists, and there is questionable effect on survival time.

Other factors

Myocardial injury induced by free radicals may play a role in a number of diseases. Evidence for increased oxidative stress has been found in dogs with CHF and myocardial failure, but the clinical ramifications of this are unclear. Diseases such as hypothyroidism, pheochromocytoma, and diabetes mellitus have been associated with reduced myocardial function, but clinical CHF is unusual in dogs secondary to these conditions alone. Excessive sympathetic stimulation stemming from brain or spinal cord injury results in myocardial hemorrhage, necrosis, and arrhythmias (brain-heart syndrome). Muscular dystrophy of the fasciohumoral type (reported in English Springer Spaniels) can result in atrial standstill and heart failure. Canine X-linked (Duchenne) muscular dystrophy in Golden Retrievers and other breeds also has been associated with myocardial fibrosis and mineralization, with subsequent LV systolic dysfunction and CHF. Rarely, nonneoplastic (e.g., glycogen storage disease) and neoplastic (metastatic and primary) infiltrates interfere with normal myocardial function. Immunologic mechanisms also could play an important role in the pathogenesis of myocardial dysfunction in some dogs with myocarditis.

ISCHEMIC MYOCARDIAL DISEASE

Acute myocardial infarction resulting from coronary embolization is uncommon. An underlying disease associated with increased risk for thromboembolism, such as bacterial endocarditis, neoplasia, protein-losing nephropathy or enteropathy, immune-mediated hemolytic anemia, acute pancreatitis, disseminated intravascular coagulopathy, and/or corticosteroid use, underlies most cases. Sporadic reports of myocardial infarction have been associated with congenital ventricular outflow obstruction, patent ductus arteriosus, hypertrophic cardiomyopathy, and mitral insufficiency. Atherosclerosis of the major coronary arteries, which can accompany severe hypothyroidism in dogs, rarely leads to acute myocardial infarction. Clinical signs of acute major coronary artery obstruction are likely to include arrhythmias, pulmonary edema, marked ST segment change on ECG, and evidence of regional or global myocardial contractile dysfunction on echocardiogram. High circulating cardiac troponin concentrations and possibly creatine kinase activity occur after myocardial injury and necrosis.

Disease of small coronary vessels is recognized as well. Nonatherosclerotic narrowing of small coronary arteries could be more clinically important than previously assumed. Hyalinization of small coronary vessels and intramural myocardial infarctions have been described in dogs with chronic degenerative mitral valve disease; however, they can occur in older dogs without valve disease as well. Fibromuscular

arteriosclerosis of small coronary vessels also has been described. These changes in the walls of the small coronary arteries cause luminal narrowing and can impair resting coronary blood flow, as well as vasodilatory responses. Small myocardial infarctions and secondary fibrosis lead to reduced myocardial function. Various arrhythmias can occur. Eventual CHF is a cause of death in many cases with intramural coronary arteriosclerosis. Sudden death is a less common sequela. Larger breeds of dog may be predisposed, although Cocker Spaniels and Cavalier King Charles Spaniels appear to be commonly affected smaller breeds.

TACHYCARDIA-INDUCED CARDIOMYOPATHY

The term *tachycardia-induced cardiomyopathy* (TICM) refers to the progressive myocardial dysfunction, activation of neurohormonal compensatory mechanisms, and CHF that result from rapid, incessant tachycardias. The myocardial failure may be reversible if the heart rate can be normalized in time. Tachyarrhythmias inducing TICM usually are supraventricular in origin, since rapid incessant ventricular tachyarrhythmias typically lead to more hemodynamic instability (syncope, sudden cardiac death) before TICM develops. TICM has been described in several dogs with AV nodal reciprocating tachycardia associated with accessory conduction pathways that bypass the AV node (e.g., Wolff-Parkinson-White; see p. 44). Labrador Retrievers appear to be predisposed to accessory pathway-mediated supraventricular tachycardias and thus TICM; this often is in association with tricuspid dysplasia. Rapid artificial pacing (e.g., >200 beats/min) is a common model for inducing experimental myocardial failure that simulates DCM.

HYPERTROPHIC CARDIOMYOPATHY

Etiology and Pathophysiology

In contrast to cats, HCM is uncommon in dogs. Other causes of LV hypertrophy (subaortic stenosis, systemic hypertension, or other metabolic diseases) should always be excluded. A genetic basis for HCM is suspected in Pointers, although the disease occurs sporadically in other breeds. The pathophysiology is similar to that of HCM in cats (see Chapter 8). Abnormal, excessive myocardial hypertrophy increases ventricular stiffness and leads to diastolic dysfunction. The LV hypertrophy usually is symmetric, but regional variation in wall or septal thickness can occur. Compromised coronary perfusion is likely with severe ventricular hypertrophy. This leads to myocardial ischemia, which exacerbates arrhythmias, delays ventricular relaxation, and further impairs filling. High LV filling pressure predisposes to pulmonary venous congestion and edema. Besides diastolic dysfunction, systolic dynamic LV outflow obstruction occurs in the majority of affected dogs. Malposition of the mitral apparatus can contribute to systolic anterior mitral valve motion and LV outflow obstruction, as well as to mitral regurgitation. LV outflow obstruction increases ventricular wall stress and myocardial oxygen requirement while also impairing coronary blood flow. Heart rate elevations magnify these abnormalities.

Clinical Features

HCM is most commonly diagnosed in young to middle-aged large-breed dogs, often less than 3 years of age, although there is a wide age distribution. Males are more commonly affected. Most dogs diagnosed with HCM are presented for evaluation of an asymptomatic heart murmur. In some dogs, clinical signs of CHF, episodic weakness, and/or syncope might be evident. Sudden death without premonitory signs can occur. Ventricular arrhythmias secondary to myocardial ischemia are presumed to cause the low-output signs and sudden death. A systolic murmur, related to either LV outflow obstruction or mitral insufficiency, can be heard on auscultation. The systolic ejection murmur of ventricular outflow obstruction becomes louder when ventricular contractility is increased (e.g., with exercise or excitement) or when afterload is reduced (e.g., from vasodilator use). An S_4 gallop sound is heard in some affected dogs.

Diagnosis

Echocardiography is the best diagnostic tool for HCM. LV hypertrophy (more commonly symmetric) and LA enlargement are characteristic findings. Mitral regurgitation might be evident on Doppler studies. Systolic anterior motion of the mitral valve often is present, indicating dynamic LV outflow obstruction. Other causes of LV hypertrophy to be ruled out include congenital subaortic stenosis, systemic hypertension, thyrotoxicosis, chronic phenylpropanolamine administration, and pheochromocytoma. Thoracic radiographs can indicate LA and LV enlargement, with or without pulmonary edema. Some cases appear radiographically normal. ECG findings might include ventricular tachyarrhythmias and conduction abnormalities, such as AV or bundle branch blocks. Criteria for LV enlargement are variably present.

Treatment and Prognosis

The general goals of HCM treatment are to enhance myocardial relaxation and ventricular filling, control pulmonary edema, and suppress arrhythmias. A β-blocker such as atenolol (see p. 93) commonly is used to lower heart rate, prolong ventricular filling time, reduce ventricular contractility, and minimize myocardial oxygen requirement. β-blockers also can reduce dynamic LV outflow obstruction and may suppress arrhythmias induced by heightened sympathetic activity. A Ca^{++}-channel blocker such as diltiazem could also be considered to decrease heart rate and facilitate myocardial relaxation, although such drugs are less commonly chosen due to their vasodilatory effects. If CHF occurs, furosemide and an ACEI are indicated; pimobendan could be considered, particularly if myocardial failure develops, although presence of LV outflow obstruction is a relative contraindication to positive inotropic therapy. Exercise restriction is advised in dogs with HCM.

Prognosis for canine HCM is variable. Although some dogs develop clinical signs and CHF and others experience

sudden death, many affected dogs live a normal life span with stable disease and minimal to no clinical signs. There also are reports of young dogs (most commonly terrier breeds) in which dynamic LV outflow tract obstruction, systolic anterior motion of the mitral valve, and LV hypertrophy are documented at a young age (less than 1 year), but echocardiographic changes spontaneously regress after the dog reaches adulthood. Some of these dogs were treated with β-blockers (usually atenolol), yet others received no treatment. It is unknown whether these cases represent a variant of congenital HCM in dogs or a transient physiologic process associated with aging.

MYOCARDITIS

A wide variety of agents can affect the myocardium, although disease manifestations in other organ systems may overshadow the cardiac involvement. The heart can be injured by direct invasion of the infective agent, by toxins it elaborates, or by the host's immune response. Noninfective causes of myocarditis include cardiotoxic drugs and drug hypersensitivity reactions. Myocarditis can cause persistent cardiac arrhythmias and progressively impair myocardial function.

INFECTIVE MYOCARDITIS

Etiology and Pathophysiology

Viral myocarditis

Lymphocytic myocarditis has been associated with acute viral infections in experimental animals and people. Cardiotropic viruses can play an important role in the pathogenesis of myocarditis and subsequent cardiomyopathy in several species, but this is not recognized commonly in dogs. The host animal's immune responses to viral and nonviral antigens contribute to myocardial inflammation and damage.

A syndrome of parvoviral myocarditis was recognized in the late 1970s and early 1980s. It is characterized by a peracute necrotizing myocarditis and sudden death (with or without signs of acute respiratory distress) in apparently healthy puppies about 4 to 8 weeks old. Cardiac dilation with pale streaks in the myocardium, gross evidence of CHF, large basophilic intranuclear inclusion bodies, myocyte degeneration, and focal mononuclear cell infiltrates are typical necropsy findings. This syndrome is uncommon now, probably as a result of maternal antibody production in response to virus exposure and vaccination. Parvovirus may cause a form of DCM in young dogs that survive neonatal infection; viral genetic material has been identified in some canine ventricular myocardial samples in the absence of classic intranuclear inclusion bodies.

Canine distemper virus may cause myocarditis in young puppies, but multisystemic signs usually predominate. Histologic changes in the myocardium are mild compared with those in the classic form of parvovirus myocarditis. Experimental herpesvirus infection of pups during gestation also causes necrotizing myocarditis with intranuclear inclusion bodies leading to fetal or perinatal death.

West Nile virus is uncommon in dogs but has been reported to cause severe lymphocytic and neutrophilic myocarditis and vasculitis, with areas of myocardial hemorrhage and necrosis. Vague clinical signs can include lethargy, poor appetite, arrhythmias, neurologic signs, and fever. Immunohistochemistry, reverse transcription polymerase chain reaction (RT-PCR), serology, and virus isolation have been used in diagnosis.

Bacterial myocarditis

Bacteremia and bacterial endocarditis or pericarditis can cause focal or multifocal suppurative myocardial inflammation or abscess formation. Localized infections elsewhere in the body may be the source of the organisms. Clinical signs include malaise, weight loss, and, inconsistently, fever. Arrhythmias and cardiac conduction abnormalities are common, but murmurs are rare unless concurrent valvular endocarditis or another underlying cardiac defect is present. Serial bacterial (or fungal) blood cultures, serology, or PCR may allow identification of the organism. Organisms reported to be implicated in bacterial myocarditis include *Staphylococcus, Streprotococcus, Citrobacter, Bacillus, Moraxella,* and others. *Bartonella vinsonii* subspecies have also been associated with cardiac arrhythmias, myocarditis, endocarditis, and sudden death. Serology and PCR using an enriched growth medium specific for *Bartonella* (*Bartonella* α Proteobacteria Growth Medium, BAPGM) are used for diagnosis.

Lyme carditis

Lyme disease (infection with the spirochete *Borrelia burgdorferi)* is often mentioned as a cause of myocarditis in dogs, although definitive diagnosis is rarely proven; systemic manifestations related to immune-complex deposition usually predominate (polyarthritis, glomerulonephritis, meningoencephalitis). The prevalence of this disease is higher in certain geographic areas, especially the northeastern, western coastal, and north central United States, as well as in Japan and Europe, among other areas. Lyme disease was the most common cause of canine myocarditis in a recent case series from Ireland. *Borrelia* is transmitted to dogs by ticks (especially *Ixodes* genus) and possibly other biting insects (see Chapter 69). High-grade AV block is the classic finding in dogs with Lyme disease. Syncope, CHF, reduced myocardial contractility, and ventricular arrhythmias are also reported in affected dogs. Pathologic findings of Lyme myocarditis include infiltrates of plasma cells, macrophages, neutrophils, and lymphocytes, with areas of myocardial necrosis. These are similar to findings in human Lyme carditis. A presumptive diagnosis is made on the basis of positive (or increasing) serum titers or a positive SNAP test and concurrent signs of myocarditis, with or without other systemic signs. Endomyocardial biopsy with immunohistochemical staining can confirm the diagnosis. Resolution of AV conduction block may or may not occur in dogs despite appropriate antimicrobial therapy, and temporary or permanent artificial pacing may be required.

Protozoal myocarditis

Trypanosoma cruzi, Toxoplasma gondii, Neosporum caninum, Babesia canis, Hepatozoon americanum, and *Leishmania* spp. are known to affect the myocardium (see p. 1525).

Trypanosomiasis (Chagas disease) is an important zoonosis in Central and South America; within the United States, the disease occurs mainly in young dogs in Texas, Louisiana, Oklahoma, Virginia, and other southern states. The possibility for human infection should be recognized; Chagas myocarditis is the most common cause of human cardiomyopathy in the world. The organism is transmitted by blood-sucking insects of the family Reduviidae and is enzootic in wild animals of the region. Amastigotes of *T. cruzi* cause myocarditis with a mononuclear cell infiltrate and disruption and necrosis of myocardial fibers. Acute, latent, and chronic phases of Chagas myocarditis have been described. The acute stage can involve lethargy, depression, and other systemic signs, as well as various tachyarrhythmias, AV conduction defects, or sudden death. Clinical signs are sometimes subtle. The disease is diagnosed in the acute stage by finding trypomastigotes in thick peripheral blood smears; the organism can be isolated in cell culture or by inoculation into mice. Animals that survive the acute phase enter a subclinical latent phase of variable duration. During this phase, the parasitemia resolves, and antibodies develop against both the organism and cardiac antigens. Chronic Chagas disease is characterized by progressive right-sided or generalized cardiomegaly and various arrhythmias. Ventricular tachyarrhythmias are most common, but supraventricular tachyarrhythmias may occur. Right bundle branch block and AV conduction disturbances are also reported. Ventricular dilation and reduced myocardial function are usually evident echocardiographically. End-stage disease is indistinguishable from idiopathic DCM, although the RV is generally preferentially affected in Chagas disease. Clinical signs of right-sided or biventricular failure are common, and sudden death can occur. Antemortem diagnosis in chronic cases is usually made with a combination of serologic testing and compatible clinical signs. Therapy in the acute stage is aimed at eliminating the organism and minimizing myocardial inflammation. Currently, the preferred treatment in both humans and dogs is benznidazole; in the United States, this drug is available only through the Centers for Disease Control and Prevention (CDC). In dogs with chronic Chagas disease, antiparasitic treatments do not affect outcome. Therapy is aimed at supporting myocardial function, controlling CHF, and suppressing arrhythmias. Prevention strategies in endemic areas include limiting contact with vectors and reservoirs, using insecticides, and screening canine blood donors.

Toxoplasmosis and neosporosis can cause clinical myocarditis in conjunction with generalized systemic infection, especially in the immunocompromised animal. The organism becomes encysted in the heart and various other body tissues after the initial infection. With rupture of these cysts, expelled bradyzoites induce hypersensitivity reactions and tissue necrosis. Other systemic signs, including encephalitis, pneumonia, and chorioretinitis, often overshadow signs of myocarditis. Diagnosis is based on serologic testing with rising antibody titers. Antiprotozoal therapy with clindamycin or trimethoprim sulfa is recommended.

Hepatozoon americanum, identified as a new species distinct from *Hepatozoon canis,* was originally found in dogs along the Texas coast but has a much wider range. Coyotes, rodents, and other wildlife are an important wild reservoir. Dogs become infected by ingesting the organism's tick host *(Amblyomma maculatum)* or through predation. Skeletal and cardiac muscles are the main tissues affected by *H. americanum.* A severe inflammatory reaction to merozoites released from ruptured tissue cysts leads to pyogranulomatous myositis and myocarditis. Clinical signs include stiffness, anorexia, fever, neutrophilia, periosteal new bone reaction, muscle atrophy, and often death.

Leishmaniosis, endemic in certain regions, can cause myocarditis, various arrhythmias, and pericardial effusion with cardiac tamponade, as well as other systemic and cutaneous signs. Babesiosis has also occasionally been reported to cause cardiac lesions in dogs, including myocardial hemorrhage, inflammation, and necrosis. Pericardial effusion and variable ECG changes may be noted.

Other causes

Rarely, fungi *(Aspergillus, Cryptococcus, Coccidioides, Blastomyces, Histoplasma, Paecilomyces, Inonota);* non-*Bartonella* rickettsiae *(Rickettsia rickettsii, Ehrlichia canis);* algae-like organisms (*Prototheca* spp.); and nematode larval migration (*Toxocara* spp.) cause myocarditis. Except for *Coccidioides immitis,* an important cause of pericarditis and pericardial effusion in the southwestern United States (see p. 1505), affected animals are usually immunosuppressed and have systemic signs of disease. Rocky Mountain spotted fever *(R. rickettsii)* occasionally causes fatal ventricular arrhythmias, along with necrotizing vasculitis, myocardial thrombosis, and ischemia.

NONINFECTIVE MYOCARDITIS

Occasionally myocarditis is diagnosed histopathologically with no obvious etiologic agent. Lymphocytic, lymphocytic-plasmacytic, and eosinophilic myocardial inflammation have been described with no infectious agents noted on histopathology or serologic screening. It is unknown whether myocarditis in these dogs is an immune-mediated or autoimmune process, or a response to an infectious agent that was not identifiable postmortem. Clinical findings in such cases often include high-grade AV block and sinus arrest, with sudden death being a common outcome.

Clinical Findings and Diagnosis

Unexplained onset of arrhythmias or CHF after a recent episode of infective disease or drug exposure is the classic clinical presentation of acute myocarditis. However, definitive diagnosis can be difficult because clinical and clinicopathologic findings are usually nonspecific and inconsistent. A database including complete blood count, serum biochemical profile with creatine kinase activity, serum cardiac troponin I (and NT-proBNP) concentration, thoracic and abdominal radiographs, and urinalysis are usually obtained. ECG changes may include an ST segment shift, T-wave or QRS voltage changes, AV conduction abnormalities, and

various other arrhythmias. Echocardiographic signs of poor regional or global ventricular systolic function, altered myocardial echogenicity, or pericardial effusion can be evident. In dogs with persistent fever, serial bacterial (or fungal) blood cultures could be useful. Serologic screening for specific infective causes might be helpful in some cases. Histopathologic criteria for a diagnosis of myocarditis include inflammatory infiltrates with myocyte degeneration and necrosis. Endomyocardial biopsy specimens are currently the only means of obtaining a definitive antemortem diagnosis, but if the lesions are focal, the findings may not be diagnostic.

Treatment

Unless a specific etiologic agent can be identified and treated, therapy for suspected myocarditis is largely supportive. Strict rest, antiarrhythmic drugs (see Chapter 4), therapy to support myocardial function and manage CHF signs (see Chapter 3), and other supportive measures are used as needed. Corticosteroids have not proven clinically beneficial in dogs with myocarditis and, considering the possible infective causes, are not recommended as nonspecific therapy. Exceptions would be confirmed immune-mediated disease, drug-related or eosinophilic myocarditis, or myocarditis unresponsive to other therapies. Nonsteroidal antiinflammatory drugs could be considered in some cases.

SEPSIS-INDUCED MYOCARDIAL DYSFUNCTION

Sepsis-induced myocardial dysfunction describes a syndrome of reversible myocardial depression that occurs in the setting of sepsis or other critical illness. This is a common and well-recognized phenomenon in human intensive care units and has also been described in dogs. The syndrome is characterized by ventricular dilation and systolic dysfunction (a DCM phenotype), and can involve both the LV and RV. Unlike idiopathic DCM, patients with sepsis-induced myocardial dysfunction have normal or even high cardiac output and low systemic vascular resistance. The underlying mechanisms are multifactorial and unclear but likely include release of proinflammatory cytokines, peroxynitrate toxicity, coronary hypoperfusion, catecholamine and calcium insensitivity, and mitochondrial or cytoskeletal abnormalities. Sepsis-induced myocardial dysfunction further compromises perfusion in patients with septic shock and can also lead to CHF. This syndrome is associated with worsened prognosis among humans with sepsis. Diagnosis is based on echocardiographic evidence of new LV dilation and systolic dysfunction in a critically ill patient. Cardiac biomarkers (particularly cardiac troponin I) can be used as screening tools to identify affected patients. Treatment involves inotropic support with either dobutamine or pimobendan, depending on the patient's level of hemodynamic compromise. If treatment for sepsis is successful and the patient survives the period of critical illness, ventricular size and function completely normalize (usually within 7-10 days).

Traumatic Myocarditis

Nonpenetrating or blunt trauma to the chest and heart is more common than penetrating wounds. Cardiac arrhythmias frequently are observed after such trauma. Cardiac damage can result from impact against the chest wall, compression, or acceleration-deceleration forces. Other possible mechanisms of myocardial injury and arrhythmogenesis include autonomic imbalance, ischemia, reperfusion injury, and electrolyte and acid-base disturbances. Thoracic radiographs, serum biochemistries, cardiac troponin I concentrations, ECG, and echocardiography are recommended in the assessment of these cases. Echocardiography can define preexisting heart disease, global myocardial function, and unexpected cardiovascular findings, but it may not identify small areas of myocardial injury.

Arrhythmias usually appear within 24 to 48 hours after trauma. VPCs, ventricular tachycardia, and accelerated idioventricular rhythm (with rates of 60-100 beats/min) are more common than supraventricular tachyarrhythmias or bradyarrhythmias in these patients. An accelerated idioventricular rhythm often is manifested only when the sinus rate slows; this rhythm is benign in most dogs with normal underlying heart function, does not require antiarrhythmic treatment, and disappears usually within a week of the trauma. More serious arrhythmias (e.g., with a faster rate) or hemodynamic deterioration may require antiarrhythmic therapy (see Chapter 4).

Avulsion of a papillary muscle, septal perforation, and rupture of the heart or pericardium have also been reported with cardiac trauma. Traumatic papillary muscle avulsion causes acute volume overload with acute onset of CHF. Signs of low-output failure and shock, as well as arrhythmias, can develop rapidly after cardiac trauma.

Suggested Readings

Primary Myocardial Disease

Baumwart RD, Orvalho J, Meurs KM. Evaluation of serum cardiac troponin I concentration in Boxers with arrhythmogenic right ventricular cardiomyopathy. *Am J Vet Res*. 2007;68:524–528.

Beddies G, et al. Comparison of the pharmacokinetic properties of bisoprolol and carvedilol in healthy dogs. *Am J Vet Res*. 2008;69:1659–1663.

Borgarelli M, et al. Prognostic indicators for dogs with dilated cardiomyopathy. *J Vet Intern Med*. 2006;20:104–110.

Calvert CA, et al. Results of ambulatory electrocardiography in overtly healthy Doberman Pinschers with echocardiographic abnormalities. *J Am Vet Med Assoc*. 2000;217:1328–1332.

Calvert CA, et al. Association between result of ambulatory electrocardiography and development of dilated cardiomyopathy during long-term follow-up of Doberman Pinschers. *J Am Vet Med Assoc*. 2000;216:34–39.

Cunningham SM, et al. Echocardiographic ratio indices in overtly healthy Boxer dogs screened for heart disease. *J Vet Intern Med*. 2008;22:924–930.

Dukes-McEwan J, et al. Proposed guidelines for the diagnosis of canine idiopathic dilated cardiomyopathy. *J Vet Cardiol*. 2003;5:7–19.

Falk T, Jonsson L. Ischaemic heart disease in the dog: a review of 65 cases. *J Small Anim Pract*. 2000;41:97–103.

Fine DM, Tobias AH, Bonagura JD. Cardiovascular manifestations of iatrogenic hyperthyroidism in two dogs. *J Vet Cardiol*. 2010;12:141–146.

Freeman LM, et al. Relationship between circulating and dietary taurine concentration in dogs with dilated cardiomyopathy. *Vet Ther*. 2001;2:370–378.

Fuentes VL, et al. A double-blind, randomized, placebo-controlled study of pimobendan in dogs with dilated cardiomyopathy. *J Vet Intern Med*. 2002;16:255–261.

Maxson TR, et al. Polymerase chain reaction analysis for viruses in paraffin-embedded myocardium from dogs with dilated cardiomyopathy or myocarditis. *Am J Vet Res*. 2001;62:130–135.

Meurs KM, et al. A prospective genetic evaluation of familial dilated cardiomyopathy in the Doberman Pinscher. *J Vet Intern Med*. 2007;21:1016–1020.

Meurs KM, et al. Genome-wide association identifies a deletion in the 3′ untranslated region of striatin in a canine model of arrhythmogenic right ventricular cardiomyopathy. *Hum Genet*. 2010;128:315–324.

Meurs KM, Miller MW, Wright NA. Clinical features of dilated cardiomyopathy in Great Danes and results of a pedigree analysis: 17 cases (1990-2000). *J Am Vet Med Assoc*. 2001;218:729–732.

Meurs KM, et al. Natural history of Arrhythmogenic Right Ventricular Cardiomyopathy in the Boxer dog: a prospective study. *J Vet Intern Med*. 2014;28:1214–1220.

Meurs KM, et al. Association of dilated cardiomyopathy with the striatin mutation genotype in Boxer dogs. *J Vet Intern Med*. 2013;27:1437–1440.

Motskula PF, et al. Prognostic value of 24-hour ambulatory ECG (Holter) monitoring in Boxer dogs. *J Vet Intern Med*. 2013;27:904–912.

O'Grady MR, et al. Effect of pimobendan on case fatality rate in Doberman Pinschers with congestive heart failure caused by dilated cardiomyopathy. *J Vet Intern Med*. 2008;22:897–904.

O'Sullivan ML, O'Grady MR, Minors SL. Plasma big endothelin-1, atrial natriuretic peptide, aldosterone, and norepinephrine concentrations in normal Doberman Pinschers and Doberman Pinschers with dilated cardiomyopathy. *J Vet Intern Med*. 2007;21:92–99.

O'Sullivan ML, O'Grady MR, Minors SL. Assessment of diastolic function by Doppler echocardiography in normal Doberman Pinschers and Doberman Pinschers with dilated cardiomyopathy. *J Vet Intern Med*. 2007;21:81–91.

Oyama MA, et al. Carvedilol in dogs with dilated cardiomyopathy. *J Vet Intern Med*. 2007;21:1272–1279.

Scansen BA, et al. Temporal variability of ventricular arrhythmias in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med*. 2009;23:1020–1024.

Singletary GE, et al. Prospective evaluation of NT-proBNP assay to detect occult dilated cardiomyopathy and predict survival in Doberman Pinschers. *J Vet Intern Med*. 2012;26:1330–1336.

Sleeper MM, et al. Dilated cardiomyopathy in juvenile Portuguese Water Dogs. *J Vet Intern Med*. 2002;16:52–62.

Smith CE, et al. Omega-3 fatty acids in Boxers with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med*. 2007;21:265–273.

Spier AW, Meurs KM. Evaluation of spontaneous variability in the frequency of arrhythmias in boxers with arrhythmogenic right ventricular cardiomyopathy. *J Am Vet Med Assoc*. 2004;224:538–541.

Stern JA, et al. Ambulatory electrocardiographic evaluation of clinically normal adult Boxers. *J Am Vet Med Assoc*. 2010;236:430–433.

Summerfield NJ, et al. Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman Pinschers with preclinical dilated cardiomyopathy (the PROTECT study). *J Vet Intern Med*. 2012;26:1337–1349.

Tidholm A, Jonsson L. Histologic characterization of canine dilated cardiomyopathy. *Vet Pathol*. 2005;42:1–8.

Thomason JD, et al. Bradycardia-associated syncope in seven Boxers with ventricular tachycardia (2002-2005). *J Vet Intern Med*. 2008;22:931–936.

Vollmar AC, Fox PR. Long-term outcome of Irish Wolfhound dogs with preclinical cardiomyopathy, atrial fibrillation, or both treated with pimobendan, benazepril hydrochloride, or methyldigoxin monotherapy. *J Vet Intern Med*. 2016;30:553–559.

Wess G, et al. Evaluation of N-terminal pro-B-type natriuretic peptide as a diagnostic marker of various stages of cardiomyopathy in Doberman Pinschers. *Am J Vet Res*. 2011;72:642–649.

Wess G, et al. Prevalence of dilated cardiomyopathy in Doberman pinschers in various age groups. *J Vet Intern Med*. 2010;24:533–538.

Wess G, et al. Ability of a 5-minute electrocardiography (ECG) for predicting arrhythmias in Doberman Pinschers with cardiomyopathy in comparison with a 24-hour ambulatory ECG. *J Vet Intern Med*. 2010;24:367–371.

Wess G, et al. Cardiac troponin I in Doberman Pinschers with cardiomyopathy. *J Vet Intern Med*. 2010;24:843–849.

Myocarditis and Secondary Cardiomyopathies

Barr SC. Canine Chagas' disease (American trypanosomiasis) in North America. *Vet Clin North Am Small Anim Pract*. 2009;39:1055–1064.

Bradley KK, et al. Prevalence of American trypanosomiasis (Chagas disease) among dogs in Oklahoma. *J Am Vet Med Assoc*. 2000;217:1853–1857.

Breitschwerdt EB, et al. Bartonellosis: an emerging infectious disease of zoonotic importance to animal and human beings. *J Vet Emerg Crit Care*. 2010;20:8–30.

Calvert CA, Thomason JD. Cardiovascular infections. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 4th ed. St Louis: Elsevier; 2012:912.

Cannon AB, et al. Acute encephalitis, polyarthritis, and myocarditis associated with West Nile virus infection in a dog. *J Vet Intern Med*. 2006;20:1219–1223.

Church WM, et al. Third degree atrioventricular block and sudden death secondary to acute myocarditis in a dog. *J Vet Cardiol*. 2006;9:53–57.

Costa ND, Labuc RH. Case report: efficacy of oral carnitine therapy for dilated cardiomyopathy in Boxer dogs. *J Nutr*. 1994;124:2687S–2692S.

Dvir E, et al. Electrocardiographic changes and cardiac pathology in canine babesiosis. *J Vet Cardiol*. 2004;6:15–23.

Fascetti AJ, et al. Taurine deficiency in dogs with dilated cardiomyopathy: 12 cases (1997-2001). *J Am Vet Med Assoc*. 2003;223:1137–1141.

Fitzpatrick WM, Dervisis NG, Kitchell BE. Safety of concurrent administration of dexrazoxane and doxorubicin in the canine cancer patient. *Vet Comp Oncol*. 2010;8:273–282.

Fritz CL, Kjemtrup AM. Lyme borreliosis. *J Am Vet Med Assoc*. 2003;223:1261–1270.

Gillings SL, et al. Effect of 1-hour IV infusion of doxorubicin on the development of cardiotoxicity in dogs as evaluated by electrocardiography and echocardiography. *Vet Ther*. 2009;10:46–58.

Janus I, et al. Myocarditis in dogs: etiology, clinical and histopathological features (11 cases: 2007-2013). *Ir Vet J*. 2014;67:28.

Kaneshige T, et al. Complete atrioventricular block associated with lymphocytic myocarditis of the atrioventricular node in two young adult dogs. *J Comp Pathol*. 2007;137:146–150.

Keeshen TP, Chalkley M, Stauthammer C. A case of unexplained eosinophilic myocarditis in a dog. *J Vet Cardiol*. 2016;18:278–283.

Kittleson MD, et al. Results of the multicenter spaniel trial (MUST): taurine- and carnitine-responsive dilated cardiomyopathy in American cocker spaniels with decreased plasma taurine concentration. *J Vet Intern Med*. 1997;11:204–211.

Kjos SA, et al. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. 2007;152:249–256.

Mauldin GE, et al. Doxorubicin-induced cardiotoxicosis: clinical features in 32 dogs. *J Vet Intern Med*. 1992;6:82–88.

Nelson OL, Thompson PA. Cardiovascular dysfunction in dogs associated with critical illnesses. *J Am Anim Hosp Assoc*. 2006;42: 344–349.

Ratterree W, et al. Value of echocardiography and electrocardiography as screening tools prior to doxorubicin administration. *J Am Anim Hosp Assoc*. 2012;48:89–96.

Saunders AB, et al. Bradyarrhythmias and pacemaker therapy in dogs with Chagas disease. *J Vet Intern Med*. 2013;27:890–894.

Schmiedt C, et al. Cardiovascular involvement in 8 dogs with *Blastomyces dermatitidis* infection. *J Vet Intern Med*. 2006;20: 1351–1354.

Wright KN, et al. Radiofrequency catheter ablation of atrioventricular accessory pathways in 3 dogs with subsequent resolution of tachycardia-induced cardiomyopathy. *J Vet Intern Med*. 1999;13:361–371.

CHAPTER 8

Myocardial Diseases of the Cat



Myocardial disease in cats encompasses a diverse collection of idiopathic and secondary processes affecting the myocardium. The spectrum of anatomic and pathophysiologic features is wide. Disease characterized by myocardial hypertrophy is most common, although features of multiple pathophysiologic categories coexist in some cats. Restrictive pathophysiology often develops. Classic dilated cardiomyopathy (DCM) is now uncommon in cats; its features are similar to those of DCM in dogs (see Chapter 7). Myocardial disease in some cats does not fit neatly into the categories of hypertrophic, dilated, or restrictive cardiomyopathy (RCM), and therefore it is considered "unclassified" cardiomyopathy. Rarely, arrhythmogenic right ventricular cardiomyopathy (ARVC) is identified in cats. In contrast to dogs, arterial thromboembolism is a major complication in cats with myocardial disease (see Chapter 12).

HYPERTROPHIC CARDIOMYOPATHY

Etiology

The cause of primary or idiopathic hypertrophic cardiomyopathy (HCM) in cats is unknown, but a heritable abnormality is likely in many cases. Autosomal dominant inheritance has been identified in the Maine Coon, Ragdoll, Sphynx, and American Shorthair breeds. Disease prevalence is high in other breeds as well, including British Shorthairs, Norwegian Forest Cats, Scottish Folds, Bengals, Siberians, and Rex. There also are reports of HCM in littermates and other closely related domestic shorthair cats. In human familial HCM, many different genetic mutations involving sarcomeric proteins have been identified.

Two separate mutations in the cardiac myosin binding protein C gene have been associated with HCM in cats, one in Maine Coon cats and one in Ragdolls. However, these mutations exhibit incomplete penetrance and variable expressivity. Prevalence of the mutation in Maine Coons has been estimated at approximately 30% to 40%, with some geographic variation. Maine Coon cats homozygous for the mutation are likely to develop HCM (penetrance approximately 70%-80%), whereas heterozygotes are much less commonly affected. The prevalence of the Ragdoll mutation is estimated at approximately 20% to 30%, and Ragdoll cats homozygous for the mutation frequently are severely affected with HCM at an early age (often less than 2 years). The discrepancy in phenotype between homozygous and heterozygous cats suggests a "partial" or "incomplete" dominance pattern. Besides the two identified mutations, other mutations are likely involved because not all cats with evidence for HCM have the identified breed-specific mutation. Testing for these mutations is available and can be particularly helpful in directing breeding programs (contact https://cvm.ncsu.edu/genetics/).

In addition to mutations of genes that encode for myocardial contractile or regulatory proteins, possible causes of the disease include an increased myocardial sensitivity to or excessive production of catecholamines; an abnormal hypertrophic response to myocardial ischemia, fibrosis, or trophic factors; a primary collagen abnormality; and abnormalities of the myocardial calcium-handling process. Cats with HCM are skeletally larger and may be more likely to be obese compared with cats without HCM, possibly suggesting a role of early growth and nutrition in development of cardiomyopathy. Some cats with HCM have high serum growth hormone and insulin-like growth factor-1 (IGF-1) concentrations. Myocardial hypertrophy with foci of mineralization occurs in cats with hypertrophic feline muscular dystrophy, an X-linked recessive dystrophin deficiency similar to Duchenne muscular dystrophy in people; however, congestive heart failure (CHF) is uncommon in these cats. It is not clear whether viral myocarditis has a role in the pathogenesis of feline cardiomyopathy.

Pathophysiology

Abnormal sarcomere function is thought to underlie activation of abnormal cell signaling processes that eventually produce myocyte hypertrophy and disarray, as well as increased collagen synthesis. The characteristic result is thickening of the left ventricular (LV) wall and/or interventricular septum, but the extent and distribution of

hypertrophy in cats with HCM are variable. Many cats have symmetric hypertrophy, but some have asymmetric septal thickening, and a few have hypertrophy limited to the free wall or papillary muscles. The LV lumen usually appears small. Focal or diffuse areas of fibrosis occur within the endocardium, conduction system, or myocardium. Narrowing of small intramural coronary arteries is commonly noted and probably contributes to ischemia-related fibrosis. Areas of myocardial infarction and myocardial fiber disarray can be present. Cats with pronounced systolic anterior motion (SAM) of the anterior mitral leaflet could have a fibrous endocardial patch on the interventricular septum (IVS) where repeated valve contact has occurred.

Myocardial hypertrophy and the accompanying changes increase ventricular wall stiffness. Additionally, early active myocardial relaxation may be slow and incomplete, especially in the presence of myocardial ischemia or abnormal Ca^{++} kinetics. This further reduces ventricular distensibility and promotes diastolic dysfunction. The increased ventricular stiffness impairs LV filling and increases diastolic pressure. LV volume remains normal or decreased. Reduced ventricular volume results in a lower stroke volume, which may contribute to neurohormonal activation. Higher heart rates further interfere with LV filling, promote myocardial ischemia, and contribute to pulmonary venous congestion and edema by shortening the diastolic filling period. Contractility, or systolic function, usually is normal in cats with HCM. However, some cats experience progression to ventricular systolic failure and dilation.

Higher LV filling pressures lead to increased left atrial (LA) and pulmonary venous pressures. Progressive LA dilation, as well as pulmonary congestion and edema, can result. LA enlargement can become massive over time. Intracardiac thrombi can form, usually within the left auricle but occasionally in the body of the left atrium (LA) or left ventricle (LV), or attached to a ventricular wall. Arterial thromboembolism is a major complication of HCM and other forms of cardiomyopathy in cats (see Chapter 12). Mitral regurgitation develops in some affected cats and usually is associated with changes in LV geometry, abnormal papillary muscle structure, and/or mitral SAM that prevent complete valve closure. Valve insufficiency exacerbates increases in LA size and pressure.

Dynamic LV outflow obstruction occurs during systole in some cats with HCM. This variant is known as *hypertrophic obstructive cardiomyopathy* (HOCM). LV papillary muscle hypertrophy and abnormal LV or mitral valve geometry are thought to produce abnormal hemodynamic forces that pull the anterior mitral leaflet toward the IVS during ejection (SAM; see echocardiography images later). Excessive asymmetric hypertrophy of the basilar IVS can contribute to the dynamic obstruction. Both mitral valve SAM and basilar IVS hypertrophy can interfere with normal LV outflow. Systolic outflow obstruction increases LV pressure, wall stress, and myocardial oxygen demand and promotes myocardial ischemia as well as LV hypertrophy. SAM also causes or exacerbates mitral regurgitation. Increased LV outflow turbulence often causes an ejection murmur of variable intensity in these cats. Cats with HOCM are thus more likely to have heart murmurs than cats with nonobstructive HCM. A diastolic gallop sound (usually S_4) might be heard, associated with high LV filling pressure.

Several factors probably contribute to the development of myocardial ischemia in cats with HCM. These include narrowing of intramural coronary arteries, increased LV filling pressure, decreased coronary artery perfusion pressure, and insufficient myocardial capillary density for the degree of hypertrophy. Tachycardia contributes to ischemia by increasing myocardial O_2 requirements while reducing diastolic coronary perfusion time. Ischemia impairs early active ventricular relaxation, which further increases ventricular filling pressure, and over time leads to myocardial fibrosis. Ischemia can provoke arrhythmias and, potentially, sudden death.

If present, atrial fibrillation (AF) and other tachyarrhythmias further impair diastolic filling and exacerbate venous congestion; the loss of the atrial "kick" and the rapid heart rate associated with AF are especially detrimental. Ventricular tachycardia or other arrhythmias can lead to syncope or sudden death.

Eventually, pulmonary venous congestion and edema result from increasing LA pressure. Cavitary effusions also occur commonly in cats with HCM and CHF; in addition to pulmonary edema, approximately half of cats develop pleural effusion, and nearly 25% of cats have mild pericardial effusion. These effusions usually are modified transudates, although they can be (or become) chylous. These cavitary effusions, usually associated with right-sided CHF, often occur despite echocardiographic appearance of predominately left heart involvement. This pattern of fluid distribution could relate to feline-specific patterns of lymphatic drainage of body cavities, could suggest postcapillary pulmonary hypertension with reactive vasoconstriction, or might represent underdiagnosis of right heart dysfunction in HCM. Recent evidence suggests that up to 30% to 50% of cats with HCM may have right heart involvement, characterized by segmental or diffuse right ventricular hypertrophy and right atrial (RA) dilation. Cats that manifest CHF with pleural effusion have decreased LA function and larger RA volumes compared with cats that develop pulmonary edema exclusively.

Clinical Features

HCM is most commonly identified in middle-aged cats, with an average age at diagnosis of approximately 6 years; however, diagnosis at any age is possible. The disease has a male sex predilection. Overall prevalence of HCM in cats is estimated to be at least 15% and increases with age. Affected cats have a relatively long occult period before development of clinical disease. Many cats are not diagnosed until complications arise. The natural history of HCM is highly variable among cats. Some cats have relatively mild hypertrophy that does not worsen or cause clinical disease during the cat's lifetime. Other cats have more rapidly progressive disease. The overall median survival time for cats diagnosed with

asymptomatic HCM is estimated at 5 years. Between 20% to 40% of cats diagnosed with HCM will eventually develop CHF; between 5% to 10% suffer an arterial thromboembolism; and approximately 20% of cats with HCM experience sudden cardiac death.

Subclinical (occult) HCM can be detected using echocardiography. However, echocardiography is typically only undertaken in cats where a murmur, arrhythmia, or gallop sound is heard on routine examination. Heart murmur prevalence in apparently healthy cats ranges from 20% to more than 40% (see p. 11). Among cats with heart murmurs, the reported prevalence of HCM based on echocardiography has ranged from about 33% to more than 50%. Conversely, among cats diagnosed echocardiographically with HCM, the prevalence of heart murmurs varies from 30% to 80% in different reports. Most murmurs in HCM are caused by dynamic left ventricular outflow tract (LVOT) obstruction. Murmur auscultation is thus a crude screening test for subclinical HCM, and tends to preferentially identify cats with HOCM yet missing cases of nonobstructive HCM.

Symptomatic cats most often are presented for respiratory signs (indicating CHF) or acute thromboembolism (see p. 224). Respiratory signs include tachypnea, open-mouth breathing associated with activity, or dyspnea; unlike in dogs, coughing is an uncommon clinical sign of CHF in cats. Disease onset can seem acute in sedentary cats, even though pathologic changes have developed gradually. Occasionally, lethargy or anorexia is the only evidence of CHF. Some cats have syncope or sudden death in the absence of other signs. Stresses such as anesthesia, surgery, fluid administration, systemic illnesses (e.g., fever, anemia), recent injection of long-acting corticosteroids, or boarding can precipitate CHF in an otherwise compensated cat.

RADIOGRAPHY

Diagnosis

Although the cardiac silhouette appears normal in most cats with mild HCM, radiographic features of advanced HCM include prominent LA and variable LV enlargement (Fig. 8.1, *A* and *B*). Radiographically apparent LA enlargement generally occurs only when echocardiographic measurements suggest severe LA enlargement (ratio of LA to aortic size > 2.0). The classic valentine-shaped appearance of the heart on dorsoventral or ventrodorsal views is not always present, although usually the point of the LV apex is maintained. Vertebral heart score (VHS) can be useful when differentiating cardiac versus noncardiac causes of respiratory distress in cats; VHS of > 9.3v suggests significant heart disease (normal VHS in cats is about 7.5v). Enlarged and tortuous pulmonary veins might be noted in cats with chronically high LA and pulmonary venous pressure. However, the pattern of pulmonary vascular change is inconsistent in feline CHF; pulmonary artery enlargement reportedly occurs in approximately two thirds of cats with CHF and may be even more common than lobar vein enlargement. Left-sided CHF produces variable degrees of patchy interstitial or alveolar pulmonary edema infiltrates (Fig. 8.1, *C* and *D*). The radiographic distribution of pulmonary edema is variable; a diffuse or multifocal distribution throughout the lung fields is common, in contrast to the characteristic perihilar distribution of cardiogenic pulmonary edema seen in dogs. Pleural effusion also is common (Fig. 8.1, *E* and *F*).

ELECTROCARDIOGRAPHY

Most cats with HCM have an underlying normal sinus rhythm. Sinus tachycardia is common in hospital environments; either sinus tachycardia or bradycardia can occur in cats with CHF. Electrocardiogram (ECG) complex abnormalities that can be seen in cats with HCM include criteria for LA or LV enlargement and a left anterior fascicular block pattern (see Fig. 8.2 and Chapter 2). Occasional ventricular arrhythmias are common. A small study of Holter monitoring in cats showed that all cats with asymptomatic HCM had at least 1 ventricular premature complex (VPC) per day, though the overall number of VPCs was relatively low (geometric mean of 124 ventricular complexes/24 hours). More clinically significant arrhythmias such as AF or high-grade AV block can occur in cats with severe HCM (often with concurrent CHF). An ECG is too insensitive to be useful as a screening test for HCM but can be useful to characterize concurrent arrhythmias.

ECHOCARDIOGRAPHY

Echocardiography is the best means of diagnosis and differentiation of HCM from other disorders. The extent of hypertrophy and its distribution within the ventricular wall, septum, and papillary muscles is shown by two-dimensional (2-D) and M-mode echo studies (Fig. 8.3). Doppler techniques can demonstrate LV diastolic or systolic abnormalities. Widespread myocardial thickening is common, and the hypertrophy is often asymmetrically distributed among various LV wall, septal, and papillary muscle locations. Focal areas of hypertrophy also occur. Use of 2-D–guided M-mode echocardiography helps ensure proper beam position. Standard M-mode views and measurements are obtained, but thickened areas outside these standard positions also should be measured (using 2-D or perpendicularly aligned M-mode images). The 2-D right parasternal long-axis view is useful for measuring basilar IVS thickness. The diagnosis of early disease may be questionable in cats with mild or only focal thickening. Falsely increased thickness measurements (pseudohypertrophy) can occur with dehydration and sometimes tachycardia. Spurious diastolic thickness measurements also arise when the beam does not transect the wall/septum perpendicularly, when the septal tricuspid leaflet is included in the IVS measurement, or when the measurement is not taken at the end of diastole, as can happen without simultaneous ECG recording or when using 2-D imaging of insufficient frame rate. A (properly obtained) end-diastolic LV wall or septal thickness greater than 6.0 mm is considered diagnostic for LV hypertrophy in cats, though a thickness of 5.5 to 5.9 mm is likely abnormal except in cats of very large body size. Cats with severe HCM can have diastolic LV wall or

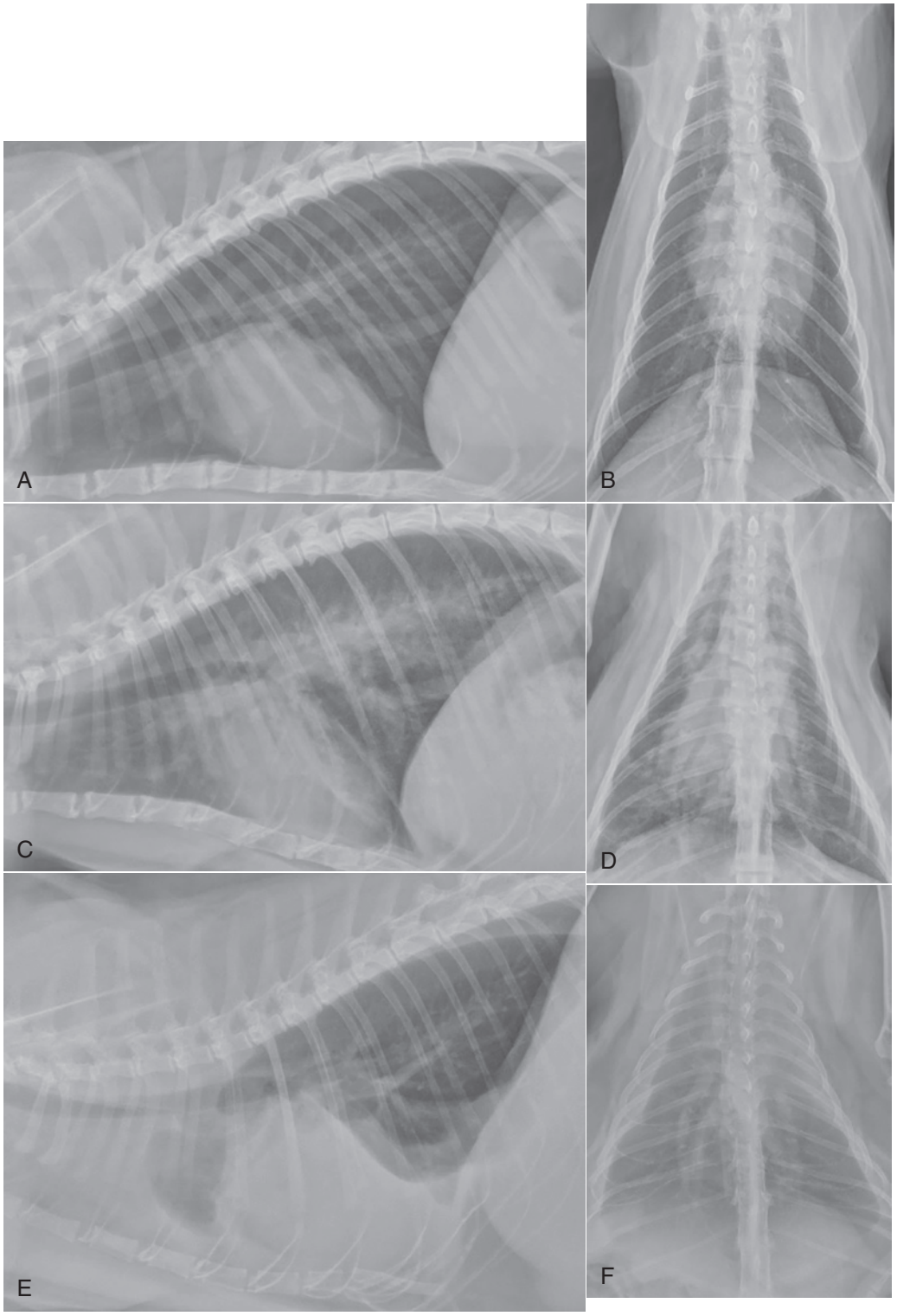


FIG 8.1
Radiographic examples of feline hypertrophic cardiomyopathy. Lateral **(A)** and dorsoventral **(B)** views showing mild cardiomegaly in a male domestic shorthair cat with hypertrophic cardiomyopathy. Lateral **(C)** and dorsoventral **(D)** views of the same cat during an episode of congestive heart failure, demonstrating patchy multifocal pulmonary edema and distension of both pulmonary arteries and veins. Lateral **(E)** and dorsoventral **(F)** views of a domestic longhair cat with hypertrophic cardiomyopathy and congestive heart failure, manifesting as pleural effusion.

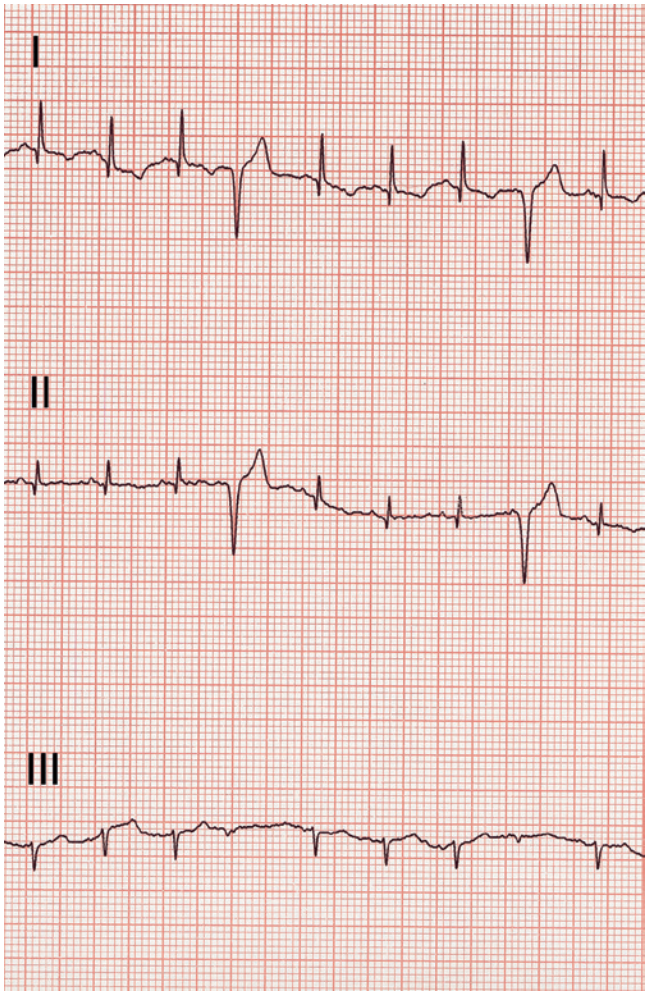


FIG 8.2
Electrocardiogram from a cat with hypertrophic cardiomyopathy showing occasional ventricular premature complexes and a left axis deviation. Leads I, II, III, at 25 mm/sec. 1 cm = 1 mV.

septal thicknesses of 8 mm or more, although the degree of hypertrophy is not necessarily correlated with the severity of clinical signs. Papillary muscle hypertrophy can be marked, and systolic LV cavity obliteration is observed in some cats with HCM. Increased echogenicity (brightness) of papillary muscles and subendocardial areas is thought to be a marker for chronic myocardial ischemia, with resulting fibrosis.

LV fractional shortening (FS) generally is normal to increased. However, some cats have mild to moderate LV dilation and reduced contractility (FS ≈ 23%-29%; normal FS is 35%-65%). Some cats eventually develop "end-stage" or "remodeled" HCM, where chronic severe ischemia and fibrosis lead to areas of LV wall thinning and reduced contractility. Echocardiographically, such cases can be difficult to distinguish from RCM or DCM, as LV hypertrophy becomes less dramatic. Excessive moderator bands (also known as "false tendons") appear as bright linear echoes spanning the LV cavity in various configurations. The functional significance of these moderator bands is unclear, but they seem to occur more commonly in cats with HCM compared with cats without structural heart disease. Although LV changes predominate, 30% to 50% of cats with HCM can have at least segmental RV hypertrophy, and some cats have RA dilation as well.

LA enlargement in cats with HCM can range from mild to marked (see Chapter 2 and Figs. 8.3, *A* and *D*, and 8.4). Prominent LA enlargement is expected in cats with clinical signs of CHF. Spontaneous echocontrast (swirling, smoky echoes) is visible within the enlarged LA of some cats. This is thought to result from blood stasis with cellular aggregations, and to be a harbinger of thromboembolism. A thrombus occasionally is visualized within the LA, usually in the auricle (see Fig. 8.4).

Cats with dynamic LV outflow tract obstruction often have SAM of the mitral valve (Fig. 8.5) or premature closure of the aortic valve leaflets on M-mode scans. Abnormalities of the mitral valve apparatus, including increased papillary muscle hypertrophy and anterior mitral leaflet length, have been associated with SAM and severity of dynamic LV outflow obstruction. Doppler modalities can demonstrate mitral regurgitation and LV outflow turbulence (Fig. 8.6). Continuous-wave Doppler can be used to demonstrate high-velocity and late-peaking blood flow through the LV outflow tract, confirming the dynamic obstruction. The left apical five-chamber view may be most useful.

Doppler-derived estimates of diastolic function are now routinely employed to define disease characteristics in HCM. Pulsed wave (PW) Doppler may show a delayed relaxation mitral inflow pattern (E wave:A wave velocity < 1) or evidence for more advanced diastolic dysfunction. Prolonged isovolumic relaxation time is associated with early diastolic dysfunction. Tissue Doppler imaging of the lateral or septal mitral valve annulus can detect reduced early annular motion in diastole, another hallmark of diastolic dysfunction. However, the rapid heart rate in many cats, as well as changes in loading conditions, often confounds accurate assessment of diastolic function.

Other causes of myocardial hypertrophy, particularly systemic hypertension and hyperthyroidism (see p. 167), should be excluded before a diagnosis of idiopathic HCM is made. Myocardial thickening in cats also can result from infiltrative disease (such as lymphoma). Variation in myocardial echogenicity or wall irregularities may be noted in such cases.

Clinicopathologic Findings

Routine clinical pathology tests often are noncontributory. The pleural effusion in cats with CHF usually is a modified transudate, although it can be chylous. Circulating cardiac troponins are higher in cats with moderate to severe HCM compared with unaffected cats, but low sensitivity and specificity limit diagnostic value of this test. NT-proBNP testing has proven diagnostically useful in two clinical settings involving HCM. First, elevated NT-proBNP (performed on blood or pleural fluid) can discriminated between CHF and noncardiac disease in cats presenting with respiratory distress. Various studies have identified diagnostic cutoff values

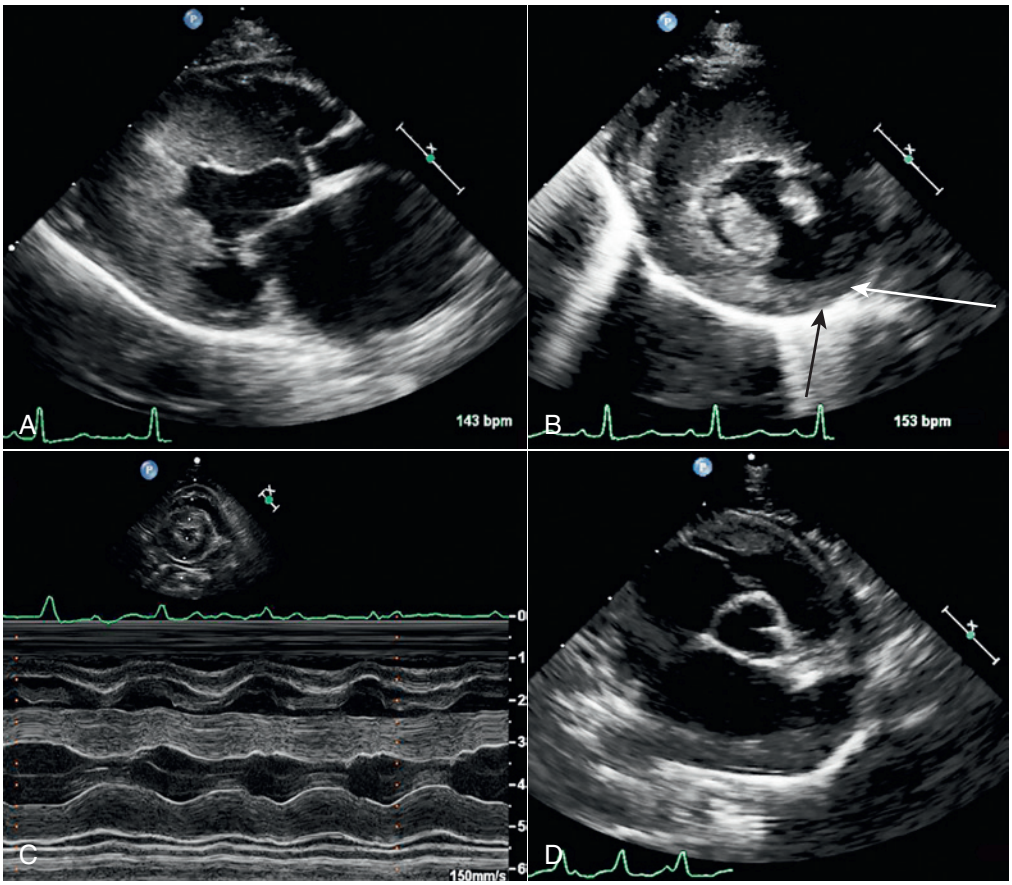


FIG 8.3
Echocardiographic examples of feline hypertrophic cardiomyopathy. Right parasternal four-chamber long-axis view **(A)** and short-axis view at the level of the left ventricular papillary muscles **(B)** from a 2-year-old male domestic longhair cat. The left ventricular free-wall and septal thicknesses are about 8 mm. There is a focal area of wall thinning in the basilar free wall (*arrows*), likely representing an area of previous infarction, and papillary muscle hypertrophy. Severe left atrial enlargement is also noted. M-mode image of the left ventricle **(C)** in a 3-year-old male domestic shorthair cat with hypertrophic cardiomyopathy and congestive heart failure. Thickening of the interventricular septum and left ventricular free wall are seen, as well as small volume pleural end pericardial effusion. Two-dimensional right parasternal short-axis view at the level of the heart base **(D)** in an 8-year-old male domestic shorthair cat with moderate left atrial enlargement. *Ao,* Aortic root; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVPW,* left ventricular posterior (free) wall; *RA,* right atrium; *RV,* right ventricle.

of 212 to 258 pmol/L, resulting in sensitivity and specificity of approximately 90%. A point-of-care test (SNAP proBNP, IDEXX Laboratories) has been developed for this purpose, with visual positive test result at >200 pmol/L. The other setting in which NT-proBNP has proven helpful is as a "second-line screening" test for cats with abnormal cardiovascular physical examination findings (heart murmur or arrhythmia). In this context, an elevated NT-proBNP (using a lower cutoff value than the SNAP test) can raise index of suspicion for HCM, helping to prioritize the value of echocardiography for a particular cat. A cutoff value of greater than 46 pmol/L had 86% sensitivity and 91% specificity for detecting occult HCM in one study. In other words, NT-proBNP elevation can increase clinical suspicion for HCM in an otherwise healthy cat with a heart murmur from ~30% to 50% (based on murmur alone) to more than 90%. However, as false positives occur, echocardiography is recommended for definitive diagnosis.

SUBCLINICAL HYPERTROPHIC CARDIOMYOPATHY (STAGE B DISEASE)

Treatment

Whether (and how) asymptomatic cats should be treated is controversial. It is unclear if disease progression can be slowed or survival prolonged by medical therapy before the onset of clinical signs. Various small studies using a β-blocker, diltiazem, an angiotensin-converting enzyme

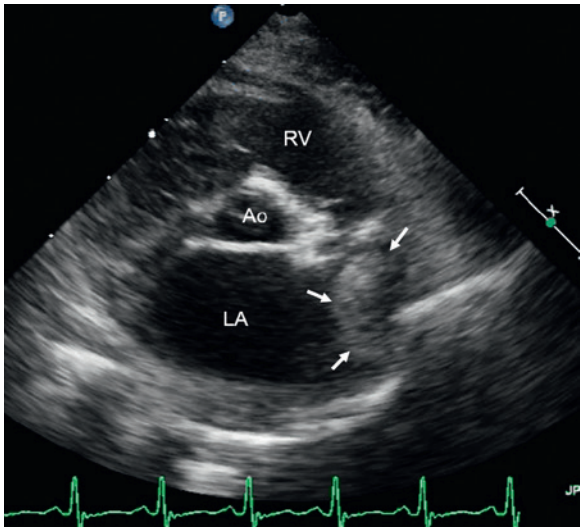


FIG 8.4
Right parasternal short-axis echocardiographic image obtained at the level of the heart base in a 5-year-old female domestic shorthair cat with hypertrophic cardiomyopathy. Note the massive left atrial enlargement and thrombus *(arrows)* within the auricle. *Ao,* Aorta; *LA,* left atrium; *RV,* right ventricle.

inhibitor (ACEI), or spironolactone have been performed, but clear benefit from any of these interventions has yet to be proven. With this in mind, some clinicians still suggest using a β-blocker in cats with evidence of substantial dynamic LV outflow obstruction or arrhythmias. In cats with marked, nonobstructive myocardial hypertrophy, particularly with evidence of myocardial fibrosis and remodeling, an ACEI might be suggested. For cats with LA enlargement, especially with spontaneous echocontrast, instituting antithrombotic prophylaxis with clopidogrel is prudent (see Chapter 12).

Avoidance of stressful situations likely to cause persistent tachycardia and reevaluation on a semiannual or annual basis are usually advised. Secondary causes of myocardial hypertrophy, such as systemic arterial hypertension and hyperthyroidism, should be ruled out (or treated, if found).

CONGESTIVE HEART FAILURE (STAGE C DISEASE)

Goals of therapy are to enhance ventricular filling, relieve congestion, control arrhythmias, minimize ischemia, and prevent thromboembolism (Box 8.1). Furosemide is used only at the dosage needed to help control congestive signs for long-term therapy. Moderate to severe pleural effusion is treated by thoracocentesis, with the cat restrained gently in sternal position (and sedated with butorphanol if needed).

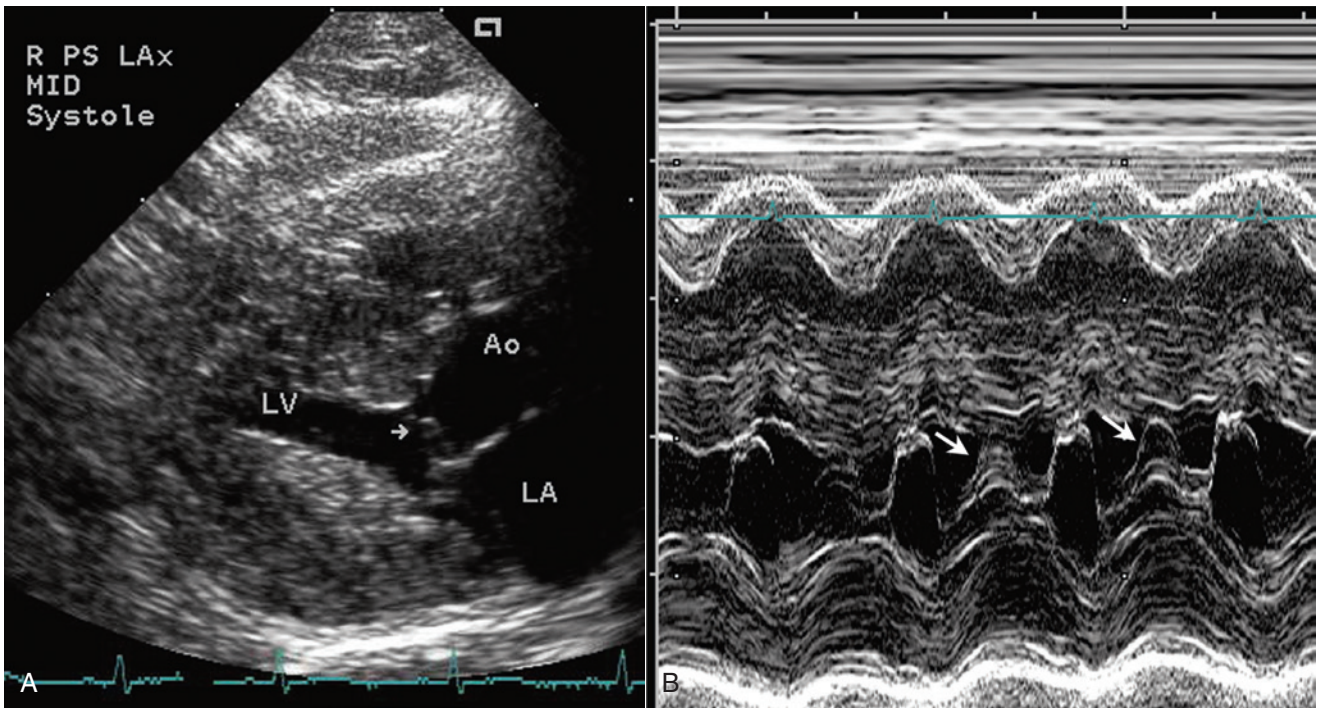


FIG 8.5
(A) Two-dimensional echo image in midsystole from a middle-aged domestic shorthair cat. Echoes from the anterior mitral leaflet appear within the LV outflow tract *(arrow)* because of abnormal systolic anterior (toward the septum) motion (SAM) of the valve. **(B)** The M-mode echocardiogram at the mitral valve level also shows the mitral SAM *(arrows). Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

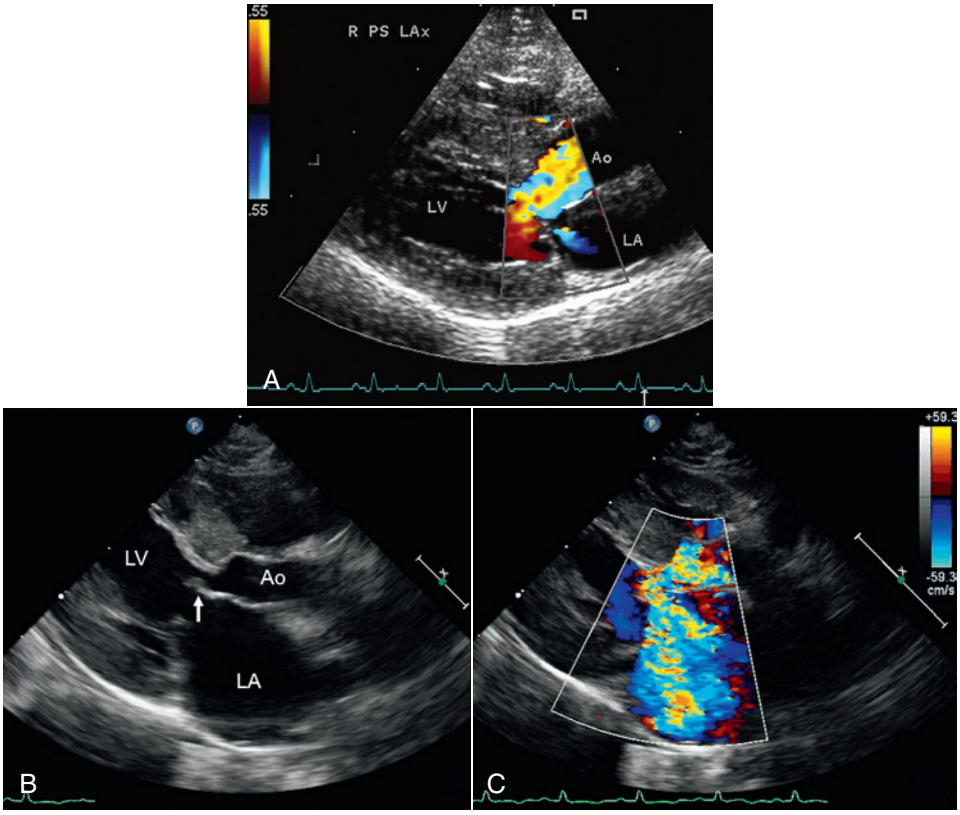


FIG 8.6
(A) Color flow Doppler image taken in systole from a male domestic longhair cat with hypertrophic obstructive cardiomyopathy. Note the turbulent flow just above where the thickened interventricular septum protrudes into the LV outflow tract and a small mitral insufficiency jet, typical with systolic anterior motion (SAM) of the anterior mitral leaflet. **(B)** and **(C)** show two-dimensional and corresponding color Doppler images from a male domestic shorthair cat with hypertrophic obstructive cardiomyopathy. There is hypertrophy of the basilar interventricular septum and severe left atrial enlargement. The anterior mitral leaflet's SAM (*arrow*, **B**) contributes to dynamic LV outflow obstruction. **(C)** Color Doppler imaging in midsystole reveals turbulent, high-velocity flow in the LV outflow tract and, in this cat, severe mitral regurgitation. Right parasternal long-axis view. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

Cats with severe pulmonary edema are given supplemental oxygen and parenteral furosemide, usually intramuscular (IM) initially (2 mg/kg q1-4h; see Box 3.1, p. 62 and p. 65), until an intravenous (IV) catheter can be placed without excessive stress to the cat. Butorphanol can be helpful to reduce anxiety that accompanies dyspnea and hospitalization (see Box 3.1). Nitroglycerin ointment can be used (q4-6h), although no studies of its efficacy in this situation have been done. Once initial medications have been given, the cat should be allowed to rest. The respiratory rate is noted initially and then every 15 to 30 minutes or so without disturbing the cat. Respiratory rate and effort are used to guide ongoing diuretic therapy. Catheter placement, blood sampling, radiographs, and other tests and therapies should be delayed until the cat's condition is more stable. Airway suctioning and mechanical ventilation with positive end-expiratory pressure can be considered in extreme cases.

The use of pimobendan in cats with CHF is the subject of ongoing study. In theory, positive inotropes such as pimobendan are not indicated in cats with HCM, because systolic function generally is well preserved and increased force of contraction could worsen dynamic outflow tract obstruction. However, pimobendan could improve cardiac output without increasing myocardial oxygen demand, and its balanced vasodilatory properties might be beneficial in both acute and chronic CHF regardless of underlying structural disease. Nevertheless, great caution is advised when HOCM is suspected or confirmed, because vasodilation, especially combined with increased contractility, could worsen the dynamic LV outflow obstruction and promote hypotension. If pimobendan is used in a cat with HOCM, blood pressure measurement and close monitoring for signs of hypotension are advised. Pimobendan is clearly indicated in cats with systolic dysfunction or cardiogenic shock, and several studies

BOX 8.1

Treatment Outline for Cats with Hypertrophic Cardiomyopathy

Severe, Acute Signs of Congestive Heart Failure*

Supplemental O_2
Minimize patient handling
Furosemide (parenteral)
Sedation (butorphanol)
Thoracocentesis, if pleural effusion present
Pimobendan (±; see p. 69, caution if LV outflow obstruction)
Antiarrhythmic therapy or heart rate control, if indicated†
±Nitroglycerin (cutaneous)
±Dobutamine (if needed for cardiogenic shock)
Monitor: respiratory rate, HR and rhythm, arterial blood pressure, renal function, serum electrolytes, etc.

Mild to Moderate Signs of Congestive Heart Failure*

Furosemide
ACE inhibitor
Pimobendan (±; see p. 69, caution if LV outflow obstruction)
Antithrombotic prophylaxis (clopidogreal ± anticoagulant)‡
Exercise restriction
Reduced-salt diet, if the cat will eat it
±β-blocker (e.g., atenolol) or diltiazem (see text)

Refractory Congestive Heart Failure Management*

Furosemide (optimize dosage and frequency)
ACE inhibitor
Pimobendan (caution if severe LV outflow tract obstruction)
Antithrombotic prophylaxis (clopidogrel ± anticoagulant)‡
Thoracocentesis as needed
±Spironolactone
±β-blocker or diltiazem
±Additional antiarrhythmic drug therapy, if indicated
±Hydrochlorothiazide (closely monitor renal function/electrolytes)
Home monitoring of resting respiratory rate and effort
Dietary salt restriction, if accepted
Monitor renal function, electrolytes, etc.
Manage other medical problems (rule out hyperthyroidism and hypertension if not done previously)

ACE, Angiotensin-converting enzyme; *CHF,* congestive heart failure; *HR,* heart rate; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *LV,* left ventricular.
*See text, Box 3.1 (p. 62), and Chapter 3 for further details.
†See text, Table 4.2 (p. 90), and Chapter 4 for further details.
‡See Chapter 12 for further details.

have demonstrated that the drug is well tolerated in cats. More recently, pimobendan has shown apparent long-term benefit and improved survival in "typical" HCM with normal systolic function. In a retrospective case control study of cats with HCM and CHF, cats that received pimobendan lived significantly longer (~21 months) compared with cats that did not receive pimobendan (~4 months). Further clarification regarding potential benefits of pimobendan on heart failure progression, optimal management, and survival time await results of prospective study. If pimobendan is elected for a cat with CHF, the drug is given as soon as oral medication is feasible, at the same initial dose as recommended for dogs (0.2-0.3 mg/kg PO q12h). For most average-sized cats, this dose equates to one 1.25 mg chewable tablet twice daily. Cats with poor cardiac output or cardiogenic shock can receive pimobendan every 8 hours during initial stabilization, if needed. Cats with more severe cardiogenic shock may require IV dobutamine (usually given as a continuous ratet infusion (CRI) of 1-5 mcg/kg/min). Adverse effects of dobutamine can include sinus tachycardia, ventricular ectopy, and seizures; if these occur, the infusion rate is halved or discontinued.

As respiratory distress resolves, furosemide can be continued at a reduced dose (≈1 mg/kg q8-12h). Once pulmonary edema is controlled, supplemental oxygen is withdrawn and the patient is transitioned to oral medications. The furosemide dose is gradually titrated downward to the lowest effective level. For example, a starting dose of 6.25 mg/cat q8-12h can be slowly reduced over days to weeks, depending on the cat's response. Some cats do well with once daily or every other day dosing, whereas others require furosemide several times per day. If instituted, oral pimobendan is continued at the starting dose. Once initial acute respiratory distress has resolved and the cat is eating and drinking, ACEI therapy should be added. An ACEI usually is prescribed in the hope of reducing neurohormonal activation and abnormal cardiac remodeling. Enalapril and benazepril are the agents used most often in cats, although others are available (see Chapter 3 and Table 3.3).

The decision to use other drugs is influenced by echocardiographic or other findings in the individual cat. β-blockers offer several theoretical benefits for cats with HCM, although clinical evidence for increased survival time is lacking, and the possibility of a negative effect in cats with CHF exists. Nevertheless, β-blockers can reduce heart rate (including ventricular response rate in AF), reduce or resolve dynamic LV outflow obstruction, and suppress tachyarrhythmias. Sympathetic inhibition also can reduce myocardial O_2 demand, which could be important in cats with myocardial ischemia or infarction. By inhibiting catecholamine-induced myocyte damage, β-blockers might reduce myocardial fibrosis. Although β-blockers slow active myocardial relaxation, an increase in ventricular filling time from their heart rate lowering effect might outweigh this. If a β-blocker is used, the selective β-1 blocker, atenolol, is most commonly chosen. β-blockers, especially nonselective agents like propranolol, are not recommended for cats in active CHF. Blockade of bronchial β-2 receptors could exacerbate bronchospasm, which might occur with pulmonary edema. Additionally, in cats with reduced myocardial contractility, the negative inotropic effect of β-blockers could promote acute CHF decompensation. For cats receiving atenolol (or other β-blocker) before CHF, the drug could be continued or its dosage

reduced by half during the acute episode. The most common indication for starting atenolol in a cat that previously has experienced CHF is rate control in AF; it also can be useful for suppressing other tachyarrhythmias.

Diltiazem also has theoretical benefits for cats with severe LV hypertrophy, although it likewise has not been shown to improve survival, and side effects can be problematic in some cats. Its Ca^{++}-blocking effect can modestly reduce heart rate and contractility (which reduces myocardial O_2 demand). Diltiazem promotes coronary vasodilation and may have a positive effect on myocardial relaxation. Longer-acting diltiazem products are more convenient for chronic use, although the serum concentrations achieved can be variable. Diltiazem ER (or XR; Dilacor), dosed at one half of an internal (60-mg) tablet from the 240-mg capsule q12h, or Cardizem CD, compounded and dosed at 10 mg/kg q24h, have been used most often. Similar to atenolol, the most common reason for initiating diltiazem therapy in a cat with previous CHF is rate control in AF. Occasionally, a β-blocker might be added to diltiazem therapy (or vice versa) to further reduce heart rate in cats with AF. However, care must be taken to prevent bradycardia or hypotension in animals receiving this combination.

The negative chronotropic drug ivabradine is another pharmacologic option that could prove helpful in controlling heart rate in cats with HCM. Ivabradine is a selective "funny" current (I_f) inhibitor. The I_f is important in sinus node (pacemaker) function. Activation of the I_f current increases membrane permeability to Na^+ and K^+, thereby increasing the slope of spontaneous phase 4 (diastolic) depolarization in sinus node cells, which increases the heart rate. Preliminary studies have shown ivabradine to produce dose-dependent heart rate reduction with minimal adverse effects. Specific recommendations await further study.

Long-term management of cats with CHF also includes therapy to reduce the likelihood of arterial thromboembolism (see Chapter 12). Dietary sodium restriction is recommended if the cat will accept such a diet, but it is more important to forestall anorexia.

CHRONIC REFRACTORY CONGESTIVE HEART FAILURE

Refractory pulmonary edema or pleural effusion is difficult to manage. Moderate to large pleural effusions should be treated by thoracocentesis. Various medical strategies may help slow the rate of abnormal fluid accumulation. These include increasing the dosage of furosemide (up to ≈4 mg/kg q8h), maximizing the dosage of an ACEI, adding or increasing dosage of pimobendan (up to ≈0.5 mg/kg q8h), using diltiazem or a β-blocker for greater heart rate control if AF or other tachyarrhythmias are present, adding spironolactone, or using an additional diuretic (e.g., hydrochlorothiazide; see Table 3.3). Spironolactone has been reported to cause facial pruritus and excoriations in some cats. Digoxin could be considered for additional heart rate control or for cats with severe systolic dysfunction; however, toxicity can occur easily. Frequent monitoring for azotemia, electrolyte disturbances, and other complications is warranted.

Prognosis

Several factors influence the prognosis for cats with HCM, including the speed with which the disease progresses, the occurrence of thromboembolic events and/or arrhythmias, and the response to therapy. Asymptomatic cats with only mild to moderate LV hypertrophy and atrial enlargement often live with no clinical signs for many years. Median survival time for all asymptomatic cats after diagnosis of HCM is approximately 5 years. Cats with marked LA enlargement and more severe hypertrophy appear to be at greater risk for CHF, thromboembolism, and sudden death. Median survival time for cats with CHF is between 1 and 2 years, although this varies greatly with individual response to therapy and patient compliance with medication administration. The prognosis is worse for older cats and cats with severe LA enlargement, severe LV hypertrophy, LV or LA systolic dysfunction, AF, and/or refractory CHF. Cats with low or high body weight may have a worse prognosis than those with normal weight. Thromboembolism confers a guarded prognosis (see p. 224) and recurrence of thromboembolism is common.

SECONDARY MYOCARDIAL HYPERTROPHY

Myocardial hypertrophy is a compensatory response to certain identifiable stresses or diseases. Marked LV wall and septal thickening and CHF can occur in some of these cases, mimicking idiopathic HCM. Secondary causes should therefore be ruled out whenever LV hypertrophy is identified before making a diagnosis of idiopathic HCM. The most common causes of secondary myocardial hypertrophy in cats are hyperthyroidism and systemic hypertension; less frequent causes include subaortic stenosis, hypersomatotropism (acromegaly), and infiltrative myocardial diseases.

Evaluation for hyperthyroidism is indicated in cats with myocardial hypertrophy or CHF older than 6 years of age. Hyperthyroidism alters cardiovascular function by its direct effects on the myocardium and through the interaction of heightened sympathetic nervous system activity and excess thyroid hormone on the heart and peripheral circulation. Cardiac effects of thyroid hormone include myocardial hypertrophy and increased heart rate and contractility. The metabolic acceleration that accompanies hyperthyroidism causes a hyperdynamic circulatory state characterized by increased cardiac output, oxygen demand, blood volume, and heart rate. Systemic hypertension can further stimulate myocardial hypertrophy. Manifestations of hyperthyroid heart disease often include a systolic murmur, hyperdynamic arterial pulses, a strong precordial impulse, sinus tachycardia, and various arrhythmias. Criteria for LV enlargement or hypertrophy often are found on ECG, thoracic radiographs, or echocardiogram. Signs of CHF develop in approximately

15% of hyperthyroid cats; most have normal to high FS, but a few have poor contractile function. Cardiac therapy, in addition to treatment of the hyperthyroidism, is indicated for cats with severe hyperthyroid heart disease. Treatment for CHF is the same as that described for HCM. Treatment for preclinical disease with marked LA enlargement also is similar to that for HCM, including thromboprophylaxis with clopidogrel and potentially, vasodilation with an ACEI. Concurrent systemic hypertension should be treated with amlodipine. A β-blocker can temporarily control many of the adverse cardiac effects of excess thyroid hormone, especially tachyarrhythmias; for this reason, atenolol is a common adjunct treatment for hyperthyroid heart disease. Cardiac therapy, including a β-blocker, is not a substitute for antithyroid treatment. Regression of myocardial hypertrophy ("reverse remodeling") can sometimes occur in cats after treatment for hyperthyroidism, particularly definitive treatment with I-131. Treatment with methimazole might or might not resolve or prevent hyperthyroid heart disease, presumably because periodic spikes in circulating thyroid hormone can still occur despite apparent disease control.

LV concentric hypertrophy is the expected response to increased ventricular systolic pressure (afterload). Systemic arterial hypertension (see Chapter 11) increases afterload because of high arterial pressure and resistance. Increased resistance to ventricular outflow also occurs with a fixed (e.g., congenital) subaortic stenosis. In addition, cardiac hypertrophy develops in cats with hypersomatotropism (acromegaly) as a result of the trophic effects of growth hormone on the heart. Increased myocardial thickness occasionally results from infiltrative myocardial disease, most notably from lymphoma. Cats with hypertensive heart disease, acromegalic heart disease, or myocardial lymphoma might require cardiac medications in addition to treatment for the underlying disease. In general, treatment for secondary myocardial hypertrophy is the same as that described for HCM.

RESTRICTIVE CARDIOMYOPATHY

Etiology and Pathophysiology

RCM is a myocardial disease phenotype associated with extensive endocardial, subendocardial, or myocardial fibrosis of unclear, but probably multifactorial, etiology. Characteristic features include diastolic dysfunction (restrictive filling physiology) and severe LA enlargement in the absence of myocardial hypertrophy. This condition could be a consequence of endomyocarditis or infiltrative neoplastic disease (e.g., lymphoma), or may be idiopathic; no specific familial associations or genetic mutations have been identified. It is important to remember that advanced HCM also is characterized by restrictive LV filling, and that chronic ischemia and fibrosis can result in an end-stage or "remodeled" HCM phenotype with minimal hypertrophy and focal areas of wall thinning. Thus without serial echocardiography it can be difficult to differentiate "true" RCM from end-stage remodeled HCM.

There are a variety of histopathologic findings in cats with RCM, including marked perivascular and interstitial fibrosis, intramural coronary artery narrowing, and myocyte hypertrophy, as well as areas of degeneration and necrosis. Some cats have extensive LV endomyocardial fibrosis with chamber deformity or fibrous tissue bridging between the septum and LV wall. In such cases, the mitral apparatus and papillary muscles may be fused to surrounding tissue or distorted. LA or biatrial enlargement is prominent in cats with RCM as a consequence of chronically high ventricular filling pressure from increased wall stiffness. The LV may be normal to reduced in size or mildly dilated. Intracardiac thrombi and systemic thromboembolism are common.

LV fibrosis impairs diastolic filling. Most affected cats have normal to only mildly reduced contractility, but this can progress with time as more functional myocardium is lost. Some cases develop regional LV dysfunction, possibly from myocardial ischemia or infarction. If mitral regurgitation is present, it is usually mild. Chronically elevated left heart filling pressures, combined with compensatory neurohormonal activation, lead to left-sided or biventricular CHF. The duration of subclinical disease progression in RCM is unknown.

Clinical Features

Middle-aged and older cats are most often diagnosed with RCM, though young cats are sometimes affected. Clinical features are similar to those seen with HCM. Preclinical disease might be discovered by detection of abnormal heart sounds or arrhythmias on routine examination or radiographic evidence of cardiomegaly. Clinical signs of CHF most commonly involve respiratory signs from pulmonary edema or pleural effusion; inactivity, poor appetite, vomiting, and weight loss also are common in the history. Clinical signs can be precipitated or acutely worsened by stress or concurrent disease that causes increased cardiovascular demand. Signs associated with thromboembolic events depend on the location and extent of vascular obstruction but can be severe (see Chapter 12, p. 224).

Physical examination might reveal a systolic murmur of mitral or tricuspid regurgitation, an S_4 gallop sound, and/or an arrhythmia. Pulmonary sounds can be abnormal in some cats with pulmonary edema, or muffled with pleural effusion. Femoral arterial pulses could be normal, slightly weak, or absent (if caudal aortic thromboembolism has occurred). Jugular vein distention and pulsation are common in cats with right-sided CHF. Acute signs of distal aortic (or other) thromboembolism may be the reason for presentation.

Diagnosis

Diagnostic test results are similar to those in cats with HCM. Routine clinicopathologic findings are nonspecific, although NT-proBNP can be useful in some clinical scenarios, as in HCM (see p. 162). Radiographs indicate LA or biatrial enlargement (sometimes massive) and LV or generalized

heart enlargement (Fig. 8.7). Typical radiographic findings in cats with CHF include pulmonary venous distension, infiltrates of pulmonary edema, pleural effusion, and sometimes hepatomegaly and ascites. Although normal sinus rhythm predominates, ECG abnormalities often include various arrhythmias such as ventricular or atrial premature complexes, supraventricular tachycardia, or AF. Wide QRS complexes, tall R waves, evidence of intraventricular conduction disturbances, or wide P waves also might be evident.

Echocardiography typically shows marked LA (and sometimes RA) enlargement with normal LV wall thickness. LV systolic function generally is normal (FS usually > 25%), although some cats have regional wall dysfunction. End-stage RCM can be associated with LV and RV dilation. Pulse-wave Doppler shows a restrictive pattern of mitral inflow, and tissue Doppler confirms severe diastolic dysfunction. Hyperechoic areas of fibrosis within the LV wall and/or endocardial areas sometimes are evident. Extraneous intraluminal echoes representing excess moderator bands are seen in some cases. Sometimes, extensive LV endocardial fibrosis, with scar tissue bridging between the free-wall and septum, constricts part of the ventricular chamber. An intracardiac thrombus might be found, usually in the left auricle or LA but occasionally in the LV. Mild mitral or tricuspid regurgitation often is present. As previously discussed, differentiation between RCM and end-stage remodeled HCM can be challenging. Cases that do not fit within the typical classification scheme often are termed "unclassified" cardiomyopathy (UCM) (see p. 171).

Treatment and Prognosis

Therapy for acute and chronic CHF is the same as for cats with HCM (see p. 164). Because cats with RCM do not typically have dynamic outflow tract obstruction, there is no contraindication to positive inotropic agents. Pimobendan is an appropriate therapy; severe cardiogenic shock can be managed with dobutamine. As with HCM, atenolol or diltiazem usually are added only as treatment for tachyarrhythmias, particularly AF. Sotalol could be used for refractory ventricular tachyarrhythmias. Management of thromboembolism is described in Chapter 12, p. 227.

The prognosis generally is guarded to poor for cats with RCM and CHF. Nevertheless, some cats survive more than a year after diagnosis. Thromboembolism and refractory pleural effusion commonly occur.

DILATED CARDIOMYOPATHY

Etiology

DCM has become uncommon in cats since the late 1980s, when taurine deficiency was identified as its major cause, and pet food manufacturers subsequently increased the taurine content of feline diets. Other factors besides a

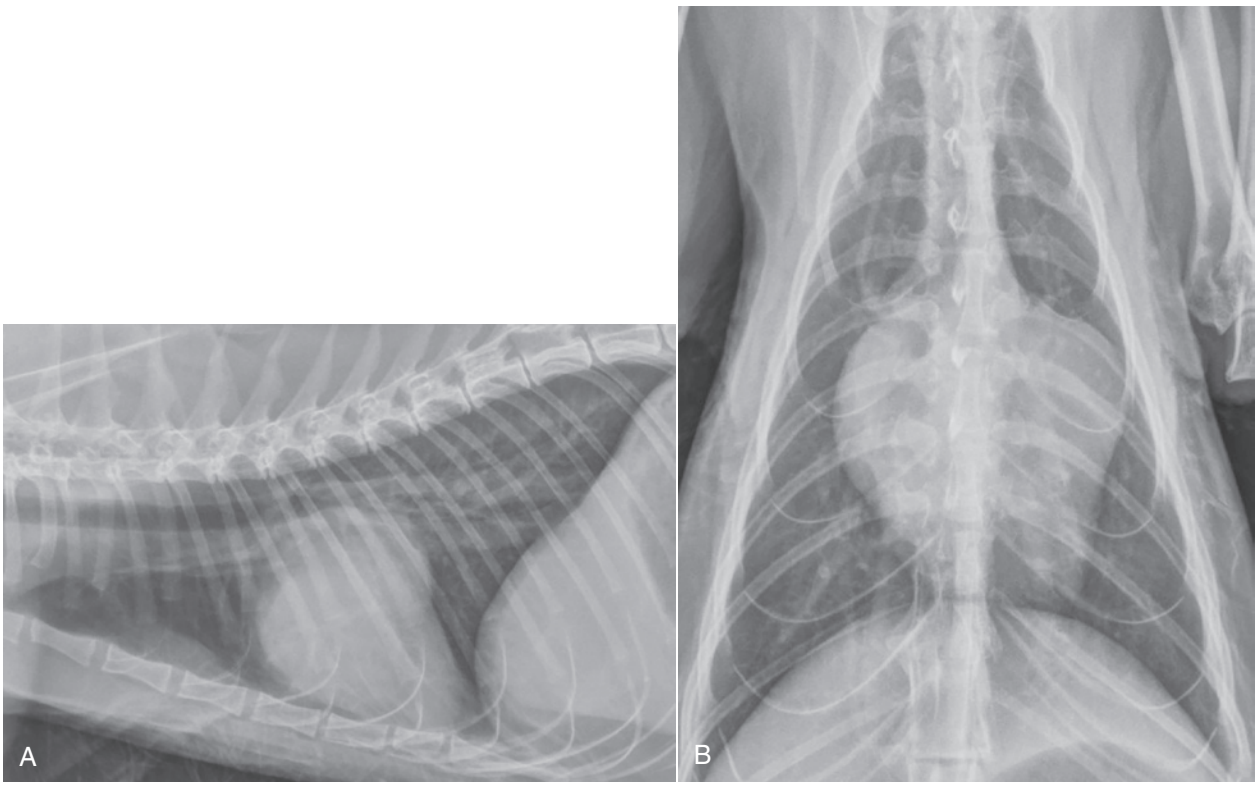


FIG 8.7
Lateral **(A)** and dorsoventral **(B)** radiographs from a domestic shorthair cat with restrictive cardiomyopathy show marked left atrial enlargement and prominent pulmonary vessels.

simple deficiency of this essential amino acid are likely to be involved in the pathogenesis, including genetic factors and a possible link with potassium depletion. Not all cats fed a taurine-deficient diet develop DCM, and taurine deficiency can occur even in cats fed a balanced commercial diet. Relatively few cases of DCM are identified now, and most of these cats are not taurine deficient. DCM in these cats could be idiopathic or represent the end stage of another myocardial metabolic abnormality, toxicity, or infection.

Doxorubicin can cause characteristic myocardial histopathologic lesions in cats as it does in dogs, and in rare instances echocardiographic changes consistent with DCM can occur after cumulative doses of 170 to 240 mg/m^2. However, clinically relevant doxorubicin-induced cardiomyopathy is not an issue in the cat; anecdotally, total cumulative doses of up to about 600 mg/m^2 (23 mg/kg) have been administered without evidence of cardiotoxicity.

Pathophysiology

DCM in cats has a similar pathophysiology to that in dogs (see p. 141). Poor myocardial contractility is the characteristic feature. Usually, all cardiac chambers become dilated. AV valve insufficiency occurs secondary to chamber enlargement and papillary muscle atrophy. As cardiac output decreases, compensatory neurohormonal mechanisms are activated, leading eventually to signs of CHF and low cardiac output. Pulmonary edema, pleural effusion, and arrhythmias are common in cats with DCM.

Clinical Features

DCM can occur at any age, although most affected cats are late-middle aged to geriatric. There is no breed or sex predilection. Clinical signs of CHF often include anorexia, lethargy, and increased respiratory effort or dyspnea. Evidence of poor cardiac output is usually found in conjunction with congestive signs (right-sided, left-sided, or biventricular CHF). Hypothermia, jugular venous distention, an attenuated precordial impulse, weak femoral pulses, a gallop sound (usually S_3), and a left or right apical systolic murmur (of mitral or tricuspid regurgitation) are common. Bradycardia and arrhythmias can be present, although many affected cats have normal sinus rhythm. Increased lung sounds and pulmonary crackles may be auscultated, but pleural effusion often muffles the lung sounds. Some cats have signs of arterial thromboembolism (see p. 224).

Diagnosis

Generalized cardiomegaly with rounding of the cardiac apex is often seen on radiographs. Pleural effusion is quite common and may obscure the heart shadow and coexisting evidence of pulmonary edema or venous congestion. Hepatomegaly and ascites also might be detected. Normal sinus rhythm predominates; variable ECG findings can include ventricular or supraventricular tachyarrhythmias (although AF is rare), AV conduction disturbance, and an LV enlargement pattern.

Echocardiography is an important tool to differentiate DCM from other myocardial pathophysiology. Findings are analogous to those in dogs with DCM (see p. 144). Poor FS (<26%), increased LV end-systolic (e.g., >1.1 cm) and end-diastolic (e.g., >1.8 cm) diameters, and wide mitral E point–septal separation (>0.4 cm) have been described as diagnostic criteria for DCM in cats. Cats with only focal hypokinesis (for example, of only the LV wall or septum) may actually have UCM or end-stage remodeled HCM, particularly if focal areas of hypertrophy are present. In DCM, ventricular wall thickness is normal or decreased. An intracardiac thrombus is identified in some cats, usually within the LA.

As with other feline heart diseases, routine clinicopathologic testing is generally nonspecific. Prerenal azotemia, mildly increased liver enzyme activity, and a stress leukogram are common. Elevated NT-proBNP and cardiac troponin concentrations are expected, particularly in cats with CHF.

Plasma or whole blood taurine concentration measurement is recommended to detect possible deficiency, even in cats fed commercial diets. Specific instructions for sample collection and mailing should be obtained from the laboratory used. Plasma taurine concentrations are influenced by the amount of taurine in the diet, the type of diet, and the time of sampling in relation to eating; an 8-hour fast is recommended. A plasma taurine concentration of less than 40 nmol/mL in a cat with DCM is diagnostic for taurine deficiency. Nonanorexic cats with a plasma taurine concentration of less than 60 nmol/mL probably should receive taurine supplementation or a different diet. Whole blood samples produce more consistent results than plasma samples. Normal whole blood taurine concentrations exceed 200 nmol/mL; < 150 nmol/L is diagnostic for taurine deficiency.

Treatment and Prognosis

The goals of acute and chronic CHF treatment are similar to those for cats with other cardiomyopathies (see p. 164) and analogous to those for dogs with DCM. Emphasis is placed on inotropic support; pimobendan is indicated in all cases and should be instituted as soon as oral medication can safely be given. Dobutamine (or dopamine) is administered by CRI for critical cases (see p. 62 and Box 3.1). Frequent ventricular tachyarrhythmias might respond to lidocaine, mexiletine, conservative doses of sotalol, or combination antiarrhythmic therapy (see Table 4.2). However, β-blockers (including sotalol) must be used cautiously (if at all) in cats with DCM and CHF because of their negative inotropic effect. Hemodynamically significant supraventricular tachyarrhythmias are treated with diltiazem, again with caution because of the drug's negative inotropic effect. Management of thromboembolism is described in Chapter 12, p. 227. Hypothermia is common in cats with decompensated DCM; external warming is provided as needed.

Supplemental taurine is recommended for taurine-deficient patients. Taurine (250-500 mg orally q12h) is instituted as soon as practical in cases where plasma taurine

concentration is low or cannot be measured. Clinical improvement, if it occurs, generally is not apparent until after a few weeks of taurine supplementation. Improved systolic function is seen echocardiographically within 6 weeks of starting taurine supplementation in most taurine-deficient cats. In some taurine-responsive cats, cardiac medications might be tapered and discontinued after 6 to 12 weeks (with close monitoring for recurrence of CHF). For cats previously eating a taurine-deficient diet, it may even be possible to transition from taurine supplementation to a diet known to support adequate plasma taurine concentrations (e.g., most name-brand commercial foods). Dry diets with 1200 mg of taurine per kilogram of dry weight and canned diets with 2500 mg of taurine per kilogram of dry weight are thought to maintain normal plasma taurine concentrations in adult cats. Requirements could be higher for diets incorporating rice or rice bran. Reevaluation of the plasma taurine concentration 2 to 4 weeks after discontinuing the supplement is advised.

Taurine-deficient cats that survive a month after initial diagnosis appear to have approximately a 50% chance for 1-year survival. It might be possible to wean the cat off some or all cardiac medications long-term. The prognosis for cats with DCM that are not taurine deficient is guarded to poor, with median survival time of 49 days even with pimobendan treatment.

OTHER MYOCARDIAL DISEASES

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic RV cardiomyopathy (ARVC) is a rare idiopathic cardiomyopathy similar to ARVC in people. Characteristic features include moderate to severe RV chamber dilation, with either focal or diffuse RV wall thinning. RV wall aneurysm also can occur, as can dilation of the RA and, less commonly, the LA. Myocardial atrophy with fatty and/or fibrous replacement tissue, focal myocarditis, and evidence of apoptosis are typical histologic findings. These are most prominent in the RV wall. Fibrous tissue or fatty infiltration is sometimes found in the LV and atrial walls.

Signs of right-sided CHF are common, including jugular venous distention, ascites or hepatosplenomegaly, and labored respirations caused by pleural effusion. Syncope occurs occasionally. Lethargy and inappetence without overt heart failure are the presenting signs in some cases.

Thoracic radiographs indicate right heart and sometimes LA enlargement. Pleural effusion is common. Ascites, caudal vena caval distention, and evidence of pericardial effusion could also be evident. The ECG can document various arrhythmias in affected cats, including VPCs, ventricular tachycardia, AF, and supraventricular tachyarrhythmias. A right bundle branch block pattern appears to be common; some cats have first-degree AV block. Echocardiography shows severe RA and RV enlargement similar to that seen with congenital tricuspid valve dysplasia, except that the valve apparatus appears structurally normal. Other possible findings include abnormal muscular trabeculation, aneurysmal dilation, areas of dyskinesis, and paradoxical septal motion. Tricuspid regurgitation appears to be a consistent finding on Doppler examination. Some cats also have LA enlargement, if the LV myocardium is affected.

The prognosis is guarded once signs of heart failure appear. Recommended therapy is similar to that for other causes of CHF in cats, and includes diuretics as needed, an ACEI, pimobendan, and prophylaxis against thromboembolism. Additional antiarrhythmic therapy may be necessary (see Chapter 4). In people and Boxer dogs with ARVC, ventricular tachyarrhythmias are a prominent feature and sudden death is common. Right heart dysfunction and right-sided CHF are a more consistent feature of ARVC in cats compared with Boxer dogs.

UNCLASSIFIED CARDIOMYOPATHY

UCM is a term used in people to describe cases of myocardial disease that do not fit within other defined categories (HCM, RCM, DCM, or ARVC). In cats, this label is most often applied to cases with severe LA or biatrial dilation despite normal LV size, wall thickness, and systolic function, and without obvious evidence of endomyocardial fibrosis (which would otherwise denote RCM). It is unclear whether UCM represents a distinct disease entity in cats; more likely, UCM includes end-stage or "remodeled" phenotypes of other cardiomyopathies, particularly HCM. Prevalence of UCM varies significantly among reports, likely owing to differences in diagnostic criteria. Most commonly it is estimated that UCM comprises approximately 10% of feline cardiomyopathy cases.

Clinical features of UCM are similar to those for other feline cardiomyopathies. The median age at diagnosis in one small study (8.8 years) is higher than for HCM or RCM, again supporting the notion that UCM may represent a common end-stage disease phenotype. Heart murmurs and arrhythmias are common on physical examination. The ECG may show ventricular or supraventricular tachyarrhythmias, and/or evidence of LA or LV enlargement. Radiographs indicate cardiomegaly with LA or biatrial enlargement; pleural effusion is more common than pulmonary edema. Echocardiography confirms atrial enlargement, with characteristics of ventricular structure and function inconsistent with other cardiomyopathy categories.

Treatment of UCM is identical to treatment for RCM. Patients in CHF receive furosemide, pimobendan, and ACEI, and thromboprophylaxis with clopidogrel, as well as dietary and lifestyle management. Prognosis is variable and probably similar to that for other cardiomyopathies.

CORTICOSTEROID-ASSOCIATED HEART FAILURE

CHF has been reported in cats approximately 3 to 7 days after receiving injectable long-acting corticosteroids (such as Depo-Medrol). The proposed mechanism is the diabetogenic effect of glucocorticoids causing a transient hyperglycemia

and subsequent intravascular fluid shift, precipitating volume overload and acute CHF. Presumably, preexisting structural heart disease (i.e., occult cardiomyopathy) could play a role in making certain cats more susceptible to corticosteroid-induced CHF.

An acute onset of lethargy, anorexia, tachypnea, and respiratory distress is described in affected cats. Most cats have normal auscultatory findings without tachycardia. Moderate cardiomegaly, with diffuse pulmonary infiltrates and mild or moderate pleural effusion, appears to be typical on radiographic examination. Possible ECG findings include sinus bradycardia, intraventricular conduction abnormalities, atrial standstill, atrial fibrillation, and VPCs. On echocardiogram, most affected cats have some degree of LV wall or septal hypertrophy and LA enlargement. Some have AV valve insufficiency or SAM.

CHF is treated as for other feline cardiomyopathies; in addition, corticosteroids should be discontinued. Resolution of abnormal cardiac findings and successful weaning from cardiac medications have been reported in some cats.

MYOCARDITIS

Inflammation of the myocardium and adjacent structures can occur in cats, as it does in other species (see p. 153). Severe, widespread myocarditis could cause CHF or fatal arrhythmias. Cats with focal myocardial inflammation could be asymptomatic. Acute and chronic viral myocarditis have been suspected, though a viral cause is rarely documented. Feline coronavirus has been identified as a cause of pericarditis-epicarditis. In one study, myocarditis was histologically identified in samples from more than half of cardiomyopathic cats but none from cats in the control group; viral deoxyribonucleic acid (panleukopenia) was found in about one third of the cats with myocarditis. However, the possible role of viral myocarditis in the pathogenesis of cardiomyopathy is not clear.

Endomyocarditis has been documented, mostly in young cats. Acute death, with or without preceding signs of pulmonary edema for 1 to 2 days, is the most common presentation. Histopathologic characteristics of acute endomyocarditis include focal or diffuse lymphocytic, plasmacytic, and histiocytic infiltrates with few neutrophils. Myocardial degeneration and lysis are seen adjacent to the infiltrates. Chronic endomyocarditis may have a minimal inflammatory response but significant myocardial degeneration and fibrosis. RCM or UCM could represent the end stage of nonfatal endomyocarditis. Therapy involves managing CHF signs and arrhythmias.

Bacterial myocarditis may develop in association with sepsis or as a result of bacterial endocarditis or pericarditis. Experimental *Bartonella* sp. infection can cause subclinical lymphoplasmacytic myocarditis, but it is unclear whether natural infection plays a role in the development of cardiomyopathy in cats. *Toxoplasma gondii* has occasionally been associated with myocarditis, usually in immunosuppressed cats as part of a generalized disease process. Traumatic myocarditis is recognized infrequently in cats.

Suggested Readings

Connolly DJ, et al. Assessment of the diagnostic accuracy of circulating natriuretic peptide concentrations to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. *J Vet Cardiol*. 2009;11(suppl 1):S41–S50.

Cote E, et al. Assessment of the prevalence of heart murmurs in overtly healthy cats. *J Am Vet Med Assoc*. 2004;225:384–388.

Ferasin L, et al. Feline idiopathic cardiomyopathy: a retrospective study of 106 cats (1994-2001). *J Feline Med Surg*. 2013;5:151–159.

Finn E, et al. The relationship between body weight, body condition, and survival in cats with heart failure. *J Vet Intern Med*. 2010;24:1369–1374.

Fox PR. Endomyocardial fibrosis and restrictive cardiomyopathy: pathologic and clinical features. *J Vet Cardiol*. 2004;6:25–31.

Fox PR. Hypertrophic cardiomyopathy: clinical and pathologic correlates. *J Vet Cardiol*. 2003;5:39–45.

Fox PR, et al. Spontaneously occurring arrhythmogenic right ventricular cardiomyopathy in the domestic cat: a new animal model similar to the human disease. *Circulation*. 2000;102:1863–1870.

Fox PR, et al. Utility of N-terminal pro-brain natriuretic peptide (NT-proBNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. *J Vet Cardiol*. 2009;11(suppl 1):S51–S61.

Fox PR, et al. Multicenter evaluation of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) as a biochemical screening test for asymptomatic (occult) cardiomyopathy in cats. *J Vet Intern Med*. 2011;25:1010–1016.

Freeman LM, et al. Body size and metabolic differences in Maine Coon cats with and without hypertrophy cardiomyopathy. *J Feline Med Surg*. 2012;15:74–80.

Fries R, Heaney AM, Meurs KM. Prevalence of the myosin-binding protein C mutation in Maine Coon cats. *J Vet Intern Med*. 2008;22:893–896.

Gordon SG, et al. Effect of oral administration of pimobendan in cats with heart failure. *J Am Vet Med Assoc*. 2012;241:89–94.

Granstrom S, et al. Prevalence of hypertrophic cardiomyopathy in a cohort of British Shorthair cats in Denmark. *J Vet Intern Med*. 2011;25:866–871.

Harvey AM, et al. Arrhythmogenic right ventricular cardiomyopathy in two cats. *J Small Anim Pract*. 2005;46:151–156.

Jackson BL, Lehmkuhl LB, Adin DB. Heart rate and arrhythmia frequency of normal cats compared to cats with asymptomatic hypertrophic cardiomyopathy. *J Vet Cardiol*. 2014;16:215–225.

Koffas H, et al. Pulsed tissue Doppler imaging in normal cats and cats with hypertrophic cardiomyopathy. *J Vet Intern Med*. 2006;20:65–77.

Linney CJ, et al. Left atrial size, atrial function and left ventricular diastolic function in cats with hypertrophic cardiomyopathy. *J Small Anim Pract*. 2014;55:198–206.

Liu SK, Maron BJ, Tilley LP. Feline hypertrophic cardiomyopathy: gross anatomic and quantitative histologic features. *Am J Pathol*. 1981;102:388–395.

MacDonald KA, et al. Effect of spironolactone on diastolic function and left ventricular mass in Maine Coon cats with familial hypertrophic cardiomyopathy. *J Vet Intern Med*. 2008;22:335–341.

MacGregor JM, et al. Use of pimobendan in 170 cats (2006-2010). *J Vet Cardiol*. 2011;13:251–260.

Machen MC, et al. Multi-centered investigation of a point-of-care NT-proBNP ELISA assay to detect moderate to severe occult (pre-clinical) feline heat disease in cats referred for cardiac evaluation. *J Vet Cardiol*. 2014;16:245–255.

Mary J, et al. Prevalence of the MYBPC3-A31P mutation in a large European feline population and association with hypertrophic cardiomyopathy in the Maine Coon breed. *J Vet Cardiol*. 2010;12:155–161.

Meurs KM, et al. A substitution mutation in the myosin binding protein C gene in ragdoll hypertrophic cardiomyopathy. *Genomics*. 2007;90:261–264.

Meurs KM, et al. A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy. *Hum Mol Genet*. 2005;14:3587–3593.

Nakamura RK, et al. Prevalence of echocardiographic evidence of cardiac disease in apparently healthy cats with murmurs. *J Feline Med Surg*. 2011;13:266–271.

Paige CF, et al. Prevalence of cardiomyopathy in apparently healthy cats. *J Am Vet Med Assoc*. 2009;234:1398–1403.

Payne JR, et al. Risk factors associated with sudden death versus congestive heart failure or arterial thromboembolism in cats with hypertrophic cardiomyopathy. *J Vet Cardiol*. 2015;17(suppl 1):S318–S328.

Payne JR, et al. Prognostic indicators in cats with hypertrophic cardiomyopathy. *J Vet Intern Med*. 2013;27:1427–1436.

Payne JR, Brodbelt DC, Fuentes LV. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centers (the CatScan study). *J Vet Cardiol*. 2015;17(suppl 1):S244–S257.

Payne JR, et al. Population characteristics and survival in 127 referred cats with hypertrophic cardiomyopathy (1997 to 2005). *J Small Anim Pract*. 2010;51:540–547.

Ployngam T, et al. Hemodynamic effects of methylprednisolone acetate administration in cats. *Am J Vet Res*. 2006;67:583–587.

Reina-Doreste Y, et al. Case-control study of the effects of pimobendan on survival time in cats with hypertrophic cardiomyopathy and congestive heart failure. *J Am Vet Med Assoc*. 2014;245:534–539.

Riesen SC, et al. Effects of ivabradine on heart rate and left ventricular function in healthy cats and cats with hypertrophic cardiomyopathy. *Am J Vet Res*. 2012;73:202–212.

Rush JE, et al. Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases (1990-1999). *J Am Vet Med Assoc*. 2002;220:202–207.

Sampedrano CC, et al. Systolic and diastolic myocardial dysfunction in cats with hypertrophic cardiomyopathy or systemic hypertension. *J Vet Intern Med*. 2006;20:1106–1115.

Sampedrano CC, et al. Prospective echocardiographic and tissue Doppler imaging screening of a population of Maine Coon cats tested for the A31P mutation in the myosin-binding protein C gene: a specific analysis of the heterozygous status. *J Vet Intern Med*. 2009;23:91–99.

Schober KE, Maerz I. Assessment of left atrial appendage flow velocity and its relation to spontaneous echocardiographic contrast in 89 cats with myocardial disease. *J Vet Intern Med*. 2006;20:120–130.

Schober KE, Todd A. Echocardiographic assessment of left ventricular geometry and the mitral valve apparatus in cats with hypertrophic cardiomyopathy. *J Vet Cardiol*. 2010;12:1–16.

Singletary GE, et al. Effect of NT-proBNP assay on accuracy and confidence of general practitioners in diagnosing heart failure or respiratory disease in cats with respiratory signs. *J Vet Intern Med*. 2012;26:542–546.

Smith SA, et al. Corticosteroid-associated congestive heart failure in 12 cats. *Intern J Appl Res Vet Med*. 2004;2:159–170.

Trehiou-Sechi E, et al. Comparative echocardiographic and clinical features of hypertrophic cardiomyopathy in 5 breeds of cats: a retrospective analysis of 344 cases (2001-2011). *J Vet Intern Med*. 2012;26:532–541.

Visser LC, Sloan CQ, Stern JA. Echocardiographic assessment of right ventricular size and function in cats with hypertrophic cardiomyopathy. *J Vet Intern Med*. 2017;31:668–677.

CHAPTER 9

Pericardial Disease and Cardiac Tumors



Diseases of the pericardium and intrapericardial space can disrupt cardiac function. Although these comprise a fairly small proportion of cases presented for clinical signs of cardiac disease, it is important to recognize them because the approach to their management differs from other cardiac disorders. The normal pericardium forms a closed, double-layered sac around the heart and is attached to the great vessels at the heart base. Directly adhered to the heart is the visceral pericardium, or epicardium, which is composed of a thin layer of mesothelial cells. This layer reflects back over itself at the base of the heart to line the outer, fibrous layer (parietal pericardium). A small volume (~0.25 mL/kg) of serous fluid between these layers serves as a lubricant. The pericardium anchors the heart in place, provides a barrier to infection or inflammation from adjacent tissues, helps balance the output of the right and left ventricles, and limits acute distention of the heart. Despite these functions, there usually are no overt clinical consequences to its removal. Excess or abnormal fluid accumulation in the pericardial sac is the most common pericardial disorder. It occurs most often in dogs, and causes clinical signs from development of cardiac tamponade (see later in this chapter). Other acquired and congenital pericardial diseases are seen sporadically. Acquired pericardial disease that causes clinical signs is uncommon in cats.

CONGENITAL PERICARDIAL DISORDERS

PERITONEOPERICARDIAL DIAPHRAGMATIC HERNIA

Peritoneopericardial diaphragmatic hernia (PPDH) is the most common congenital malformation of the pericardium in dogs and cats. It occurs when abnormal embryonic development (probably of the septum transversum) allows persistent communication between the pericardial and peritoneal cavities at the ventral midline. The pleural space is not involved. Other congenital defects such as umbilical hernia, sternal malformations, and cardiac anomalies may coexist with PPDH. Abdominal contents herniate into the pericardial space to a variable degree and cause associated clinical signs. Although the peritoneal-pericardial communication is not trauma induced in dogs and cats, trauma can facilitate movement of abdominal contents through a preexisting defect.

Clinical Features

The initial onset of clinical signs associated with PPDH can occur at any age (ages between 4 weeks and 15 years have been reported). The majority of cases are diagnosed during the first 4 years of life, usually within the first year. In some animals, clinical signs never develop. Males appear to be affected more frequently than females, and Weimaraners may be predisposed. The malformation is common in cats as well; Persians, Himalayans, and domestic longhair cats may be predisposed.

Clinical signs usually relate to the gastrointestinal (GI) or respiratory system. Vomiting, diarrhea, anorexia, weight loss, abdominal pain, cough, dyspnea, and wheezing are most often reported; shock and collapse can occur also. Physical examination findings may include muffled heart sounds on one or both sides of the chest; displacement or attenuation of the apical precordial impulse; an "empty" feel on abdominal palpation (with herniation of many organs); and, rarely, signs of cardiac tamponade (see later in this chapter).

Diagnosis

Thoracic radiographs can be diagnostic or highly suggestive for PPDH. Enlargement of the cardiac silhouette, dorsal tracheal displacement, overlap of the diaphragmatic and caudal heart borders, and abnormal fat and/or gas densities within the cardiac silhouette are characteristic findings (Fig. 9.1, *A* and *B*). Especially in cats, a pleural fold (dorsal peritoneopericardial mesothelial remnant) extending between the caudal heart shadow and the diaphragm ventral to the caudal vena cava on lateral view might be evident. Gas-filled loops of bowel crossing the diaphragm into the pericardial sac, a small liver, and few organs within the abdominal cavity also may be seen. Pectus excavatum or other thoracic skeletal

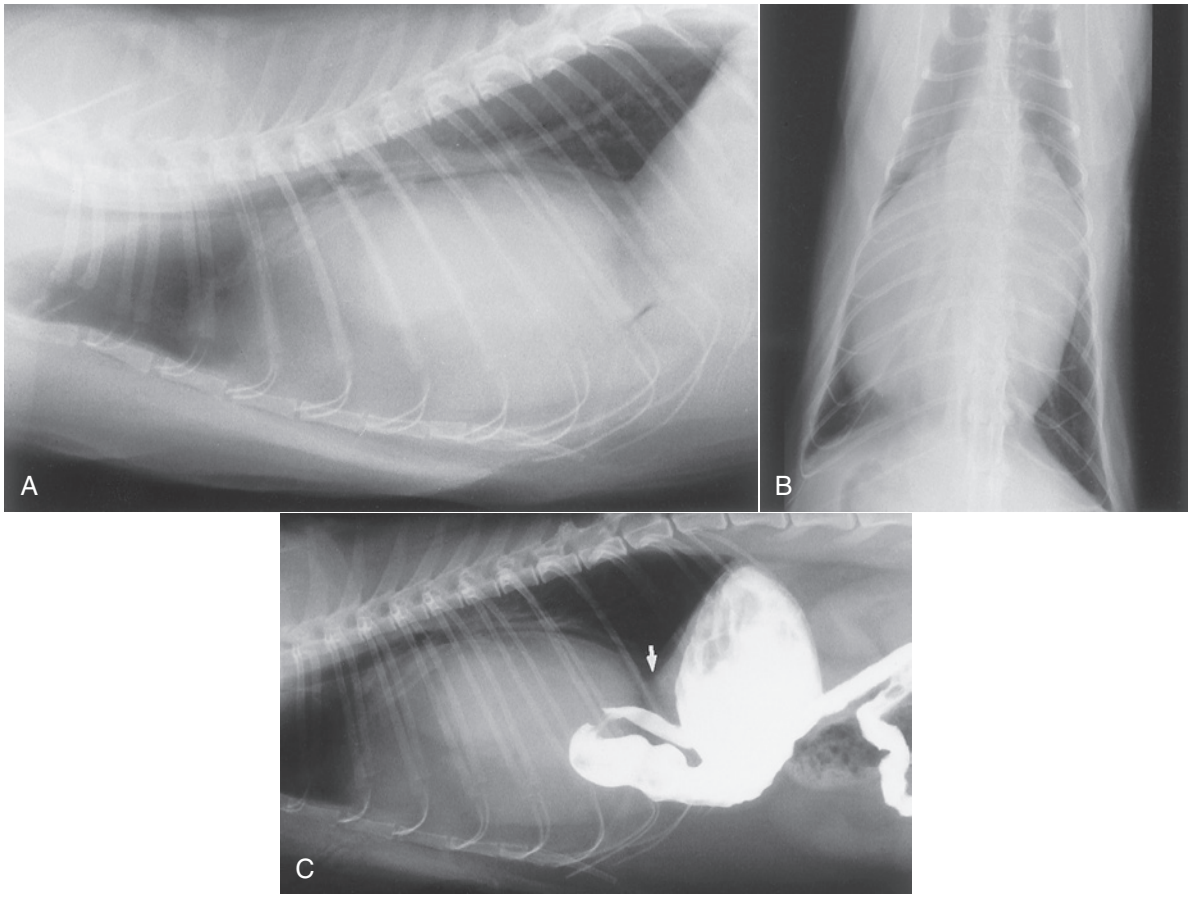


FIG 9.1
Lateral **(A)** and dorsoventral **(B)** radiographs from a 5-year-old male Persian cat with a congenital peritoneopericardial diaphragmatic hernia (PPDH). The cardiac silhouette is greatly enlarged and contains fat, soft tissue, and gas densities; the trachea has been displaced dorsally. There is overlap between the cardiac and diaphragmatic borders on both views. After barium administration, it is evident that a portion of the stomach and duodenum lie within the pericardial space **(C);** omental fat and liver also are within the pericardial sac. In **C,** the dorsal pleural fold between pericardium and diaphragm is best appreciated *(arrow)*.

deformity occasionally is present as well. Echocardiography (or abdominothoracic ultrasonography) helps confirm the diagnosis when radiographic findings are equivocal (Fig. 9.2). A GI barium series is diagnostic if the stomach and/or intestines are in the pericardial cavity (Fig. 9.1, *C*). Fluoroscopy, nonselective angiography (especially if only falciform fat or liver has herniated), positive contrast peritoneography, computed tomography (CT), magnetic resonance imaging (MRI), or pneumopericardiography also can be used for diagnosis. Electrocardiographic (ECG) changes are inconsistent; decreased amplitude complexes and axis deviations caused by cardiac position changes sometimes occur.

Treatment

Surgical closure of the peritoneal-pericardial defect can be done after viable organs are returned to their normal location. The patient's clinical signs and presence of other congenital abnormalities influence the decision to operate. The prognosis in uncomplicated cases is excellent. However, perioperative complications are common and, although usually mild, can include death. Animals without clinical signs, and some with mild signs, may do well without surgery. Trauma to organs chronically adhered to the heart or pericardium is of concern during attempted repositioning. Rare sequelae of surgery for PPDH have included pericardial cyst formation, arrhythmias, and constrictive pericardial disease. Overall, long-term survival appears similar between dogs and cats treated surgically compared with those not operated on.

OTHER PERICARDIAL ANOMALIES

Pericardial cysts are rare anomalies that could originate from abnormal fetal mesenchymal tissue or from incarcerated omental or falciform fat associated with a small PPDH. The pathophysiologic signs and clinical presentation can mimic those seen with pericardial effusion. Radiographically, the

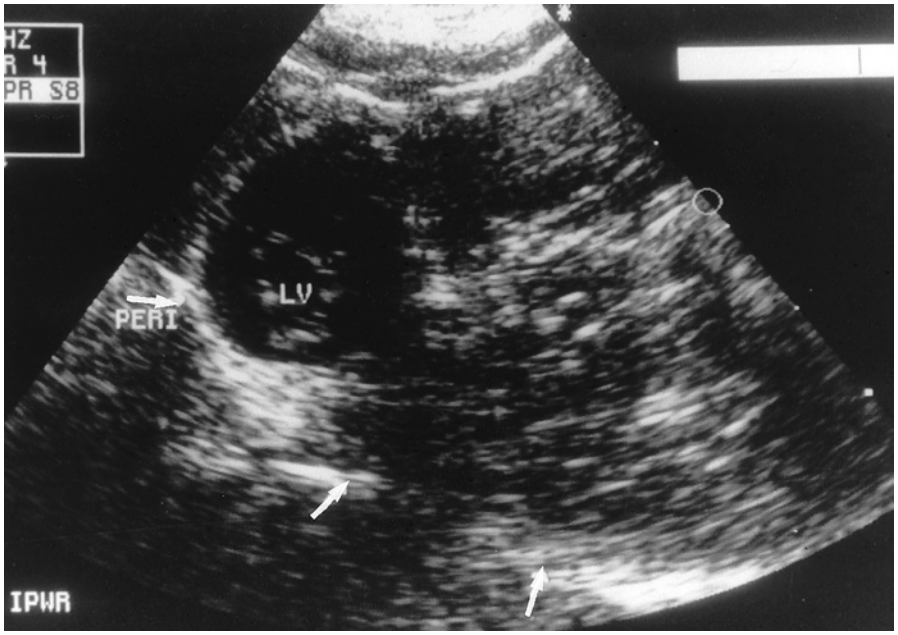


FIG 9.2
Right parasternal short-axis echocardiogram from a female Persian cat with peritoneopericardial diaphragmatic hernia (PPDH). The pericardium *(PERI),* indicated by *arrows,* surrounds liver and omental tissue, as well as the heart. *LV,* Left ventricle.

cardiac silhouette can appear enlarged and deformed. Echocardiography, CT, or MRI can reveal the diagnosis. Surgical cyst removal, combined with partial pericardiectomy, usually resolves the clinical signs.

Congenital defects of the pericardium itself are extremely rare in dogs and cats; most are incidental postmortem findings. Sporadic cases of partial (usually left-sided) or complete absence of the pericardium are reported. A possible complication of partial absence of the pericardium is herniation of a portion of the heart; this could cause syncope, embolic disease, or sudden death. Echocardiography, angiocardiography, CT, or MRI should allow antemortem diagnosis.

PERICARDIAL EFFUSION

Etiology and Types of Fluid

In dogs, most pericardial effusions are serosanguineous or hemorrhagic and are of neoplastic or idiopathic origin. Transudates, modified transudates, and exudates are found occasionally in both dogs and cats; the effusion rarely is chylous. In cats, pericardial effusion most often is associated with congestive heart failure (CHF) from cardiomyopathy, but this rarely causes cardiac tamponade. A minority of cats with pericardial effusion has neoplasia, feline infectious peritonitis (FIP), PPDH, pericarditis, or other infectious or inflammatory disease for an underlying cause.

HEMORRHAGE

Hemorrhagic effusions are most common in dogs. The fluid usually appears dark red, with a packed cell volume (PCV) greater than 7%, a specific gravity greater than 1.015, and a protein concentration greater than 3 g/dL. Cytologic analysis shows mainly red blood cells, but reactive mesothelial, neoplastic, or other cells can be seen. The fluid does not clot unless hemorrhage was recent. Neoplastic hemorrhagic effusions are more likely in dogs older than 7 years. Middle-aged, large-breed dogs are most likely to have idiopathic "benign" hemorrhagic effusion.

Hemangiosarcoma (HSA) is by far the most common neoplasm causing hemorrhagic pericardial effusion in dogs; it is rare in cats. Hemorrhagic pericardial effusion also occurs in association with various heart base tumors, pericardial mesothelioma, malignant histiocytosis, some cases of lymphoma and, rarely, metastatic carcinoma. HSAs (see p. 185) usually arise within the right heart, especially in the right auricle. Chemodectoma is the most common heart base tumor; it arises from chemoreceptor cells at the base of the aorta. Thyroid, parathyroid, lymphoid, and connective tissue neoplasms also occur at the heart base. Pericardial mesothelioma sometimes causes mass lesions at the heart base or elsewhere but often has a diffuse distribution and may mimic idiopathic disease. Lymphoma involving various parts of the heart is seen more often in cats than in dogs (and often causes a modified transudative effusion). Dogs with malignant histiocytosis and pericardial effusion usually have pleural effusion and ascites ("tricavitary effusion") despite the fact that they do not have cardiac tamponade.

Idiopathic (benign) pericardial effusion is the second-most common cause of canine hemorrhagic pericardial effusion. Its cause still is unclear. Although several viruses are associated with pericarditis in people, there is little evidence

to support an infectious cause in dogs. Idiopathic pericardial effusion is reported most frequently in medium- to large-breed dogs. Golden Retrievers, Labrador Retrievers, and Saint Bernards may be predisposed. Although dogs of any age can be affected, the median age is 6 to 7 years. More cases have been reported in males than females. Mild pericardial inflammation, with diffuse or perivascular fibrosis and focal hemorrhage, is common on histopathologic examination. Layers of fibrosis suggest a recurrent process in some cases. Constrictive pericardial disease is a potential complication.

Other, less common causes of intrapericardial hemorrhage include left atrial (LA) rupture secondary to severe mitral insufficiency (see Chapter 6, p. 130), coagulopathy (mainly rodenticide toxicity or disseminated intravascular coagulation), penetrating trauma (including iatrogenic laceration of a coronary artery during pericardiocentesis), and, possibly, uremic pericarditis.

TRANSUDATES

Pure transudates are clear, with a low cell count (usually <1000 cells/μL), specific gravity (<1.012), and protein content (<2.5 g/dL). Modified transudates might appear slightly cloudy or pink tinged. Their cellularity (≈1000-8000 cells/μL) is still low, but total protein concentration (≈2.5-5.0 g/dL) and specific gravity (1.015-1.030) are higher than those of a pure transudate. Transudative effusions occur in some dogs and cats with CHF, hypoalbuminemia, PPDH, pericardial cysts, or toxemias that increase vascular permeability (including uremia). These conditions usually are associated with relatively small-volume pericardial effusion; cardiac tamponade is rare.

EXUDATES

Exudative effusions are cloudy to opaque or serofibrinous to serosanguineous. They typically have a high nucleated cell count (usually much higher than 3000 cells/μL), protein content (often much above 3 g/dL), and specific gravity (>1.015). Cytologic findings are related to the etiology. Exudative pericardial effusions are rare in small animals, except in cats with FIP.

Infectious pericarditis usually is related to plant awn or porcupine quill migration, extension of a pleural or mediastinal infection, bite or other penetrating wounds, or possibly bacteremia. Various bacteria (aerobic and anaerobic), actinomycosis, coccidioidomycosis, aspergillosis, disseminated tuberculosis, and, rarely, systemic protozoal infections have been identified. Sterile exudative effusions have been reported in association with leptospirosis, canine distemper, and idiopathic pericardial effusion in dogs, and with FIP and toxoplasmosis in cats. FIP is the most important cause of symptomatic pericardial effusion in cats. Chronic uremia occasionally causes a sterile, serofibrinous, or hemorrhagic effusion.

Pathophysiology

Fluid accumulation within the pericardial space causes clinical signs when it raises intrapericardial pressure to or above normal cardiac filling pressure. This accumulation impedes venous return and cardiac filling. As long as intrapericardial pressure remains low, cardiac filling and output remain relatively normal. If fluid accumulates slowly, the pericardium may distend enough to accommodate the increased pericardial fluid volume at relatively low pressure. However, pericardial tissue is relatively noncompliant. Rapid fluid accumulation or a large effusion causes a steep rise in intrapericardial pressure, leading to cardiac tamponade. Pericardial fibrosis and thickening further limit the compliance of this tissue.

A pericardial effusion of extremely large volume can cause clinical signs by virtue of its size, even without overt cardiac tamponade. Lung and/or tracheal compression can compromise ventilation and stimulate cough; esophageal compression can cause dysphagia or regurgitation.

CARDIAC TAMPONADE

Cardiac tamponade develops when pericardial fluid accumulation raises intrapericardial pressure to or above the normal cardiac diastolic pressure. This external compression of the heart progressively limits filling, initially of the more compliant right heart, then the left. Cardiac output subsequently falls while systemic venous pressure rises. Pressure in all cardiac chambers and the great veins eventually becomes equilibrated during diastole. Neurohormonal compensatory mechanisms are activated as tamponade develops. Gradual pericardial fluid accumulation results in signs of CHF because of compensatory volume retention and the direct effects of impaired cardiac filling. Manifestations of systemic venous congestion and right-sided CHF (ascites and pleural effusion) usually predominate because of the right heart's thinner wall and lower pressures. Pericardial effusion does not typically affect cardiac contractility directly, but reduced coronary perfusion during tamponade can impair both systolic and diastolic function. Low cardiac output, arterial hypotension, and poor organ perfusion can ultimately lead to cardiogenic shock and death.

The rate of pericardial fluid accumulation and the distensibility of the pericardial sac determine whether and how quickly cardiac tamponade develops. Rapid accumulation of even a relatively small volume can raise intrapericardial pressure sharply. A gradual process is implied when the pericardial fluid volume is large. Cardiac tamponade is relatively common in dogs but rare in cats.

Pulsus paradoxus is the term used to describe the exaggerated variation in arterial blood pressure that occurs during the respiratory cycle because of cardiac tamponade. During inspiration intrapericardial and right atrial (RA) pressures fall, which facilitates right heart filling and pulmonary blood flow. At the same time, left heart filling is reduced as more blood is held in the pulmonary vasculature and the interventricular septum bulges leftward from the inspiratory increase in right ventricular (RV) filling; consequently, left heart output and systemic arterial pressure decrease during inspiration. The variation in systolic arterial pressure between

inspiration and expiration is usually greater than 10 mm Hg in patients with cardiac tamponade and pulsus paradoxus. Pulsus paradoxus is not always discernible by femoral pulse palpation.

Clinical Features

Clinical findings in patients with cardiac tamponade usually reflect right-sided CHF and poor cardiac output. Before obvious ascites develop, nonspecific signs might include lethargy, weakness, poor exercise tolerance, and inappetence or other GI signs. In many cases, the client history describes complaints of exercise intolerance, abdominal enlargement, tachypnea or difficulty breathing, collapse, and sometimes cough or vomiting. However, rapid pericardial fluid accumulation can cause acute tamponade, shock, and death without signs of ascites, pleural effusion, or marked radiographic cardiomegaly. Pulmonary edema, jugular venous distension, and hypotension might be evident in such cases, though. A history of collapse could be more common in dogs with neoplastic disease. Some cases with long-standing disease develop marked loss of lean body mass (cachexia; Fig. 9.3).

Jugular vein distention or a positive hepatojugular reflux, hepatomegaly, ascites, labored respirations, and weak femoral pulses are common physical examination findings. Pleural effusion and ascites also occur in both cats and dogs with cardiac tamponade. Ascites may be more prevalent in dogs without an identifiable mass lesion, reflecting a more gradual worsening or progression of tamponade. A palpable decrease in arterial pulse strength during inspiration (pulsus paradoxus) might be discernible in some dogs with tamponade. Sinus tachycardia, pale mucous membranes, and prolonged capillary refill time are common, as manifestations of high sympathetic tone. The precordial impulse is weak when the pericardial fluid volume is large. Heart sounds are muffled in patients with moderate to large pericardial effusions. Lung sounds are muffled over the ventral thorax in those with pleural effusion. Although pericardial effusion does not cause a murmur, concurrent cardiac disease may do so. Infectious pericarditis may be accompanied by fever; rarely, a pericardial friction rub may be heard.



FIG 9.3
Older male Boxer with chronic right-sided congestive heart failure signs secondary to cardiac tamponade caused by a chemodectoma. The abdomen is greatly distended with ascites. Chronic loss of lean body mass (cachexia) is evident along the spine, pelvis, and rib cage.

Diagnosis

Clinicopathologic findings

Hematologic and biochemical test results generally are nonspecific. The complete blood count (CBC) might indicate mild nonregenerative anemia, especially in patients with neoplastic disease, or may suggest inflammation or infection. Cardiac HSA can be associated with a regenerative anemia, increased numbers of nucleated red blood cells and schistocytes (with or without acanthocytes), and thrombocytopenia. Mild hypoproteinemia is seen in some patients. Mild increases in liver enzyme activities and prerenal azotemia can occur secondary to hepatic congestion and poor cardiac output. More pronounced liver enzyme elevation sometimes occurs with neoplastic effusions. Other biochemical abnormalities that have been reported in dogs with pericardial effusion include hyperlactatemia, hyponatremia, hyperglycemia, and hypermagnesemia. Pleural and peritoneal fluids in dogs and cats with cardiac tamponade are usually modified transudates.

Circulating cardiac troponin (cTnI) concentration can increase as a result of ischemia or myocardial invasion. An elevated cTnI helps differentiate pericardial effusion caused by HSA from other causes, especially in cases where a mass lesion is not obvious on echocardiogram. HSA that does not affect the heart does not increase cTnI concentration. Although pericardial fluid also can be used for cTnI measurement, this does not provide improved sensitivity. Serum NT-proBNP concentration is likely to be low in patients with pericardial effusion, in contrast to other cardiac diseases.

RADIOGRAPHY

Pericardial effusion enlarges the cardiac silhouette (Fig. 9.4). A massive amount of pericardial fluid causes the classic globoid-shaped heart shadow on both radiographic views. Nevertheless, radiographic vertebral heart score (VHS) or measures of sphericity are only moderately accurate for differentiating pericardial effusion from other cardiac disorders. These indices are not sensitive or specific enough to reliably identify dogs with pericardial effusion and cardiac tamponade from other causes of right-sided CHF signs. Smaller fluid volumes allow various cardiac contours to be identified, especially dorsally. Other findings associated with tamponade (as well as other causes of right-sided CHF) include pleural effusion, a distended caudal vena cava, hepatomegaly, and ascites. Pulmonary infiltrates of edema and distended pulmonary veins are noted only rarely. Some heart-base tumors cause tracheal deviation or a soft tissue mass effect. Metastatic lung lesions are common in dogs with HSA. CT and MRI provide greater

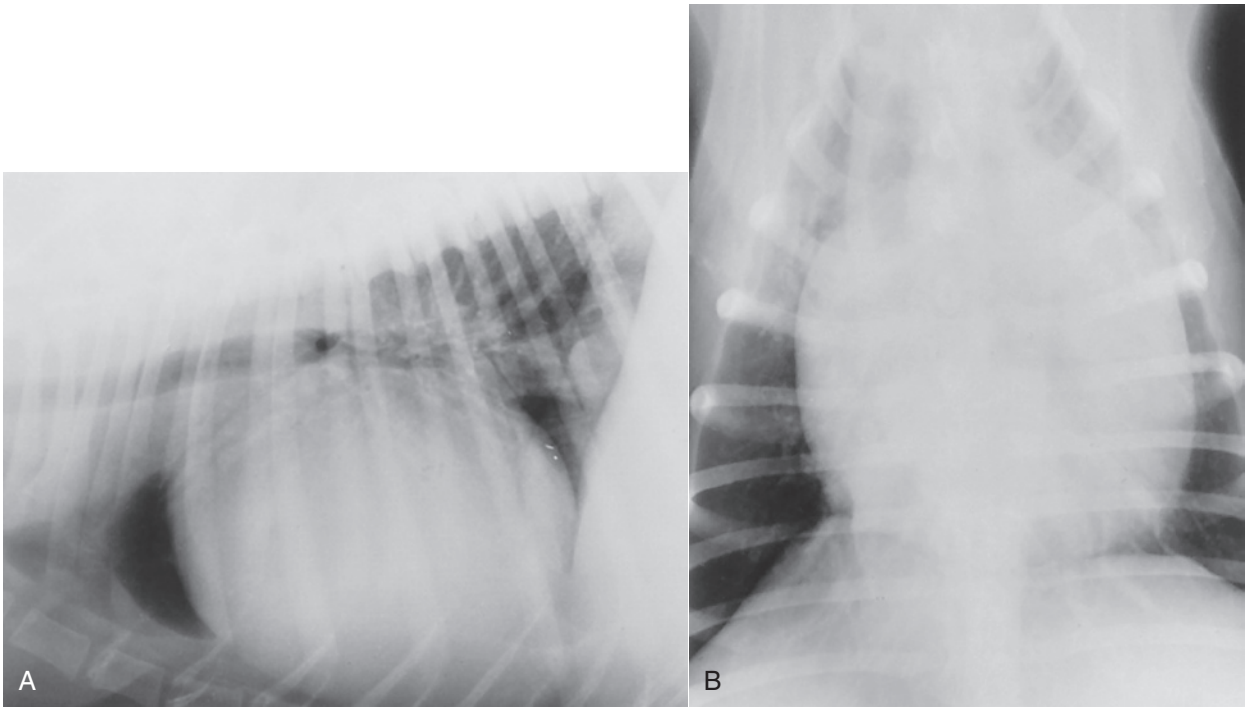


FIG 9.4
Lateral **(A)** and dorsoventral **(B)** radiographs from a mixed-breed dog with large-volume pericardial effusion. The cardiac silhouette has a globoid shape, and the caudal vena cava is distended in **A.**

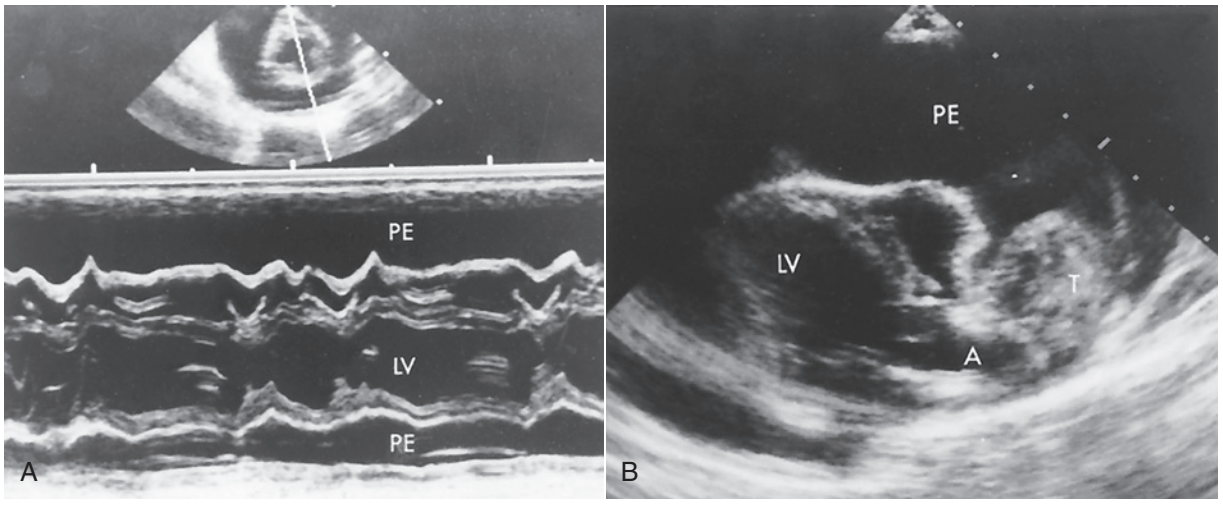


FIG 9.5
Echocardiographic examples of pericardial effusion. **(A)** Short-axis M-mode view at mitral valve (left side) and chordal levels. Large echo-free (fluid) spaces are seen on either side of the heart; the right ventricular wall is clearly visualized. The small two-dimensional image above the M-mode shows the heart (transected by the M-mode cursor line) surrounded by pericardial fluid (which appears black on the image). **(B)** Long-axis two-dimensional view from left parasternal position depicting a large heart base tumor and pericardial effusion in a Schnauzer. *A,* Aorta; *LV,* left ventricle; *PE,* pericardial effusion; *T,* tumor.

detail than plain radiographs, and can reveal some pulmonary metastases and other extracardiac lesions better. Yet they are not necessarily more accurate than echocardiography for identifying pericardial effusion and associated mass lesions.

ECHOCARDIOGRAPHY

Echocardiography is highly sensitive for detecting even small volumes of pericardial fluid. Because fluid is sonolucent, pericardial effusion appears as an echo-free space between the bright parietal pericardium and the epicardium (Fig. 9.5).

Large-volume pericardial effusions allow the heart to swing back and forth within the pericardial sac. Echocardiography also can identify intrapericardial and intracardiac mass lesions, as well as abnormal cardiac wall motion, chamber shape, and other cardiac abnormalities. Clinicians with basic training in echocardiography or just the "thoracic focused assessment with sonography for trauma" (TFAST) ultrasound examination should be able to identify pericardial and pleural effusions. Especially important in patients with collapse or respiratory distress, a TFAST examination can reveal pericardial effusion and tamponade quickly, even before radiographs are obtained. Nevertheless, after the patient has been stabilized, a more detailed echocardiographic examination is warranted to identify and define any mass lesions or other cardiac disease.

Cardiac tamponade is manifested by variable collapse of the RA and sometimes the RV (Fig. 9.6) through the cardiac cycle. Initially, the RA wall collapses transiently during ventricular systole. As tamponade worsens, the RA wall collapse intensifies and extends into diastole. Diastolic RV compression and collapse occur with advancing cardiac tamponade, and suggest that intrapericardial and intracardiac pressures have equalized. Further rise in intrapericardial pressure worsens the diastolic RV collapse and compresses the LV. These are signs of severe tamponade; immediate pericardiocentesis is especially urgent in these patients. It is important to remember that the volume of effusion is not the main determinant of hemodynamic compromise but rather the intrapericardial pressure. The RV and RA walls are often well visualized and may appear hyperechoic because of the surrounding fluid. Better visualization of the heart base and mass lesions generally is obtained before pericardiocentesis is performed. Therefore, if the patient is stable enough, it is helpful to do the echocardiographic examination just before pericardiocentesis. Careful evaluation of all portions of the RA and right auricle, RV, ascending aorta, and pericardium itself is important to screen for neoplasia. The left cranial parasternal transducer views are especially useful. Some mass lesions are difficult to visualize. Idiopathic pericardial effusion is diagnosed only after infectious and neoplastic causes have been excluded. Unfortunately, some mass lesions are not easily visualized, and mesothelioma without a discrete mass lesion cannot be reliably distinguished by noninvasive tests.

Sometimes pleural effusion, severe LA enlargement, a dilated coronary sinus, or persistent left cranial vena cava can be confused with pericardial effusion. Careful scanning from several positions helps in differentiating these conditions. Identification of the parietal pericardium in relation to the echo-free fluid helps differentiate pleural from pericardial effusion. Because the pericardium is a relatively strong ultrasound reflector, by progressively dampening the returning echo signals, pericardial echoes are usually the last to disappear. Most pericardial fluid accumulates near the cardiac apex because the pericardium adheres more tightly to the heart base; there is usually little fluid behind the LA.

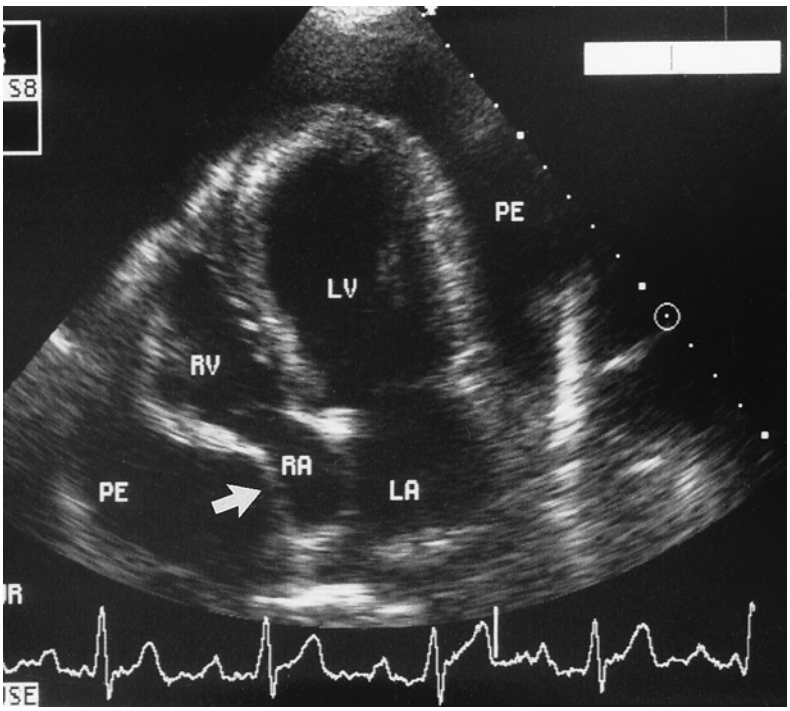


FIG 9.6
Diastolic collapse of the right atrial wall *(arrow)* is evident in this left apical four-chamber echocardiographic image from a 3-year-old female Saint Bernard with cardiac tamponade. *LA,* Left atrium; *LV,* left ventricle; *PE,* pericardial effusion; *RA,* right atrium; *RV,* right ventricle.

Furthermore, evidence of collapsed lung lobes or pleural folds often can be seen within pleural effusion.

ELECTROCARDIOGRAPHY

Although there are no pathognomonic ECG findings, the following abnormalities suggest pericardial effusion but are not seen consistently: small amplitude QRS complexes (<1 mV in dogs), electrical alternans, and ST segment elevation (epicardial injury current). Electrical alternans is a recurring alteration in the size of the QRS complex (or sometimes the T wave) with every other beat (Fig. 9.7). It results from the back-and-forth swinging motion of the heart within the pericardium and is more commonly seen in patients with large-volume pericardial effusion. Electrical alternans may be most evident at heart rates between 90 and 140/min and/or in the standing position. Sinus tachycardia is common with cardiac tamponade. Ventricular, or less often atrial, tachyarrhythmias can occur as well.

Central venous pressure

A central venous pressure (CVP) above 10 to 12 cm H_2O is common; normally, CVP is less than 8 cm H_2O. CVP measurement is helpful when the jugular veins are difficult to assess or it is unclear whether right heart filling pressure is elevated. Moderate- to large-volume pleural effusion should be drained before CVP measurement, not only to stabilize the patient but also to minimize artifactual CVP elevation.

Pericardial fluid evaluation

Cytologic evaluation helps characterize the pericardial fluid. Samples also should be saved for possible bacterial (or fungal) culture, pending cytology results. However, differentiating hemorrhagic neoplastic effusions from benign hemorrhagic pericarditis usually is not possible based on cytology alone. Reactive mesothelial cells within the effusion can closely resemble neoplastic cells; furthermore, chemodectomas and HSAs may not shed cells into the effusion. Therefore identifying a mass lesion with echocardiography is helpful for diagnosis. Depending on the accessibility and size of a visualized mass, cytologic diagnosis might be obtained by fine-needle aspiration. Patients with lymphoma typically have effusion consistent with a modified transudate, and neoplastic cells usually are identified easily. Many neoplastic (and other noninflammatory) effusions have a pH of 7.0 or greater, whereas inflammatory effusions generally have lower pH. However, there is too much overlap for pericardial effusion pH to be a reliable discriminator. Pericardial fluid culture is done if cytology and pH suggest an infectious or inflammatory cause. In some patients, fungal titers (for example, for coccidioidomycosis) or other serologic tests are helpful. Elevated cTnI, either in serum of pericardial fluid, suggests cardiac HSA or other cause of myocardial injury.

Treatment and Prognosis

It is important to differentiate cardiac tamponade from other causes of right-sided CHF signs because the treatment is very different. Positive inotropic drugs do not ameliorate the signs of tamponade; diuretics and vasodilators can further reduce cardiac output and exacerbate hypotension and shock. Immediate pericardiocentesis (discussed in the next section) is the initial therapeutic procedure for cardiac tamponade, and it also can provide diagnostic information. Most signs of CHF resolve soon after pericardial fluid is removed, although a dose or two of a diuretic may be useful after pericardiocentesis in some animals. Pericardial effusion secondary to other diseases that cause CHF, congenital malformations, or hypoalbuminemia do not usually cause tamponade and often resolve with management of the underlying condition.

Idiopathic Pericardial Effusion

Dogs with idiopathic pericardial effusion initially are treated conservatively with pericardiocentesis. Sometimes a glucocorticoid (e.g., prednisone, 1 mg/kg/day PO tapering over 2-4 weeks) is given after ruling out infectious causes by pericardial fluid analysis; however, the efficacy of glucocorticoid therapy in preventing recurrent idiopathic pericardial effusion is not known. Alternatively, a nonsteroidal antiinflammatory drug might help reduce inflammation associated with idiopathic pericardial disease; however, efficacy in preventing recurrence likewise is unknown. Some clinicians have used a course of broad-spectrum antibiotic concurrently,

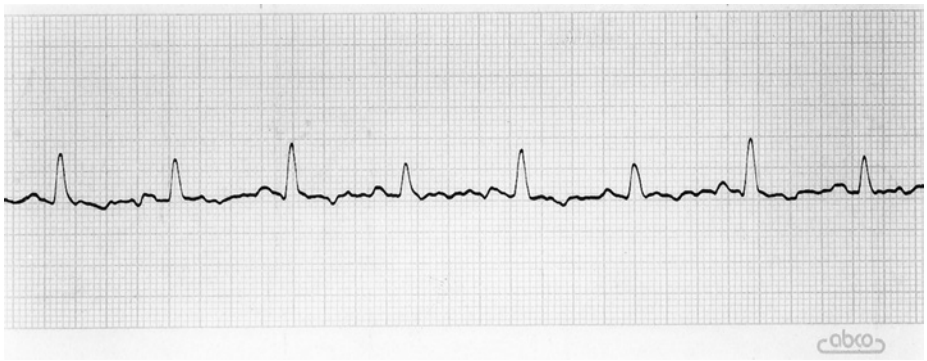


FIG 9.7
Electrical alternans is seen on this lead II electrocardiogram from a 10-year-old male Bulldog with a large pericardial effusion. Also note the small voltage QRS complexes and sinus tachycardia (heart rate ≈ 170 beats/min). 50 mm/sec, 1 cm = 1 mV.

although this should be unnecessary if sterile technique was used and the effusion shows no signs of infection. Periodic reevaluation of these dogs by radiography or echocardiography is recommended to detect recurrence. Apparent recovery occurs after one to three pericardial taps in about half of affected dogs. Cardiac tamponade can recur after a variable time span (days to years). Nevertheless, extended survival times are possible in dogs with idiopathic pericardial effusion, even in those requiring more than three pericardiocenteses. However, recurrent effusions that were thought to be idiopathic can be caused by mesothelioma or other neoplasia. Sometimes this becomes evident on repeated echocardiographic examination. Recurrent effusion that does not respond to repeated pericardiocenteses and antiinflammatory therapy (e.g., after two or three pericardial taps) usually is treated by pericardiotomy (pericardial window) or subtotal pericardiectomy (removing the pericardium ventral to the phrenic nerves), which allows drainage to the larger absorptive surface of the pleural space.

Neoplastic Pericardial Effusion

These also are drained to relieve cardiac tamponade. Recurrence of effusion is expected. Depending on tumor size, location, and histologic diagnosis, management might involve surgical biopsy or perhaps even resection, pericardiotomy or partial pericardiectomy, chemotherapy, or repeated pericardiocenteses. Surgical resection of most HSA and heart base tumors is not possible because of the tumor's invasiveness, although small tumors involving only the tip of the right auricle have been successfully removed. Surgery can be associated with significant morbidity and mortality, and is only palliative in most cases. Thoracoscopic pericardiotomy provides a less invasive option compared with partial pericardiectomy by open thoracotomy but might not be as effective as pericardiectomy. Biopsy samples for histopathologic evaluation can be obtained by both techniques. The thoracoscopic pericardial window procedure generally requires shorter procedure and hospitalization times than open thoracotomy and has low morbidity. Partial pericardiectomy also is possible using thoracoscopy in some animals. Percutaneous balloon pericardiotomy (see Suggested Readings for more information) is another minimally invasive means of providing long-term continuous pericardial drainage that might be useful if thoracoscopy is unavailable and thoracotomy is declined. These procedures can be effective for preventing recurrence of tamponade in idiopathic as well as some cases of neoplastic pericardial effusion, especially from a heart base tumor. The increased potential for tumor dissemination throughout the thoracic cavity does not appear to affect survival time, compared with pericardiocentesis alone, in dogs with HSA or mesothelioma. Chemotherapy, based on biopsy or clinicopathologic findings, may slow neoplastic progression, although most cardiac tumors are fairly resistant. Radiation therapy might provide some palliation for selected cases, as well. Consultation with a veterinary oncologist is recommended for dogs whose owner wishes to try chemo- or radiation therapy. Alternatively, many owners choose conservative therapy (repeated pericardiocentesis) until episodes of cardiac tamponade become unmanageable. Therapy with epsilon aminocaproic acid, an antifibrolytic agent that prevents activation of plasminogen to plasmin, anecdotally has been helpful in reducing hemorrhagic pericardial effusion associated with RA HSA. Conversely, a small retrospective study of dogs with a RA mass and pericardial effusion found no difference in time to recurrence of clinical signs from cardiac tamponade between dogs that had been treated with Yunnan Baiyao, a Chinese herbal remedy that can decrease clotting time and bleeding, either given alone or with epsilon aminocaproic acid compared with untreated dogs.

The prognosis in dogs with RA HSA with or without surgery alone is poor (median survival of 2-3 weeks). Multiagent chemotherapy reportedly has allowed survival times of 4 to 8 months in some dogs with atrial HSA. Survival time in dogs with mesothelioma might be slightly longer than in those with HSA, but the overall prognosis is poor. Therapy with IV doxorubicin and intracavitary cisplatin might extend survival time in some dogs. Heart base tumors (chemodectoma) tend to be slow-growing and locally invasive, although some do metastasize; pericardiotomy or partial pericardiectomy may prolong survival for years. More information about cardiac tumors is found later in this chapter (p. 185).

Infectious Pericarditis

Infection involving the pericardium should be treated aggressively with appropriate antimicrobial drugs (ideally determined by microbial culture and sensitivity testing) and pericardiocentesis as needed. Infusion of appropriate antimicrobial agent directly into the pericardium after pericardiocentesis can be helpful. Continuous drainage with an indwelling pericardial catheter or surgical debridement should be pursued if a foreign body is suspected or intermittent pericardiocentesis is ineffective. Surgery can remove a penetrating foreign body, provide more complete flushing of exudates, and manage pericardial constrictive disease. The prognosis with infective pericarditis is guarded. Even with successful elimination of infection, epicardial and pericardial fibrin deposition may lead to constrictive pericardial disease.

Intrapericardial Hemorrhage

Pure hemorrhage into the pericardial space, whether from trauma, LA rupture associated with advanced mitral valve disease, or a systemic coagulopathy, warrants pericardiocentesis if signs of cardiac tamponade exist. Only enough volume to control signs of tamponade should be removed, because continued pericardial drainage could predispose to further bleeding. The remaining blood usually is resorbed through the pericardium (autotransfusion). Surgery might be necessary to stop continued bleeding or remove large clots. Dogs that survive an initial episode of intrapericardial bleeding from LA rupture still have a guarded to poor prognosis because risk of recurrent LA tearing is high. Animals with intrapericardial hemorrhage of unclear cause should be

evaluated for a coagulation disorder. When trauma-induced intrapericardial hemorrhage persists in an animal with normal hemostasis, surgical exploration is indicated.

PERICARDIOCENTESIS

Pericardiocentesis should be done right away in animals with cardiac tamponade. As noted earlier, diuretic or vasodilator use is not indicated and can exacerbate hypotension and cause cardiogenic shock. When possible, a peripheral IV catheter should be placed before pericardiocentesis. This allows for IV fluid administration to support cardiac output during preparations for the pericardial tap procedure, and provides access for sedative, antiarrhythmic, or other drug administration as needed. Continuous ECG monitoring during the procedure is important because needle or catheter contact with the heart commonly causes ventricular arrhythmias.

Pericardiocentesis is a relatively safe procedure when performed carefully. Removal of even a small volume of pericardial fluid can markedly decrease intrapericardial pressure in animals with tamponade. Pericardiocentesis is usually approached from the right chest wall to minimize the risk of trauma to the lung (via the cardiac notch) and major coronary vessels (located mostly on the left). The need for sedation depends on the clinical status and temperament of the patient. The animal usually is placed in left lateral or sternal recumbency for more secure restraint, especially if the animal is weak or excitable. Although, in some cases, needle pericardiocentesis can be performed successfully on the standing animal, the risk of injury increases with sudden movement. An alternative approach is to use an elevated echocardiography table with a large cutout, if available; the animal is placed in right lateral recumbency, and the tap is performed from underneath. An advantage to this method is that fluid moves to the right (dependent) side with gravity; however, if adequate space is not available for wide sterile skin preparation or needle/catheter manipulation, this approach is not advised. Echocardiographic guidance can be used but generally is not necessary unless the effusion is of small volume or appears compartmentalized.

A variety of equipment can be used for pericardiocentesis. A butterfly needle/catheter (19- to 21-gauge) or appropriately long hypodermic or spinal needle attached to extension tubing is adequate in emergency situations. However, an over-the-needle catheter system can be a safer alternative because it reduces the risk of cardiopulmonary laceration during fluid aspiration. The catheter is chosen according to patient size. For example, a 12 to 16 gauge, 10 to 15 cm (4- to 6-in) long catheter system, or a commercially available over-the-wire pericardial drainage catheter allows for faster fluid removal in large dogs. For small dogs, an 18 to 20 gauge, 3.75 to 5.0 cm (1.5-2.0 in) long catheter could be adequate. Additional equipment to assemble before the procedure includes sterile extension tubing (except if using a butterfly needle), a three-way stopcock, a 20 to 60 mL collection syringe, a 3-mL syringe and small-gauge needle for local block, lidocaine, small surgical blade (for stab incision when using a larger catheter), sterile ethylenediaminetetraacetic acid (EDTA) and clot (red-top) tubes for fluid samples, and a large fluid collection receptacle. Personnel able to help restrain the animal and assist with fluid aspiration also are essential.

The skin is shaved and surgically prepared over the right precordium, from about the third to seventh intercostal spaces and from sternum to well above the costochondral junction. Before the final scrub, locate and mark the point of strongest precordial impulse; this usually is between the fourth and sixth rib near the costochondral junction. Usually this is the best site for needle entry. Ultrasound also can be used to locate an optimal puncture site. Infiltrate a small volume of 2% lidocaine (0.5-1 mL) into the skin and underlying intercostal muscle to the pleura at the puncture site (alternatively, some clinicians prefer to do this later using sterile technique). Local anesthesia is necessary when using a larger catheter and also recommended for needle pericardiocentesis.

After sterile skin preparation is complete, don sterile gloves and prepare the drainage catheter assembly. When using a large-gauge catheter, a couple of tiny (~1 mm) side holes can be cut (smoothly) with a sterile sharp blade or iris scissors near the catheter tip to facilitate fluid drainage. Care must be taken to offset these holes from each other and avoid making them too large, so that the catheter tip is not excessively weakened, lest it break off within the pericardium or pleural space. Carefully replace the catheter over the needle/stylet and attach the extension tubing to this. Then attach the three-way stopcock to the other end of the tubing, and the collection syringe to the stopcock. The stopcock should be set "off" to air. If not done previously, infiltrate lidocaine (with sterile technique) at the puncture site. When using a large-gauge catheter system, make a small stab incision into the skin to facilitate catheter entry. The puncture should be just cranial to the closest rib; when entering the chest, care should be taken to avoid the intercostal vessels that run caudal to each rib.

Before inserting the needle/catheter into the chest, pass the attached collection syringe to an assistant. Although a perpendicular orientation of needle/catheter to the skin initially may help avoid intercostal vessels, it often is helpful to "aim" the needle tip toward the point of the patient's opposite (left) shoulder as the chest is entered. Once the needle has penetrated the skin, the assistant should gently apply negative pressure to the attached syringe as the operator slowly advances the needle toward the heart. This way, any fluid will be detected as soon as it is encountered. Pleural fluid, usually straw-colored, may enter the tubing first. It is important to hold the needle/catheter steady during insertion to avoid extraneous motion of the sharp tip within the chest. When contacted, the pericardium creates increased resistance to needle advancement and may produce a subtle scratching sensation. With gentle pressure, slowly advance the needle through the pericardium. A loss of resistance may be felt with needle penetration, and pericardial fluid (usually dark red) will appear in the tubing. During initial insertion, the

extension tubing is attached to the needle stylet. The needle/catheter unit must be advanced far enough into the pericardial space so that the catheter is not deflected out of the pericardium as the needle stylet is removed; advance the catheter before pulling back on the stylet. After advancing the catheter into the pericardial space and removing the needle, attach the extension tubing directly to the catheter. Initial pericardial fluid samples should be saved into the sterile EDTA and serum clot tubes for evaluation. Then aspirate as much pericardial fluid as possible. When fluid drainage becomes difficult or stops, adjusting the catheter position slightly or tilting the patient more sternally may allow additional fluid retrieval. A small backflush into the catheter also may help.

If the needle contacts the heart, a prominent scratching or tapping sensation usually is felt, the needle may move with the heartbeat, and ventricular premature complexes are often provoked. The needle should be retracted slightly if cardiac contact occurs. It is important to avoid excessive needle motion within the chest.

When no additional pericardial fluid can be aspirated, the catheter is slowly withdrawn under continued but gentle negative pressure. A quick echocardiographic recheck should verify whether tamponade is resolved, cardiac filling is improved, and if any pericardial fluid remains. If substantial pericardial effusion remains, pericardiocentesis is repeated using a fresh catheter system and slight adjustment in the patient's position, if needed. A sample of the effusion should be submitted for fluid analysis and cytologic evaluation, and additional fluid reserved in the sterile clot tube for possible culture, pending cytology results. Further echocardiographic monitoring of the patient for acute recurrence of pericardial effusion before hospital discharge is wise, especially with suspected HSA.

Verifying Catheter Location

Pericardial effusion usually appears quite hemorrhagic. It can be distressing to see dark, bloody fluid being aspirated from near the heart, but pericardial fluid can be differentiated from intracardiac blood in several ways. Unless the fluid is caused by recent pericardial hemorrhage, it will not clot. A few drops can be placed on the table or into a serum tube to check this. The PCV of pericardial fluid usually is much lower than that of peripheral blood (except in some dogs with HSA); also, the supernatant is xanthochromic (yellow tinged). As the pericardial fluid is drained, the animal's ECG complexes usually increase in amplitude, tachycardia diminishes, and some dogs take a deep breath and appear to be more comfortable. On the other hand, if intracardiac blood is being aspirated, the patient is likely to become more tachycardic and hypotensive. Another method to verify catheter location, if an echo/ultrasound transducer is available, is to rapidly inject a small bolus of sterile, agitated saline through the pericardiocentesis catheter (via the three-way stopcock) to create an echocontrast ("bubble") study. If the catheter tip is within the pericardial space, small bright microbubbles will appear within the pericardial fluid around the heart. If the catheter tip has penetrated a cardiac chamber, the bubbles will appear within the heart.

Complications of Pericardiocentesis

Complications can include cardiac injury or puncture causing arrhythmias (the most common complication, although usually self-limiting when the needle is withdrawn); lung laceration causing pneumothorax and/or hemorrhage; coronary artery laceration with myocardial infarction or further bleeding into the pericardial space; dissemination of infection or neoplastic cells into the pleural space; and, occasionally, death.

CONSTRICTIVE PERICARDIAL DISEASE

Etiology and Pathophysiology

Constrictive pericardial disease is diagnosed occasionally in dogs but only rarely in cats. This condition occurs when thickening and scarring of the visceral, parietal, or both pericardial layers restrict ventricular diastolic expansion and prevent normal cardiac filling. Both ventricles are affected. Usually the entire pericardium is involved symmetrically. Fusion of parietal and visceral pericardial layers obliterates the pericardial space in some cases. In others, the visceral layer (epicardium) alone is involved. A small amount of pericardial effusion (constrictive-effusive pericarditis) may be present.

Although the etiology of constrictive pericardial disease often is unknown, acute inflammation with fibrin deposition and possibly varying degrees of pericardial effusion are thought to precede its development. Some cases in dogs were attributed to recurrent idiopathic hemorrhagic effusion, infectious pericarditis (especially from coccidioidomycosis but potentially also from actinomycosis, mycobacteriosis, blastomycosis, or bacteria), a metallic foreign body in the pericardium, tumors, prior PPDH surgery, and idiopathic pericardial osseous metaplasia and fibrosis.

Increased fibrous connective tissue and variable amounts of inflammatory and reactive pericardial infiltrates are seen on histopathologic examination. Pericardial fibrosis creates a stiff shell around the heart and increases ventricular interdependence. Ventricular filling is limited to early diastole, after which ventricular expansion is abruptly curtailed, in cases of advanced constrictive pericardial disease. Any further ventricular filling is accomplished only at high venous pressures. Compromised filling reduces cardiac output. Compensatory neurohormonal activation causes fluid retention with congestive signs of pleural effusion and ascites, as well as tachycardia and vasoconstriction.

Clinical Features

Middle-aged, large- to medium-breed dogs are affected most often. Males and German Shepherd Dogs may be at higher risk. Some dogs have a history of pericardial effusion. Clinical signs of right-sided CHF predominate. Abdominal distention (ascites), tachypnea or labored breathing, tiring,

syncope, weakness, and weight loss are common complaints. These signs may develop over weeks to months. Ascites and jugular venous distention are the most consistent clinical findings, as in dogs with cardiac tamponade. Weakened femoral pulses and muffled heart sounds are also typical. A diastolic pericardial "knock" sound, resulting from abrupt deceleration of ventricular filling in early diastole, has been described but usually is not identified in dogs. A systolic murmur or click, probably caused by valvular disease rather than the pericardial pathology, or a diastolic gallop sound may be heard.

Diagnosis

The diagnosis of constrictive pericardial disease can be challenging. Typical radiographic findings include mild to moderate cardiomegaly, pleural effusion, and caudal vena cava distention. Reduced cardiac motion may be evident on fluoroscopy (as with cases of pericardial effusion). Echocardiographic changes in dogs with constrictive pericardial disease can be subtle. Suggestive findings on M-mode and 2-D examination include diastolic flattening of the LV free wall and abnormal diastolic septal motion. During inspiration, leftward deviation of the interventricular and atrial septa reflects the relative increase in right heart filling at the expense of left heart filling during this phase of respiration. During exhalation, the septa shift rightward. The pericardium may appear thickened and intensely echogenic, but differentiating this from normal pericardial echogenicity may be impossible. Mild pericardial effusion is seen in some cases. RA collapse is not expected with constrictive disease, in contrast to effusion with cardiac tamponade. Other observations include vena cava and hepatic vein dilation, as well as pleural and abdominal effusions. Doppler mitral and tricuspid inflow velocities show increased variability with respiration. The transtricuspid early filling (E-wave) peak velocity is greatest in early inspiration, whereas the maximum peak transmitral E-wave velocity occurs with the onset of expiration. ECG abnormalities described with constrictive pericardial disease include sinus tachycardia, P-wave prolongation, and reduced-voltage QRS complexes.

A CVP greater than 15 mm Hg is common. Intracardiac hemodynamic measurements are diagnostic. In addition to high mean atrial and diastolic ventricular pressures, the atrial pressure waveform shows a prominent y descent (during ventricular relaxation). In contrast, with cardiac tamponade, the y descent is diminished because ventricular diastolic expansion immediately raises intrapericardial pressure and impairs caval flow into the RA (preventing the normal early diastolic decrease in CVP and y descent). With constrictive pericardial disease, filling pressure is low only in early diastole (during the time of y descent). Another classic finding with constrictive pericardial disease is an early diastolic dip in ventricular pressure, followed by a mid-diastolic plateau as filling is curtailed; however, this is not seen consistently in dogs. Angiocardiography could be unremarkable or might show vena caval and mild atrial enlargement with increased endocardial-pericardial distance.

Treatment and Prognosis

Pericardiectomy is necessary to improve ventricular filling. This is more likely to be successful when only the parietal pericardium is involved. Constrictive pericardial disease involving the visceral layer requires epicardial stripping. This procedure increases the surgical difficulty and associated complications. Pulmonary thrombosis reportedly is a common postoperative complication and can be life-threatening. Tachyarrhythmias are another complication of surgery. In the postoperative period, modest diuretic doses, and possibly an angiotensin-converting enzyme inhibitor, may be helpful. Positive inotropic and vasodilating drugs are not indicated. Constrictive pericardial disease is progressive and, without successful surgical intervention, ultimately fatal. Serologic testing for *Coccidioides* (or other fungal agent) is advisable in endemic regions. Adjunctive antifungal therapy has improved prognosis of affected dogs that survive pericardiectomy.

CARDIAC TUMORS

Etiology and Pathophysiology

Echocardiography has made the antemortem diagnosis of cardiac tumors more common, although the overall prevalence of such neoplasms is low. Some cardiac tumors cause severe clinical signs, whereas others are diagnosed fortuitously. By far, the most common cardiac tumor in dogs is HSA. The RA, especially the right auricle, most frequently is the site of origin. Some HSAs also infiltrate the ventricular wall extensively. Occasionally, this tumor is found within the LV, interventricular septum, or at the heart base. HSAs usually are associated with hemorrhagic pericardial effusion and cardiac tamponade (see p. 176). Primary cardiac HSA is likely to metastasize to other organs, including the lung and spleen. Primary splenic HSA only occasionally metastasizes to the heart. Golden Retrievers, German Shepherds, Afghan Hounds, Cocker Spaniels, English Setters, and Labrador Retrievers, among others, are at higher risk for this tumor.

Masses involving the heart base and ascending aortic region usually are aortic body tumors (also known as chemodectomas or nonchromaffin paragangliomas). This is the second-most-common cardiac tumor type in dogs. These are neoplasms of the chemoreceptor aortic bodies. However, ectopic thyroid or parathyroid or mixed-cell–type tumors also can occur at the heart base. Heart base tumors mainly tend to be locally invasive around the root of the aorta and surrounding structures, although metastases to other organs can occur and could be more common than previously appreciated. Unless they cause symptomatic pericardial effusion or dysfunction of surrounding structures, heart base tumors can be an incidental finding. Chemodectomas are reported more frequently in brachycephalic dogs (specifically Boxers, Boston Terriers, and Bulldogs) but affect individuals of other breeds as well. Clinical signs associated with heart base tumors most often are related to pericardial effusion and cardiac tamponade.

Mesothelioma occurs sporadically but may be more prevalent in some geographic regions. There appears to be no gender or breed predisposition in dogs, although in Golden Retrievers with mesothelioma, chronic inflammation associated with prior idiopathic pericardial disease is a postulated predisposing factor. Mesothelioma is rare in cats. This neoplasm can appear in variable forms and can be difficult to identify echocardiographically. Other primary tumors involving the heart are rare in dogs but include myxoma, various types of sarcoma, and other neoplasms. Most cases involve right-heart structures. Metastatic or systemic tumors, especially lymphoma, but also other sarcomas (including HSA), malignant histiocytosis, and various carcinomas, may involve the heart or pericardium as well. Most breeds affected with malignant histiocytosis are Golden Retrievers, Labrador Retrievers, Rottweilers, or Greyhounds; mild pericardial effusion, without overt signs of cardiac tamponade, coexists with pleural and abdominal effusion. Rarely, nonneoplastic mass lesions can affect the heart or pericardium, including fungal granuloma or pyogranuloma (as with coccidioidomycosis or blastomycosis), other granulomatous or cystic inflammatory lesions, and auricular aneurysm.

Lymphoma is the most common cardiac tumor in cats. Various (mostly metastatic) carcinomas occur less frequently. HSA is rare; other tumors (such as aortic body tumor, fibrosarcoma, rhabdomyosarcoma) also have been reported sporadically in cats.

Cardiac tumors can cause several pathophysiologic abnormalities, depending on their location and size. Many tumors impede cardiac filling by causing pericardial effusion and cardiac tamponade (discussed earlier). An intrapericardial mass can itself externally compress the heart, as well as cause pericardial effusion. Alternatively, a tumor that grows into the lumen of a cardiac chamber or great vessel can physically obstruct blood inflow or outflow and lead to low cardiac output signs. Myocardial tumor infiltration or secondary ischemia can disrupt the cardiac rhythm and impair contractility. Ultimately, the patient's clinical signs relate to one or a combination of these disturbances. If the tumor is small or has not yet markedly impaired cardiac function, clinical signs may be absent.

Clinical Features

Dogs with cardiac tumors tend to be middle-aged and older. More than 85% of affected dogs are between 7 and 15 years of age; however, very old dogs (>15 years) have a surprisingly low prevalence. Reproductive status influences the relative risk for cardiac tumors in dogs, despite a similar frequency of occurrence in males and females overall. Gonadectomized dogs have a greater relative risk, especially spayed females, which have a risk that is four to five times greater compared with that of intact females. Intact and neutered males also have greater risk than intact females. Certain breeds of dog have a higher prevalence of cardiac tumor compared with the general population (Table 9.1). The age distribution of cats with cardiac tumors is different from that of dogs; about 28% are 7 years old or younger. It is unknown whether reproductive status affects relative risk for cardiac tumors in cats.

Signs of right-sided CHF result from cardiac tamponade or from blood flow obstruction within the RA or RV. Syncope, weakness associated with exertion, and other low output signs also result from cardiac tamponade, blood flow obstruction, arrhythmias, or impaired myocardial function secondary to cardiac tumors. Tachyarrhythmias of any type can also occur; intracardiac conduction disturbances sometimes result from tumor infiltration. Lethargy or collapse might

TABLE 9.1

Dog Breeds with High Prevalence of Cardiac Tumors

BREED	# WITH TUMOR	# IN DATABASE	RELATIVE RISK	95% CI
Saluki	6	401	7.75	3.92-15.38
French Bulldog	3	215	7.19	2.72-19.23
Irish Water Spaniel	2	168	6.13	1.81-20.83
Flat-Coated Retriever	4	534	3.85	1.54-9.62
Golden Retriever	215	32,940	3.73	3.26-4.27
Boxer	52	8496	3.22	2.47-4.18
Afghan Hound	12	2080	2.97	1.72-5.10
English Setter	21	3796	2.86	1.89-4.31
Scottish Terrier	16	3290	2.50	1.55-4.03
Boston Terrier	25	5225	2.47	1.68-3.62
Bulldog	24	5580	2.22	1.49-3.29
German Shepherd	129	37,872	1.81	1.52-2.17

CI, Confidence interval.
Modified from WA, Hopper DL: Cardiac tumors in dogs: 1982-1995, *J Vet Intern Med* 13:95, 1999.

relate to bleeding tumors (e.g., HSA) present in extracardiac locations as well.

Auscultatory findings vary. Arrhythmias or muffled heart sounds (if large pericardial effusion is present) are common. Sometimes a murmur is caused by partial obstruction of intracardiac blood flow caused by the tumor mass, but murmurs associated with unrelated disease (for example, chronic mitral valve disease) are more common. Conversely, auscultatory findings can be normal.

Diagnosis

Hematologic and serum biochemical tests generally are nonspecific in dogs and cats with cardiac tumors; with flow cytometry based hematology analyzers, neoplastic cells are frequently detected in the graphics of dogs with lymphoma or malignant histiocytosis. Plasma cTnI concentrations are likely to be elevated (>0.25 ng/mL) in dogs with cardiac HSA, compared with dogs with noncardiac HSA, other neoplasms, or pericardial effusion not caused by HSA. Mild increases in serum alanine aminotransferase activity and azotemia might occur in dogs with CHF signs. HSA can be associated with a regenerative anemia, increased number of nucleated red blood cells and schistocytes (with or without acanthocytes), leukocytosis, and thrombocytopenia. Pleural and peritoneal fluids, if present, are usually modified transudates.

Radiographic findings are quite variable. The cardiac silhouette may be normal or show an unusual bulge, a mass effect adjacent to the heart, or a globoid cardiac silhouette compatible with pericardial effusion. Intrapericardial masses usually are obscured by pericardial effusion. Caudal vena caval distension, pleural effusion, and/or ascites commonly occur with RV inflow or outflow obstruction. Dorsal deviation of the trachea and increased perihilar opacity are seen in some dogs with heart base tumors. Evidence of pulmonary metastases is found with some primary or secondary (metastatic) cardiac neoplasms; however, radiographic sensitivity for detecting small pulmonary metastases is low. CT, MRI, or other imaging techniques also can help in identifying and defining the extent of cardiac tumors.

The ECG might suggest pericardial effusion (see p. 181). Myocardial infiltration can provoke atrial or ventricular premature complexes or paroxysmal tachycardias. Likewise, varying degrees of AV or intraventricular conduction block and symptomatic bradycardia can develop from conduction system infiltration. Intracardiac tumors that obstruct RV outflow, causing RV systolic pressure overload and compensatory myocardial hypertrophy, can produce a right axis shift and RV hypertrophy pattern on the ECG. Other chamber enlargement or abnormal conduction patterns could result, depending on tumor location and hemodynamic sequelae.

Echocardiography can depict cardiac masses and determine the presence or absence of pericardial effusion, as well as secondary changes in cardiac chamber size, shape, and ventricular function. Doppler techniques allow assessment of associated blood flow abnormalities. Heart base tumors that extend into the pericardial space are easier to see when surrounded by pericardial effusion, just as intracardiac masses are accentuated by the echolucent intracardiac blood surrounding them (Fig. 9.8). The left cranial parasternal transducer position is especially useful for evaluating the ascending aorta, right auricle, and surrounding structures. The location and echocardiographic characteristics of a mass lesion can suggest the type of tumor, although cytologic or histopathologic evaluation is necessary for definitive diagnosis. HSA typically has variable echogenicity, with areas that appear cystic (hypoechoic). Chemodectoma and other heart base masses tend to have a more uniform soft tissue echogenicity. Myocardial lymphoma also can have a mottled appearance with areas of varying echogenicity. Echocardiographic assessment of the tumor's location, size, attachment (pedunculated or broad based), and extent (superficial or deeply invading adjacent myocardium) may help in determining whether surgical resection or biopsy is possible. Visualizing a suspected mass lesion in more than one echocardiographic plane helps verify it and prevent the misinterpretation of artifacts. Fine-needle aspirates for cytologic evaluation can be done under echocardiographic guidance in some cases. A discrete mass lesion often is not found with mesothelioma.

Pericardial fluid analysis is recommended, although definitive diagnosis of neoplasia usually cannot be made based on cytologic findings alone (see p. 181). Cardiac lymphoma or malignant histiocytosis is more likely to be diagnosed on pericardial fluid cytology. Nevertheless, visualization

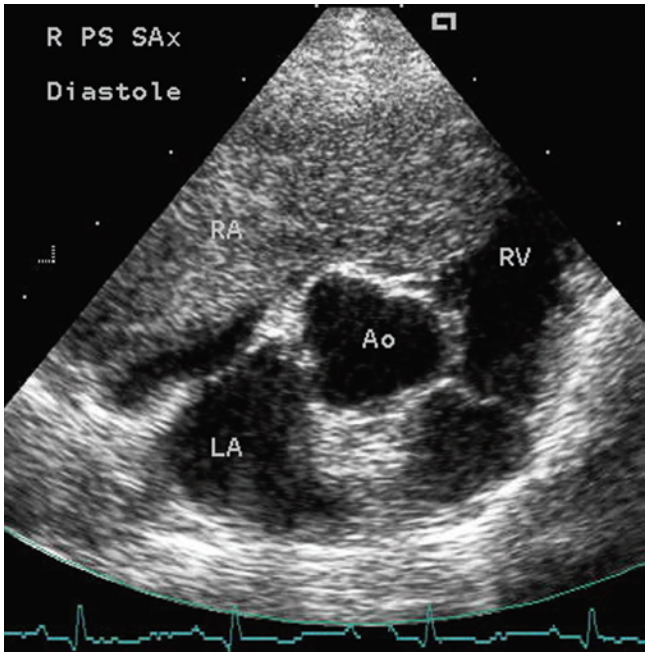


FIG 9.8
Right parasternal short-axis echocardiographic image from a 16-year-old Cocker Spaniel and Poodle mix with ascites and weakness. A large right atrial tumor extends across the tricuspid orifice into the ventricle in this diastolic frame. Pericardial effusion was not present in this dog. *Ao,* Aorta; *LA,* left atrium; *RA,* right atrium; *RV,* right ventricle.

of a cardiac mass using echocardiography, CT, or another modality usually is necessary for tumor identification. Ultrasound-guided transthoracic fine-needle aspiration of some cardiac mass lesions might be possible depending on their location and can yield cytologic diagnosis. Anesthesia or sedation alone may be adequate in some cases.

Treatment and Prognosis

Unfortunately, for most patients with a heart tumor, there are few good long-term options. This is especially so for HSA, mesothelioma, and other masses that cause recurrent tamponade or obstruct blood flow. Pericardiocentesis is indicated immediately for cardiac tamponade (see p. 183). Conservative management, with pericardiocentesis as needed, is used in some patients until episodes of cardiac tamponade become unmanageable. Whether antiinflammatory doses of a glucocorticoid are of benefit is unclear. Surgical pericardiotomy or subtotal pericardiectomy can help prevent recurrent tamponade. Heart base tumors (e.g., chemodectoma) tend to be slow-growing; some never cause clinical signs and are found incidentally on echocardiogram or necropsy. For those that cause cardiac tamponade, partial pericardiectomy or pericardiotomy potentially could prolong survival for months or possibly even years.

Complete surgical resection rarely is possible because heart base, as well as many other tumors, are so locally invasive. Nevertheless, an occasional mass might be amenable to surgical resection depending on its location and extent; an example would be a small tumor localized to the tip of the right auricle. However, surgical biopsy of a nonresectable mass could be helpful if chemotherapy is contemplated.

Many, if not most, cardiac tumors are fairly unresponsive to chemotherapy, although some are treated with short-term success. Doxorubicin or carboplatin have been used in dogs with HSA for temporary palliation, with or without surgical mass resection. Lymphoma and malignant histiocytosis are treated using standard protocols. In regions where available, radiation therapy might provide another palliative option for dogs with chemodectoma or other masses. Early experience in dogs presumed to have HSA suggests that radiation therapy can slow the recurrence rate of cardiac tamponade, and therefore provide increased time before repeated pericardiocentesis is required. Current sources for antineoplastic drug protocols, radiation therapy, or other tumor treatment modalities should be consulted as needed. Overall, the long-term prognosis for animals that have shown clinical signs because of a cardiac tumor generally is guarded to poor.

Suggested Readings

Ajithdoss DK, et al. Coccidioidomycosis presenting as a heart base mass in two dogs. *J Comp Pathol*. 2011;145:132–137.

Amati M, et al. Pericardial lymphoma in seven cats. *J Feline Med Surg*. 2014;16:507–512.

Aronsohn MG, Carpenter JL. Surgical treatment of idiopathic pericardial effusion in the dog: 25 cases (1978-1993). *J Am Anim Hosp Assoc*. 1999;35:521–525.

Atencia S, Doyle RS, Whitley NT. Thoracoscopic pericardial window for management of pericardial effusion in 15 dogs. *J Small Anim Pract*. 2013;54:564–569.

Boddy KN, et al. Cardiac magnetic resonance in the differentiation of neoplastic and nonneoplastic pericardial effusion. *J Vet Intern Med*. 2011;25:1003–1009.

Boston SE, Higginson G, Monteith G. Concurrent splenic and right atrial mass at presentation in dogs with HSA: a retrospective study. *J Am Anim Hosp Assoc*. 2011;47:336–341.

Brisson BA, Holmberg DL. Use of pericardial patch graft reconstruction of the right atrium for treatment of hemangiosarcoma in a dog. *J Am Vet Med Assoc*. 2001;218:723–725.

Burns CG, Bergh MS, McLoughlin MA. Surgical and nonsurgical treatment of peritoneopericardial diaphragmatic hernia in dogs and cats: 58 cases (1999-2008). *J Am Vet Med Assoc*. 2013;242:643–650.

Cagle LA, et al. Diagnostic yield of cytologic analysis of pericardial effusion in dogs. *J Vet Intern Med*. 2014;28:66–71.

Case JB, et al. Outcome evaluation of a thoracoscopic pericardial window procedure or subtotal pericardectomy via thoracotomy for the treatment of pericardial effusion in dogs. *J Am Vet Med Assoc*. 2013;242:493–498.

Chun R, et al. Comparison of plasma cardiac troponin I concentrations among dogs with cardiac hemangiosarcoma, noncardiac hemangiosarcoma, other neoplasms, and pericardial effusion of nonhemangiosarcoma origin. *J Am Vet Med Assoc*. 2010;237:806–811.

Cobb MA, et al. Percutaneous balloon pericardiotomy for the management of malignant pericardial effusion in two dogs. *J Small Anim Pract*. 1996;37:549–551.

Cote E, Schwarz LA, Sithole F. Thoracic radiographic findings for dogs with cardiac tamponade attributable to pericardial effusion. *J Am Vet Med Assoc*. 2013;243:232–235.

Crumbaker DM, Rooney MB, Case JB. Thoracoscopic subtotal pericardiectomy and right atrial mass resection in a dog. *J Am Vet Med Assoc*. 2010;237:551–554.

Davidson BJ, et al. Disease association and clinical assessment of feline pericardial effusion. *J Am Anim Hosp Assoc*. 2008;44:5–9.

Day MJ, Martin MW. Immunohistochemical characterization of the lesions of canine idiopathic pericarditis. *J Small Anim Pract*. 2002;43:382–387.

De Laforcade AM, et al. Biochemical analysis of pericardial fluid and whole blood in dogs with pericardial effusion. *J Vet Intern Med*. 2005;19:833–836.

Ehrhart N, et al. Survival of dogs with aortic body tumors. *Vet Surg*. 2002;31:44–48.

Fine DM, Tobias AH, Jacob KA. Use of pericardial fluid pH to distinguish between idiopathic and neoplastic effusions. *J Vet Intern Med*. 2003;17:525–529.

Ghaffari S, et al. A retrospective evaluation of doxorubicin-based chemotherapy for dogs with right atrial masses and pericardial effusion. *J Small Anim Pract*. 2014;55:254–257.

Guglielmini C, et al. Accuracy of radiographic vertebral heart score and sphericity index in the detection of pericardial effusion in dogs. *J Am Vet Med Assoc*. 2012;241:1048–1055.

Guglielmini C, et al. Sensitivity, specificity, and interobserver variability of survey thoracic radiography for the detection of heart base masses in dogs. *J Am Vet Med Assoc*. 2016;248:1391–1398.

Hall DJ, et al. Pericardial effusion in cats: a retrospective study of clinical findings and outcome in 146 cats. *J Vet Intern Med*. 2007;21:1002–1007.

Humm KR, Keenaghan-Clark EA, Boag AK. Adverse events associated with pericardiocentesis in dogs: 85 cases (1999-2006). *J Vet Emerg Crit Care*. 2009;19:352–356.

MacDonald KA, Cagney O, Magne ML. Echocardiographic and clinicopathologic characterization of pericardial effusion in dogs: 107 cases (1985-2006). *J Am Vet Med Assoc*. 2009;235:1456–1461.

Machida N, et al. Development of pericardial mesothelioma in Golden Retrievers with a long-term history of idiopathic haemorrhagic pericardial effusion. *J Comp Path*. 2004;131:166–175.

Martin MW, et al. Idiopathic pericarditis in dogs: no evidence for an immune-mediated aetiology. *J Small Anim Pract*. 2006;47:387–391.

Mayhew PD, Dunn M, Berent A. Surgical views: thoracoscopy: common techniques in small animals. *Compend Contin Educ Vet*. 2013;35:E1.

Mellanby RJ, Herrtage ME. Long-term survival of 23 dogs with pericardial effusions. *Vet Rec*. 2005;156:568–571.

Monnet E. Interventional thoracoscopy in small animals. *Vet Clin North Am Small Anim Pract*. 2009;39:965–975.

Morges M, et al. Pericardial free patch grafting as a rescue technique in surgical management of right atrial HSA. *J Am Anim Hosp Assoc*. 2011;47:224–228.

Murphy LA, et al. Constrictive pericarditis following surgical repair of a peritoneopericardial diaphragmatic hernia in a cat. *J Feline Med Surg*. 2014;16:708–712.

Murphy LA, et al. Use of Yunnan Baiyao and epsilon aminocaproic acid in dogs with right atrial masses and pericardial effusion. *J Vet Emerg Crit Care*. 2017;27:121–126.

Nolan MW, et al. Pilot study to determine the feasibility of radiation therapy for dogs with right atrial masses and hemorrhagic pericardial effusion. *J Vet Cardiol*. 2017;19:132–143.

Pedro B, et al. Cytological diagnosis of cardiac masses with ultrasound guided fine needle aspirates. *J Vet Cardiol*. 2016;18:47–56.

Ployart S, et al. Thoracoscopic resection of right auricular masses in dogs: 9 cases (2003-2011). *J Am Vet Med Assoc*. 2013;242:237–241.

Rajagopalan V, et al. Comparison of presumptive echocardiographic and definitive diagnoses of cardiac tumors in dogs. *J Vet Intern Med*. 2013;27:1092–1096.

Rancilio NJ, et al. Use of three-dimensional conformal radiation therapy for treatment of a heart base chemodectoma in a dog. *J Am Vet Med Assoc*. 2012;241:472–476.

Reimer SB, et al. Long-term outcome of cats treated conservatively or surgically for peritoneopericardial diaphragmatic hernia: 66 cases (1987-2002). *J Am Vet Med Assoc*. 2004;224:728–732.

Scollan KF, et al. Use of multidetector computed tomography in the assessment of dogs with pericardial effusion. *J Vet Intern Med*. 2015;29:79–87.

Sidley JA, et al. Percutaneous balloon pericardiotomy as a treatment for recurrent pericardial effusion in 6 dogs. *J Vet Intern Med*. 2002;16:541–546.

Stepien RL, Whitley NT, Dubielzig RR. Idiopathic or mesothelioma-related pericardial effusion: clinical findings and survival in 17 dogs studied retrospectively. *J Small Anim Pract*. 2000;41:342–347.

Stafford Johnson M, et al. A retrospective study of clinical findings, treatment and outcome in 143 dogs with pericardial effusion. *J Small Anim Pract*. 2004;45:546–552.

Tse YC, et al. Evaluation of a training course in focused echocardiography for noncardiology house officers. *J Vet Emerg Crit Care*. 2013;23:268–273.

Vicari ED, et al. Survival times of and prognostic indicators for dogs with heart base masses: 25 cases (1986-1999). *J Am Vet Med Assoc*. 2001;219:485–487.

Ware WA, Hopper DL. Cardiac tumors in dogs: 1982-1995. *J Vet Intern Med*. 1999;13:95–103.

Zini E, et al. Evaluation of the presence of selected viral and bacterial nucleic acids in pericardial samples from dogs with or without idiopathic pericardial effusion. *Vet J*. 2009;179:225–229.

CHAPTER 10

Pulmonary Hypertension and Heartworm Disease



PULMONARY HYPERTENSION

Etiology and Pathophysiology

In adult animals, the pulmonary circulation is a low pressure, low resistance, high capacitance system compared with the systemic circulation. Cardiac output from the right ventricle (RV) is equal to that of the left ventricle (in the absence of systemic-pulmonary shunts), but pulmonary vascular resistance is much lower than systemic vascular resistance. As a result, pulmonary arterial pressures are much lower than systemic arterial pressures (Pressure = Cardiac Output × Resistance). Normal pulmonary arterial pressures are approximately 20 to 25 mm Hg (systolic), 15 mm Hg (mean), and 10 mm Hg (end-diastolic).

Pulmonary arterial hypertension (PAH) is generally defined as systolic pulmonary arterial pressures greater than 35 mm Hg or mean pulmonary arterial pressures greater than 25 mm Hg. PAH severity is graded based on pulmonary arterial systolic pressure as follows: mild PAH (35-55 mm Hg), moderate PAH (55-80 mm Hg), and severe PAH (>80 mm Hg). PAH can occur secondary to a number of disease processes that increase pulmonary vascular resistance through various mechanisms. Common histopathologic changes in affected pulmonary arteries and arterioles include medial hypertrophy, intimal proliferation and fibrosis, luminal thrombosis, and eventually arterial necrosis.

The World Health Organization (WHO) classifies pulmonary hypertension using a five-group system that can be modified for application to veterinary patients. Group I PAH includes idiopathic (primary) pulmonary hypertension, congenital retention of fetal pulmonary vascular resistance, and pulmonary overcirculation from congenital left-to-right cardiac shunts causing vascular injury and pulmonary arterial remodeling. In the context of a congenital shunt, if PAH becomes severe enough that pulmonary arterial pressure exceeds systemic arterial pressure, shunt reversal occurs (Eisenmenger's physiology; see p. 114). Group II refers to PAH occurring secondary to pressure buildup across the pulmonary capillary bed due to chronically elevated pulmonary venous pressures, as seen in mitral regurgitation and other left-sided cardiac diseases. In such cases, pulmonary arterial pressure increases to maintain pulmonary blood flow in the face of resistance to pulmonary venous drainage. Typically, such "postcapillary" PAH is only mild to moderate, because pulmonary venous pressure can increase to only a certain limit before pulmonary edema develops; a disproportionate elevation in pulmonary arterial pressure suggests an element of precapillary reactive vasoconstriction in addition to pulmonary venous hypertension (see Chapter 6, p. 130). Group III PAH includes hypoxic pulmonary disease (such as pulmonary fibrosis or other chronic bronchopulmonary disease) leading to reactive vasoconstriction, reduced vascular area, and vascular remodeling. Group IV PAH refers to pulmonary thromboembolic disease. Thrombotic vascular obstruction reduces total cross-sectional pulmonary vascular area by mechanically obstructing vessels and provoking local hypoxic pulmonary vasoconstriction, as well as other reactive changes. Underlying causes of thrombotic disease and hypercoagulability are discussed in Chapter 12. Heartworm disease (HWD) is one of the most clinically important causes of PAH in dogs. The pathophysiology of PAH in HWD is multifactorial, including elements of direct pulmonary arteritis, hypoxic pulmonary disease causing reactive vasoconstriction (Group III), and pulmonary thromboembolic disease (Group IV). HWD is therefore sometimes classified separately as a "miscellaneous" cause of PAH (Group V). Retrospective studies report the most common causes of PAH in dogs to be pulmonary venous hypertension from left-sided heart disease (Group II, ~40%) and hypoxic pulmonary disease (Group III, 20%-40%), although this distribution is heavily influenced by the incidence of HWD in the region of study.

In addition to the WHO classification system, mechanisms of PAH can also be categorized as "precapillary" (primarily affecting pulmonary arteries and arterioles, before blood reaches the pulmonary capillary bed) or "postcapillary" (primarily affecting pulmonary veins, with secondary buildup of pressure across the capillary bed back to the pulmonary arterial tree). Group II PAH (pulmonary venous hypertension secondary to left-sided heart disease) is thus

an example of postcapillary PAH; all other causes of PAH are precapillary.

Clinical Findings

Clinical signs of moderate to severe PAH include reduced exercise tolerance, fatigue, persistent respiratory difficulty, cough, and syncope. As these clinical signs overlap with common clinical signs of many primary respiratory diseases, it often is challenging to determine whether clinical signs are directly attributable to PAH or to the underlying disease. Severe PAH also can lead to right heart remodeling (cor pulmonale) and eventual right-sided congestive heart failure (CHF), usually manifesting as ascites. Physical examination findings could include cyanotic mucous membranes (at rest or with exertion), a split S_2 heart sound, right-sided systolic heart murmur (of tricuspid regurgitation [TR]), and possibly jugular venous distension and/or pulsation. Heart rate and rhythm are usually normal; sinus arrhythmia and relative sinus bradycardia may reflect presence of underlying pulmonary pathology causing elevated vagal tone.

The clinical presentation of a dog with severe precapillary PAH (respiratory distress, cough, syncope) closely mimics presentation of a dog with pulmonary edema secondary to left-sided CHF. An additional confounding auscultatory finding is pulmonary crackles, which are common in dogs with pulmonary edema but can also be present in dogs with PAH secondary to pulmonary fibrosis or chronic pneumonia. Aspects of the physical examination can help differentiate these two presentations before obtaining a more definitive diagnosis with diagnostic imaging (thoracic radiographs and echocardiography). Dogs with left-sided CHF almost always have loud systolic heart murmurs (grade IV/VI or louder) with point of maximal intensity on the left hemithorax. Softer or right-sided heart murmurs raise index of suspicion for PAH. Dogs with left-sided CHF typically have sinus tachycardia with heart rates of 150 to 160 beats per minute because of sympathetic nervous system stimulation or may have tachyarrhythmias such as ventricular premature complexes or atrial fibrillation. Dogs with PAH generally have a sinus arrhythmia and/or relative sinus bradycardia related to elevated parasympathetic tone from underlying respiratory disease.

Diagnosis

RADIOGRAPHY

Radiographic findings in patients with moderate to severe PAH can include RV enlargement; main pulmonary artery dilation ("bulge" of the pulmonary trunk); and enlargement, tortuosity, and blunting of lobar pulmonary arteries (Fig. 10.1) Caudal lobar arteries can be considered enlarged if their width on dorsoventral (DV) or ventrodorsal (VD) views is greater than the width of the proximal third rib. Occasionally, dogs with severe PAH have patchy alveolar infiltrates that resolve rapidly with sildenafil administration. These infiltrates are thought to represent a variant of noncardiogenic pulmonary edema caused by regional nonuniformity in pulmonary capillary perfusion. Variable reactive pulmonary arterial vasoconstriction causes some areas of lung to be overperfused compared with others, leading to focally high hydrostatic pressure and edema formation. These alveolar infiltrates must be differentiated from cardiogenic pulmonary edema (caused by left-sided CHF), because sildenafil is the preferred treatment.

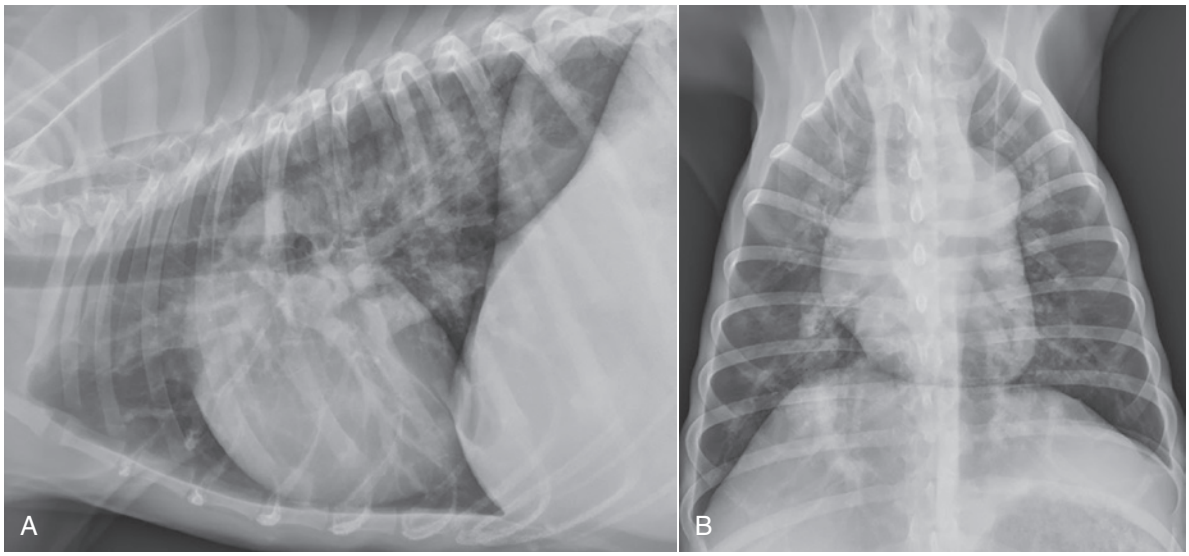


FIG 10.1
Lateral **(A)** and dorsoventral **(B)** radiographs from a young male Pit Bull with advanced heartworm disease. Note enlargement of the main pulmonary artery (particularly on dorsoventral view) and branch pulmonary arteries, as well as mild patchy interstitial pattern consistent with pneumonitis.

ELECTROCARDIOGRAPHY

Electrocardiographic (ECG) findings often are normal, although severe PAH can cause a right axis deviation from RV enlargement. Tall P waves suggestive of right atrial enlargement might also be found. Arrhythmias, such as ventricular premature complexes (originating from the RV) or atrial fibrillation, can occur with advanced cor pulmonale.

ECHOCARDIOGRAPHY

Echocardiographic findings in dogs with severe PAH include RV and RA dilation, RV hypertrophy, flattening of the interventricular septum with paradoxical septal motion, a small left heart, and pulmonary artery dilation (larger than the aorta) (Fig. 10.2). Secondary TR or pulmonic insufficiency (PI) are common, and their maximal velocity can be used to assess severity of the pulmonary hypertension by estimating pulmonary arterial systolic and diastolic pressures, respectively (see Chapter 2, p. 30). More advanced echocardiographic indices suggestive of PAH include transpulmonic flow profile, RV systolic time intervals, tissue Doppler indices of tricuspid annulus motion, tricuspid annular plane systolic excursion, and pulmonary artery distensibility index.

ADVANCED IMAGING

The gold standard diagnosis of PAH is right heart catheterization to measure pulmonary arterial pressures directly; however, this is rarely performed in clinical practice. Computed tomography with contrast can confirm size and tortuosity of pulmonary arteries, and may be useful in diagnosing underlying causes of PAH including pulmonary thromboemboli and pulmonary fibrosis.

Clinicopathologic Findings

Increased red blood cell distribution width (RDW) often is seen in dogs with severe PAH. Arterial blood gas evaluation may show hypoxemia and hypercapnia. Other routine laboratory test results (complete blood count [CBC], chemistry panel, urinalysis) will vary depending on the underlying cause of PAH. Cardiac biomarkers (NT-proBNP and cardiac troponin I) can be elevated in dogs with either precapillary or postcapillary PAH.

Diagnosis of Underlying Disease

Heartworm (HW) antigen testing should be performed in any dog diagnosed with PAH. If HWD is ruled out and echocardiography does not identify significant left-sided heart disease as a postcapillary cause for PAH, other potential etiologies of PAH should be considered. This diagnostic workup should be prioritized based on signalment and clinical presentation but may include airway imaging (bronchoscopy, fluoroscopy), airway sampling (bronchoalveolar lavage or tracheal wash), thoracic computed tomography, assessment of hypercoagulability (D-dimers or thromboelastography), or, potentially, lung biopsy.

Treatment and Prognosis

The only drugs currently available in veterinary medicine for directed therapy of precapillary PAH are the

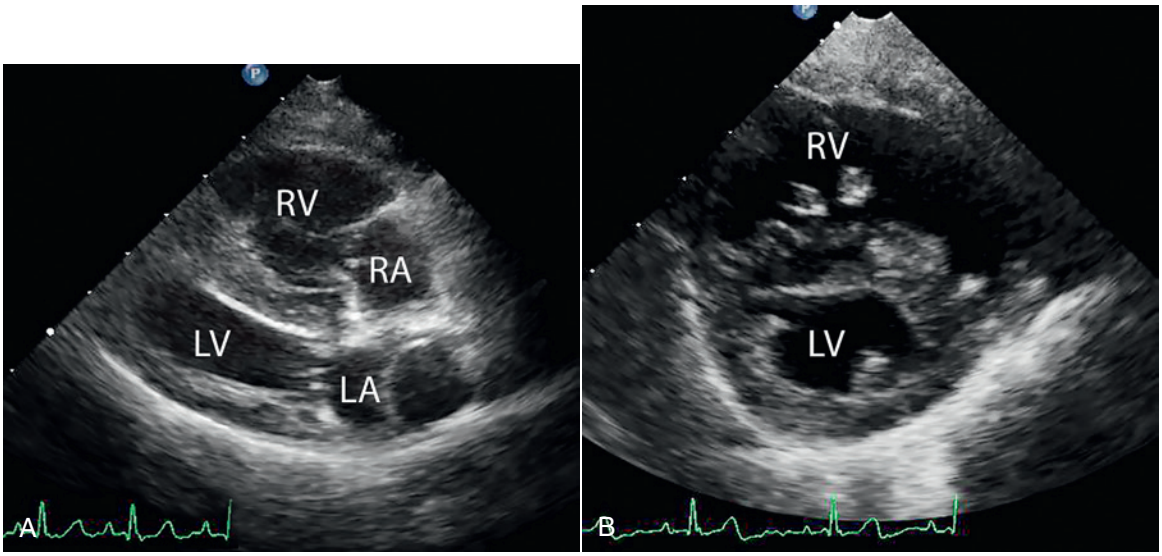


FIG 10.2
Right parasternal echocardiographic images from an older male Chihuahua with severe pulmonary arterial hypertension secondary to chronic bronchopulmonary disease. Views from the right parasternal **(A)** four-chamber long-axis and **(B)** short-axis at the level of the left ventricular papillary muscles are provided. Note the severe right ventricular hypertrophy and enlargement, right atrial enlargement, small left heart, and flattening of the interventricular septum. *RA,* Right atrium; *RV,* right ventricle; *LA,* left atrium; *LV,* left ventricle.

phosphodiesterase-5 inhibitors (sildenafil and tadalafil). These drugs decrease the inactivation of cyclic guanosine monophosphate (GMP), a second messenger of the nitric oxide pathway, leading to vasodilation. Phosphodiesterase-5 inhibitors are relatively specific for the pulmonary vasculature and thus act as selective pulmonary vasodilators. Treatment with sildenafil can improve clinical signs and quality of life in dogs with severe PAH, although effects on echocardiographically estimated pulmonary arterial pressures are variable. Dose adjustments typically are made based on clinical status. Adverse effects are uncommon but can include cutaneous flushing, hypotension, and nasal congestion. Other therapies used in people with PAH (endothelin receptor antagonists, prostacyclin analogs, and nitric oxide substrates) usually are cost-prohibitive for veterinary patients, and many require delivery via inhalation or continuous intravenous (IV) infusion.

Management of patients with PAH also involves exercise restriction and treatment of the underlying disease (if identified). Treatment of HWD is discussed later in this chapter; treatment of pulmonary thromboembolic disease is discussed in Chapter 12; and treatment of chronic bronchopulmonary disease is discussed in Chapter 21.

For dogs with postcapillary PAH secondary to left-sided heart disease, treatment focuses on decreasing left atrial (and thus pulmonary venous) pressures. This generally involves balanced systemic vasodilation with pimobendan (a phosphodiesterase-III inhibitor) and an angiotensin-converting enzyme inhibitor (ACEI), as well as preload reduction with diuretics (furosemide). Further systemic arterial vasodilation (afterload reduction) with amlodipine also can be considered; amlodipine has some vasodilatory activity in pulmonary arterioles as well. If clinically relevant PAH persists despite therapy for pulmonary venous hypertension and CHF, sildenafil can be used as adjunctive therapy. Dogs with right-sided CHF secondary to PAH (cor pulmonale) are managed similarly to those with other causes of CHF (furosemide, pimobendan, ACEI, dietary sodium restriction) with the addition of sildenafil.

Prognosis for dogs with PAH varies with underlying disease. Other than HWD, most causes of PAH are advanced and incurable, and pulmonary vascular remodeling is irreversible. The prognosis for dogs with severe PAH generally is poor, with median survival times between 3 and 6 months; treatment with sildenafil improves survival, with one study reporting nearly 75% survival at 1 year postdiagnosis.

HEARTWORM DISEASE

HWD is an important cause of PAH in regions where the disease is endemic. HW infection is widespread throughout the United States, especially along the Eastern and Gulf coasts and in the Mississippi River Valley. The infection rate in unprotected dogs can be up to 45% or higher in some areas. Sporadic cases occur in other areas of the country and Canada; the disease is prevalent in other regions of the world as well. Infection with *Dirofilaria immitis* causes a spectrum of disease ranging from mild, subclinical changes to severe pulmonary disease and secondary right-sided CHF. Dogs and other canids are the preferred host species. Although cats also are affected by HWD, they are more resistant to infection than dogs. The overall prevalence of mature HW infection in cats in the United States is 0.4%, and regionally is thought to be 5% to 15% of that in dogs in the same geographic area. However, exposure to and subsequent clearance of larvae by host reactions is estimated to be much more common.

HEARTWORM LIFE CYCLE

The HW *(D. immitis)* is transmitted by various species of mosquitoes, which act as its obligate intermediate host. A mosquito initially ingests the microfilariae, or first-stage larvae (L_1), which circulate in the blood of an infected host animal. The L_1 develops into an L_2 and then enters the infective L_3 stage within the mosquito over a period of approximately 2 to 2.5 weeks. Symbiotic bacteria of the genus *Wolbachia* are important for larval development within the mosquito. Infective larvae enter the new host when the mosquito takes another blood meal. L_3 larvae migrate subcutaneously within the new host, molting into an L_4 stage within 9 to 12 days, and then entering the L_5 (final) stage by 2 to 3 months postinfection. The juvenile L_5 worms enter the vasculature within about 100 days of infection, where they migrate preferentially to the peripheral pulmonary arteries of the caudal lung lobes. It takes at least 5 to 6 and usually between 7 and 9 months before these worms develop into mature adults; after mating, gravid females release microfilariae (L_1) and the infection becomes patent. Mature male worms grow to approximately 15 to 18 cm, whereas adult females can reach 25 to 30 cm in length. Adult worms can survive for 5 to 7 years in dogs. HW transmission is limited by climate. An average daily temperature of greater than 64° F for about a month is necessary for the L_1 larvae to mature within a mosquito to the infective stage. HW transmission peaks during July and August in temperate regions of the Northern Hemisphere.

Microfilariae passed to another animal by blood transfusion or across the placenta do not develop into adult worms because the mosquito host is required to complete the parasite's life cycle. Therefore puppies younger than 6 months of age that have circulating microfilariae most likely received them transplacentally and do not have patent HWD. Survival of microfilaria for up to 30 months has been reported.

HW development proceeds more slowly in the cat, which is not the natural host, and infection does not become patent (mature) until at least 7 to 8 months postinfection. Adult worms can live for 3 to 4 years in cats. Microfilariae are evident only in a minority of cats. Nevertheless, infection with L_3 through immature L_5 can cause substantial pulmonary disease as the host attempts to reject the parasites.

HEARTWORM DISEASE IN DOGS

Pathophysiology

The presence of adult worms in the pulmonary arteries provokes reactive vascular lesions that reduce vascular compliance and lumen size. Disease severity depends on several factors, including the number of worms, how long they have been present, and the animal's reaction to the parasites. Pathologic vessel changes begin within days after young HWs enter the pulmonary arteries. The host-parasite interaction may be more important than the worm number alone in the development of clinical signs, although a large worm burden is generally associated with severe disease. The pathogenesis of HWD is modulated by the obligate intracellular bacterium *Wolbachia,* which is harbored by *D. immitis* and is integral to its growth and development. This may involve bacterial endotoxins and the host immune response to a major *Wolbachia* surface protein (WSP), which is thought to contribute to pulmonary and renal inflammation. The increase in pulmonary blood flow associated with exercise can exacerbate the pulmonary vascular pathology. A low worm burden can produce serious lung injury and a greater rise in pulmonary vascular resistance if cardiac output is high.

Villous myointimal proliferation of the pulmonary arteries containing HWs is the characteristic lesion. The HW-induced changes begin with endothelial cell swelling, widening of intercellular junctions, increased endothelial permeability, and periarterial edema. Endothelial sloughing leads to the adhesion of activated white blood cells and platelets. Various trophic factors stimulate smooth muscle cell migration and proliferation within the media and into the intima. Villous proliferations consist of smooth muscle and collagen with an endothelium-like covering. These proliferative changes of the intima occur 3 to 4 weeks after adult worms arrive; they cause luminal narrowing of the smaller pulmonary arteries and also induce further endothelial damage and more proliferative lesions. Endothelial damage promotes thrombosis, as well as a perivascular tissue reaction and periarterial edema. However, pulmonary infarction is unusual because collateral circulation within the lung is extensive.

Hypersensitivity (eosinophilic) pneumonitis may contribute to parenchymal lung lesions, and inflammation may organize into eosinophilic granulomas. Interstitial and alveolar infiltrates may become radiographically apparent; partial lung consolidation develops in some animals. Hypoxic vasoconstriction can also play a role in the vascular changes that increase pulmonary vascular resistance and consequently cause PAH. Hypoxia can occur in lung regions where pulmonary infiltrates and/or pulmonary thromboembolism (PTE) cause ventilation/perfusion mismatch. Pulmonary vasoconstriction may be exacerbated by increased endothelin-1 production or vasoconstrictive substances elaborated by HWs. Dead worms stimulate greater host response and worsen the pulmonary disease. Worm fragments and thrombi cause embolization and a more intense inflammatory reaction, which eventually leads to fibrosis.

The worm distribution and accompanying villous proliferation are most severe in the caudal and accessory lobar arteries. Affected pulmonary arteries lose their normal tapered peripheral branching appearance and appear blunted or pruned. Aneurysmal dilation and peripheral occlusion may occur. The vessels become tortuous and proximally dilated as the increased pulmonary vascular resistance demands higher perfusion pressures.

RV dilation and concentric hypertrophy develop in response to the chronic requirement for increased systolic pressure generation. Severe PAH eventually can lead to RV myocardial failure, increased RV diastolic pressure, and signs of right-sided CHF, especially in conjunction with secondary tricuspid insufficiency. Cardiac output progressively declines as the RV fails. When cardiac output becomes inadequate during exercise, exertional dyspnea, fatigue, and syncope can occur. PTE, either postadulticide or spontaneous, can exacerbate PAH and signs of CHF.

HWD can also have systemic complications. Circulating immune complexes or possibly microfilarial antigens result in glomerulonephritis. Renal amyloidosis has been associated rarely with HWD in dogs. Chronic hepatic congestion secondary to HWD may lead to permanent liver damage and cirrhosis. Although the caudal pulmonary arteries are the preferred site, worm migration "upstream" into the right heart and even to vena cavae is associated with heavy worm burdens. A massive number of worms can cause mechanical occlusion of the RV outflow tract, pulmonary arteries, tricuspid valve region, or venae cavae; this is known as the *caval syndrome.* Caval syndrome results in not only cardiovascular instability but also intravascular hemolysis due to physical shearing of red blood cells flowing past the mass of worms, resulting in anemia and hemoglobinuria. Systemic inflammation and thrombotic complications can lead to disseminated intravascular coagulation (DIC) or systemic inflammatory response system (SIRS). Aberrant systemic arterial worm migration causing embolization of the brain, eye, or other systemic arteries occasionally occurs. Cases of hindlimb lameness, with paresthesia and ischemic necrosis, have been described sporadically.

HEARTWORM DISEASE TESTING

Serologic (Antigen) Tests

Adult HW antigen (Ag) tests are recommended as the main screening test for HWD in dogs. Although controversy exists as to whether yearly testing is necessary, for several reasons the American Heartworm Society recommends yearly testing to ensure that prophylaxis is achieved and maintained. Currently available Ag test kits are highly accurate. Circulating Ag is usually detectable by about 6.5 to 7 months after infection but not sooner than 5 months. There is no reason to test puppies younger than 6 months of age. Ideally, testing of adults is recommended at about 6 to 7 months after the preceding transmission season.

Commercially available test kits are immunoassays that detect circulating HW Ag from the adult female reproductive

tract. Most are enzyme-linked immunosorbent assays (ELISAs), although immunochromatographic test methods are also used. These tests are generally specific and have a good sensitivity. Positive results are generally obtained when at least four (and usually fewer) female worms 7 to 8 months or older are present. Most HW Ag tests do not detect infections less than 5 months old, and male worms are not detected. A weak positive or ambiguous test result may be rechecked using a different test kit or repeated after a short time with the same type of kit; microfilaria testing and thoracic radiographs can also increase or decrease index of suspicion for infection. Colorimetric intensity of an Ag test is not a reliable estimate of worm count. A false-positive Ag test result can usually be traced to a technical error. False-negative results may occur with a low worm burden, immature female worms only, male unisex infection, or inaccurate adherence to test kit instructions. False-negative Ag tests have also been reported in some dogs due to formation of HW antigen-antibody complexes in the blood, effectively preventing free Ag to react with the serologic test. Heating the blood sample test tube to 104° C for 10 minutes before Ag testing can separate Ag-Ab complexes and cause a previously negative Ag result to turn positive. Heating the sample is only recommended in cases where false-negative testing due to Ag-Ab complexation is suspected (e.g., a dog that is HW Ag-negative but microfilaria-positive). Routine heating of samples before Ag testing is not currently recommended. For these reasons, the American Heartworm Society recommends that HW antigen test results be interpreted and recorded as either "positive" or "no antigen detected" (NAD), rather than "negative."

Microfilaria identification

The American Heartworm Society recommends that all dogs screened with HW Ag testing be concurrently screened for presence of circulating microfilaria. Microfilaria testing can identify HW Ag-positive patients that are reservoirs of infection, can assess whether high numbers of microfilariae are present before a monthly preventive drug is administered, and can identify HW-positive dogs who have false negative Ag testing (due to Ag-Ab complexation).

The vast majority (~90%) of HW-positive dogs that are not treated with a monthly preventative have circulating microfilariae. The remaining so-called occult infections, in which there are no circulating microfilariae, can result from an immune response that destroys the microfilariae within the lung (true occult infection), unisex infection, sterile adult HWs, or the presence of only immature worms (prepatent infection). Low numbers of microfilariae and diurnal variations in the number of circulating microfilariae in peripheral blood can also cause false-negative microfilaria test results. Occult (microfilaria-negative) infections can still cause severe disease.

Microfilaria concentration tests that use at least 1 mL of blood are recommended for detecting circulating microfilariae. The nonconcentration tests are more likely to miss low numbers of microfilariae, although they do allow observation of microfilarial motility. *Dirofilaria* have a stationary rather than a migratory movement pattern. Nonconcentration tests include examination of a fresh wet blood smear or adjacent to the buffy coat of a spun hematocrit tube.

Concentration tests are done using either a millipore filter or the modified Knott's centrifugation technique. Both techniques lyse the red blood cells and fix any existing microfilariae. The modified Knott test, which involves formalin fixation, centrifugation, and staining with methylene blue, is preferred for measuring larval body size and differentiating *D. immitis* from nonpathogenic filarial larvae such as *Acanthocheilonema* (formerly *Dipetalonema*) *reconditum* (Table 10.1). An occasional false-positive microfilaria test result occurs in animals with microfilariae but no live adult HWs, either due to transplacental transmission of microfilaria to a young puppy or due to recent adult female worm die-off after producing microfilariae.

The macrocyclic lactone preventive drugs, administered monthly, reduce and eliminate microfilaremia by impairing the reproductive function of female and possibly also male worms. Most dogs become amicrofilaremic by 6 to 8 months after initiating treatment with these drugs. Preventive drugs that kill microfilaria very rapidly may cause life-threatening inflammatory reactions during microfilaria die-off. Therefore microfilaria testing was historically mandatory when diethylcarbamazine (DEC) was routinely used as a HW preventive and is also currently recommended if milbemycin is used (the most potent microfilaricide among the macrocyclic lactones).

Clinical Features

There is no specific age or breed predilection for HWD in dogs. Although most affected dogs are between 4 and 8 years

TABLE 10.1

Morphologic Differentiation of Microfilaria

SMEAR	*DIROFILARIA IMMITIS*	*ACANTHOCHEILONEMA RECONDITUM*
Fresh smear	Few to large numbers	Usually small numbers
	Undulate in one place	Move across field
Stained smear*	Straight body	Curved body
	Straight tail	Posterior extremity hook ("button hook" tail); inconsistent finding
	Tapered head	Blunt head
	>295-325 µm long	<275-288 µm long
	>6 µm wide	<6 µm wide

*Size criteria given for lysate prepared using the modified Knott's test (1 mL blood mixed with 9 mL of 2% formalin, then centrifuged for 5 minutes; sediment stained with methylene blue); microfilariae tend to be smaller with lysate of filter tests. Width and morphology are the best discriminating factors.

old, HWD is also diagnosed in dogs younger than 1 year (but older than 6 months) of age, as well as in geriatric animals. Males are affected two to four times as often as females. Large-breed dogs and those living mainly outdoors are at much greater risk of infection than small-breed and indoor dogs. The length of the haircoat does not appear to affect infection risk.

Dogs diagnosed by a positive routine screening test often are asymptomatic. Dogs with occult disease and those not routinely tested are more likely to have advanced pulmonary arterial changes and clinical signs associated with pulmonary hypertension, eosinophilic pneumonitis, and secondary right-sided cardiac remodeling. Dogs with clinical disease generally have a history of poor exercise tolerance, cough, respiratory difficulty, syncope, weight loss, or abdominal distension with fluid. Overall severity of HWD is classified based on severity of clinical signs, radiographic signs, and clinicopathologic abnormalities (Table 10.2). Of all dogs diagnosed with HWD, the majority (70%) are asymptomatic (Class 1), approximately 25% have exercise intolerance or respiratory signs secondary to pneumonitis or pulmonary hypertension (Class 2), and less than 5% present with right-sided CHF or caval syndrome (Class 3 or 4).

Physical examination findings are often normal in dogs with early or mild disease. However, severe disease is associated with poor body condition, tachypnea or dyspnea, clinical signs of severe PAH (see p. 191), or evidence of right-sided CHF (see p. 201). Increased or abnormal lung sounds (wheezes and crackles) can accompany pulmonary parenchymal involvement as seen with eosinophilic pneumonitis. As with other causes of PAH, a loud and often split-second heart sound (S_2) and a murmur of TR are commonly heard on auscultation. Severe pulmonary arteritis and thromboembolism (see p. 224) can lead to marked dyspnea with cyanosis, hemoptysis, fever, DIC, thrombocytopenia, and epistaxis. These signs, as well as anemia and hemoglobinuria, also are associated with caval syndrome (see p. 202). Aberrant worm migration to the central nervous system, eye, femoral arteries, subcutis, peritoneal cavity, and other sites causes signs related to the organ involved.

Diagnosis

RADIOGRAPHY

Radiographic findings can be normal early in the disease process or with only a few worms. However, marked changes develop rapidly in dogs with heavy worm burdens. Characteristic findings are those suggestive of severe PAH, including RV enlargement, a pulmonary trunk bulge, and centrally enlarged and tortuous lobar pulmonary arteries with peripheral blunting (Fig. 10.1 and p. 191). Patchy pulmonary interstitial or alveolar infiltrates suggestive of pneumonitis, PTE, or fibrosis are also common, especially in the caudal lobes. These pulmonary opacities may be mainly perivascular. Occasionally eosinophilic granulomatosis occurs, with more organized interstitial nodules, enlarged bronchial lymph nodes, and sometimes pleural effusion. In severe cases where PAH has progressed to cause right-sided CHF, caudal vena cava enlargement, hepatosplenomegaly, and abdominal or pleural effusion may be seen.

TABLE 10.2

Classification of Heartworm Disease Severity in Dogs

CLASS	CLINICAL SIGNS	RADIOGRAPHIC SIGNS	CLINICOPATHOLOGIC ABNORMALITIES
1 (mild)	None or occasional cough, fatigue on exercise, or mild loss of condition	None	None
2 (moderate)	None or occasional cough, fatigue on exercise, or mild to moderate loss of condition	Right ventricular enlargement and/or some pulmonary artery enlargement; ±perivascular and mixed alveolar/interstitial opacities (pneumonitis)	±Mild anemia (PCV to 30%); ±proteinuria (2+ on dipstick)
3 (severe)	General loss of condition or cachexia; fatigue on exercise or mild activity; occasional or persistent cough; ±dyspnea; ±right-sided heart failure	Right ventricular ±atrial enlargement; moderate to severe pulmonary artery enlargement; perivascular or diffuse mixed alveolar/interstitial opacities (pneumonitis); ±evidence of thromboembolism	Anemia (PCV < 30%); proteinuria (≥2+ on dipstick)
4 (severe) caval syndrome	See p. 202		

PCV, Packed cell volume.

ELECTROCARDIOGRAPHY

ECG findings are usually normal, although advanced disease can cause a right axis deviation or arrhythmias, as with other causes of severe PAH (see p. 192).

ECHOCARDIOGRAPHY

Echocardiographic findings in dogs with advanced HWD are as for other causes of severe PAH, with the additional possibility of visualizing HWs in the right heart. Although HWs located in peripheral pulmonary arteries cannot be seen echocardiographically, worms within the main pulmonary artery and its bifurcation, RV, RA, or vena cavae appear as small, bright parallel echoes (Fig. 10.3). Suspected caval syndrome can be quickly confirmed by echocardiography. Ascites or pleural or pericardial effusion accompanies secondary right-sided CHF. Color-flow Doppler imaging can often reveal TR even when an audible murmur is absent. Spectral Doppler measurement of maximum tricuspid (or pulmonary) regurgitant jet velocity allows estimation of PAH severity (see p. 30).

Clinicopathologic Findings

Eosinophilia, basophilia, neutrophilia, and monocytosis are common but inconsistent hematologic findings. Mild regenerative anemia of inflammatory disease might be noted. More severe anemia secondary to intravascular hemolysis occurs in caval syndrome. Thrombocytopenia can result from platelet consumption in the pulmonary arterial system, especially after adulticide treatment. DIC also develops in some dogs with advanced disease. The immune response to HWs produces a polyclonal gammopathy. Mild to moderate elevations in liver enzyme activity may be seen, especially in cases of right-sided CHF (passive congestion of the liver). Azotemia, either prerenal or secondary to immune-complex glomerulonephritis, occasionally occurs. Proteinuria is found in 10% to 30% of affected dogs and is more likely with advanced disease; hypoalbuminemia can develop in severely affected dogs. If hypoalbuminemia or proteinuria is detected, a urine protein-creatinine ratio (UPC) is advised. Tracheal washings from coughing HW-infected dogs usually indicate eosinophilic inflammation.

Treatment of Dogs With Heartworm Disease

PREADULTICIDE EVALUATION AND TREATMENT

As a general rule, adulticide treatment is recommended for dogs infected with HWs. Dogs who test positive for HW Ag should have a thorough history and physical examination. Pretreatment thoracic radiographs provide the best overall assessment of pulmonary arterial and parenchymal disease status. The risk of postadulticide PTE is increased in dogs with preexisting clinical and radiographic signs

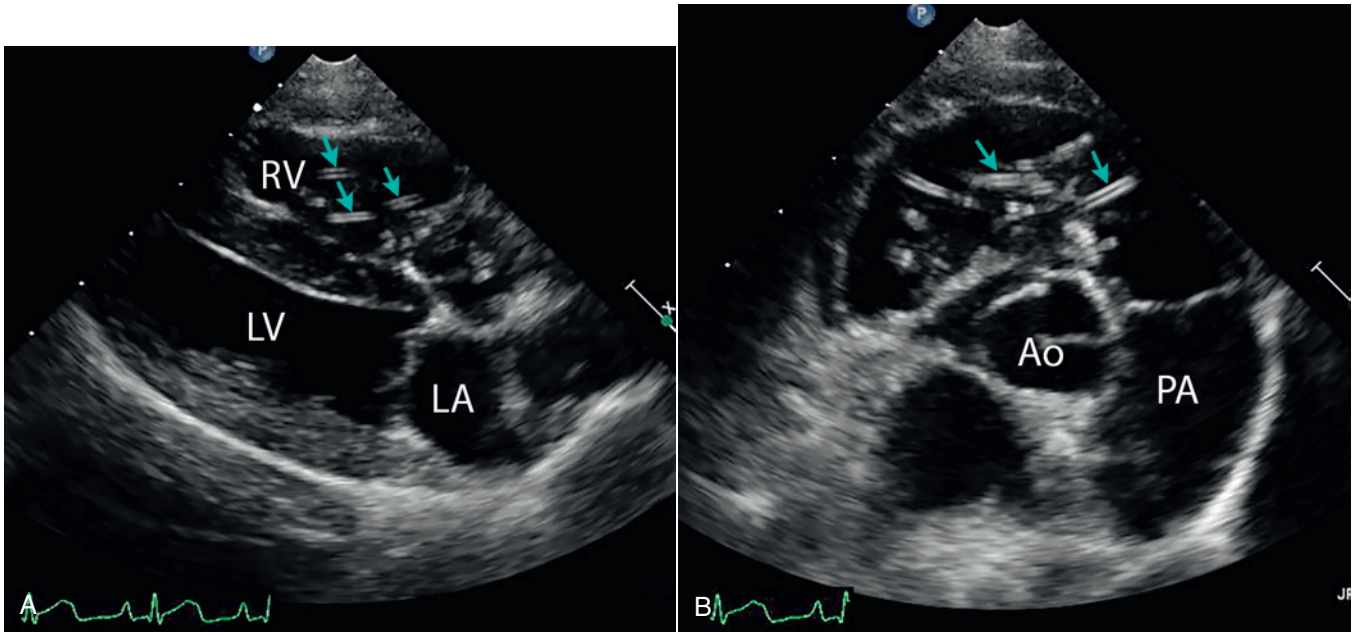


FIG 10.3
Echocardiographic images from a 4-year-old female spayed Beagle with caval syndrome. Views from the right parasternal **(A)** four-chamber long-axis and **(B)** short-axis at the level of the heart base are shown. There is enlargement of the right ventricle and main pulmonary artery, with right ventricular hypertrophy. Many small, bright parallel echoes are apparent in the body of the right ventricle *(arrows)*, caused by a clump of heartworms entangled in the tricuspid valve apparatus. *Ao,* Aortic root; *LA,* left atrium; *LV,* left ventricle; *PA,* main pulmonary artery; *RV,* right ventricle.

of severe pulmonary vascular disease, especially in those with right-sided CHF or a high worm burden. Whenever possible, other pretreatment tests should include a CBC, serum biochemical profile, urinalysis, and a microfilaria test. A platelet count is important for risk assessment in animals with severe pulmonary arterial disease. Mildly to moderately increased liver enzyme activity may be associated with hepatic congestion but does not preclude therapy with melarsomine. Liver enzyme activities usually normalize within 1 to 2 months of HW treatment in dogs without preexisting liver disease. As previously discussed, some dogs with HWD develop azotemia and/or severe proteinuria. Prerenal azotemia is treated with fluid therapy before adulticide is given. Severe glomerular disease can increase the risk for thromboembolism from loss of anticoagulant proteins (see p. 222); dogs with high UPC could benefit from ACEI treatment before adulticide therapy. Echocardiography aids in confirming and estimating severity of PAH and secondary right-sided cardiac remodeling, as well as confirming presence of caval syndrome if suspected, but is not required in most routine cases of HWD before treatment. In circumstances of shelter or owner financial limitations, adulticide treatment has frequently been undertaken with minimal pretreatment evaluation (positive Ag test only). Melarsomine injections were associated with <1% mortality rate in a high-volume shelter rescue situation after Hurricane Katrina. The risk-benefit and cost-benefit of pretreatment diagnostic testing should therefore be discussed with owners of HW-positive dogs.

Monthly HW prophylaxis with a macrocyclic lactone should begin immediately after diagnosis of HWD (if not already started). The American Heartworm Society recommends use of monthly HW preventative for 2 months before the administration of an adulticide in dogs diagnosed with HWD. This strategy can reduce HW Ag mass by decreasing or eliminating circulating microfilariae and tissue-migrating larvae, stunting immature worm growth, and damaging the adult female reproductive system. Delaying melarsomine for a few months also allows any late-stage larvae to mature further, which should increase susceptibility to the adulticidal effect. This 2-month window effectively narrows the so-called "susceptibility gap" between parasite life stages targeted by macrocyclic lactones (L_3-L_4) and adulticides (mature adult HWs). Microfilaria-positive dogs should be observed in the hospital after the first dose of macrocyclic lactone in case of adverse reaction, particularly if milbemycin oxime is used (the most microfilaricidal among macrocyclic lactones). Dogs with high numbers of microfilariae or those receiving milbemycin oxime might also benefit from administration of an antiinflammatory dose of glucocorticoid, with or without an antihistamine (e.g., diphenhydramine), an hour before the first macrolide preventive dose.

Exercise restriction should be enforced as soon as HWD is diagnosed and maintained until 1 to 2 months after final melarsomine treatment. Activity level is highly associated with progression of pulmonary arterial disease and risk of pre- or posttreatment complications, particularly PTE. More severely affected dogs warrant more strict exercise restriction (cage rest).

Use of doxycycline as therapy against *Wolbachia* contributes to reducing HW fertility and viability. Doxycycline (10 mg/kg PO q12h) is recommended in dogs for 4 weeks after diagnosis of HWD, before adulticide therapy. Doxycycline aids in reducing microfilaria, weakens and reduces reproductive ability of adult worms, kills developing larvae, and reduces pathologic immune reactions to dead and dying worms. The combination of a single preventative dose of ivermectin and doxycycline at 10 mg/kg PO q12h effectively eliminates microfilaria within 2 to 3 weeks, a rate that is appropriately rapid for reducing infectivity to other dogs but gradual enough to minimize risk of immune reaction to dying microfilaria. When the recommended combination of monthly preventative and doxycycline is used, no adjunct treatment specifically targeting microfilaria is needed (either before or after adulticide therapy). Although not specifically evaluated in HWD, the related drug minocycline has similar efficacy against *Wolbachia* and is a reasonable substitute if doxycycline is unavailable; the same dosing protocol is used for minocycline.

Antiplatelet therapy with aspirin or clopidogrel currently is not recommended as an adjunct to routine HW treatment because there is no convincing evidence for reduction in vascular lesion severity or risk of PTE. However, antiplatelet therapy should be considered in cases of documented proteinuria or PTE. Corticosteroid therapy (e.g., prednisone or dexamethasone) is reserved for treatment of eosinophilic pneumonitis or granulomatosis (see p. 201), PTE (see p. 201), treatment or prevention of microfilaricide reactions, or to mitigate tissue reaction to melarsomine injection. Otherwise corticosteroids are avoided because of their potential to cause fluid retention, reduced pulmonary blood flow, and hypercoagulability. Sildenafil is used in cases of severe PAH, PTE, and right-sided CHF secondary to PAH (see p. 201). Cardiac medications, including furosemide, pimobendan, and ACEIs, are reserved for cases of right-sided CHF secondary to PAH; ACEIs can also be considered in cases of proteinuria secondary to immune-complex glomerulonephritis. Herbal or other "natural" products have not shown efficacy in treatment or prevention of HWD and are not recommended.

The withholding of adulticide treatment in some asymptomatic HWD cases remains controversial and is not recommended. Although continuous monthly treatment with prophylactic ivermectin does eventually kill young adult worms, this effect occurs over a prolonged time period (over 1-2 years). Older worms are more resistant to ivermectin and can still cause clinical disease. Furthermore, progression of pulmonary arterial changes, pulmonary disease, and other HW-induced effects (e.g., glomerulonephritis) could increase the risks associated with adulticide treatment should this be undertaken in the future. Other macrocyclic lactones have variable adulticidal activity, with milbemycin showing the least efficacy against adult HWs at the preventative dose. It also is possible that use of HW preventive medication alone in HW-infected dogs could increase the potential for

resistant infections. The American Heartworm Society does not recommend the use of macrocyclic lactones alone (the so-called "slow kill" method) as an adulticide strategy. However, in selected cases where adulticide therapy cannot be given for one reason or another (such as during melarsomine drug shortages), dogs should be treated continuously (for at least 2 years) with ivermectin or possibly selamectin. Recent availability of a generic melarsomine product (Diroban) should reduce concerns about shortages of the brand-name product (Immiticide). If the "slow kill" method is used, doxycycline (10 mg/kg PO q12h) still should be used for a 4-week period after diagnosis, and exercise restriction should be maintained throughout the entire duration of the treatment process. HW Ag testing is recommended every 6 months. The HW infection is considered cleared when two consecutive negative test results are obtained. Lifelong HW prophylaxis is then used to prevent reinfection and disease transmission to other animals.

ADULTICIDE THERAPY IN DOGS

Melarsomine dihydrochloride (Immiticide, Diroban) is the adulticide of choice. It is effective against both immature and mature HWs; male worms are more susceptible than females. The American Heartworm Society recommends the three-dose "split" protocol for all HW-infected dogs in Classes 1 to 3 (see Box 10.1). Compared with the previously employed two-dose protocol, the three-dose protocol promotes a more gradual worm kill. It involves one initial dose, followed a month (or longer) later with two doses 24 hours apart. The first dose leads to death of approximately half of the worms, resulting in less chance for severe PTE or immune reactions associated with massive worm die-off. After the subsequent two doses, the worm kill is about 98%. This protocol does entail greater expense, higher arsenic exposure, and a requirement for more prolonged exercise restriction (from initial dose to at least a month after the final dose) compared with the two-dose protocol. The two-dose protocol remains an alternative option, especially for shelter situations, minimally affected dogs when owner financial constraints are an issue, or when marked renal or liver disease is present (because of the greater potential for arsenic toxicity). The two-dose protocol reportedly kills about 90% of adult worms. Dogs with caval syndrome (Class 4) should not be given adulticide treatment until after worms are surgically removed (see p. 202).

Melarsomine is absorbed rapidly from the intramuscular (IM) injection site. Unchanged drug and a major metabolite are rapidly eliminated in the feces; a minor metabolite is excreted in urine. The drug should be given by deep IM injection into the epaxial lumbar muscles (L_3 to L_5 region), exactly as recommended by the manufacturer. The lumbar muscle site provides good vascularity and lymphatic drainage with minimal fascial planes. Furthermore, gravity may help prevent the drug from leaking into subcutaneous tissues, where it can cause more irritation. The drug does cause a local reaction at the injection site; this is clinically noticeable in about a third of treated dogs. A tapering course of antiinflammatory prednisone beginning at the time of each melarsomine injection can help reduce local soreness, inflammatory reaction to dying worms, and clinical effects of pneumonitis (if present). Melarsomine is available as a sterile lyophilized powder in 50-mg vials. The rehydrated product is fully stable for 24 hours if kept refrigerated in the dark.

BOX 10.1

Heartworm Disease Management Protocol for Dogs*

Day 0: Dog diagnosed and verified as heartworm-positive
- Positive antigen (Ag) test verified with microfilaria (MF) test
- If no microfilariae are detected, confirm with second Ag test from a different manufacturer
- Begin exercise restriction
- The more pronounced the signs, the stricter the exercise restriction

If the dog is symptomatic:
- Stabilize with appropriate therapy and nursing care
- Prednisone prescribed at 0.5 mg/kg PO q12h first week, 0.5 mg/kg q24h second week, 0.5 mg/kg q48h third and fourth weeks

Day 1: Administer heartworm preventive
- If microfilariae are present, pretreat with antihistamine and glucocorticoid (if not already on prednisone) to reduce risk of anaphylaxis
- Observe for at least 8 hours for signs of reaction

Days 1-28: Administer doxycycline 10 mg/kg PO q12h for 4 weeks
- Reduces pathology associated with dead heartworms
- Disrupts heartworm transmission

Day 30: Administer heartworm preventive

Day 60: Administer heartworm preventive and first melarsomine injection, 2.5 mg/kg intramuscularly (IM)†
- Prescribe prednisone 0.5 mg/kg q12h first week, 0.5 mg/kg q24h second week, 0.5 mg/kg q48h third and fourth weeks

Decrease activity level even further
- Cage restriction/on leash when using yard

Day 90: Administer heartworm preventive, and second melarsomine injection, 2.5 mg/kg IM

Day 91: Third melarsomine injection, 2.5 mg/kg IM
- Prescribe prednisone 0.5 mg/kg q12h first week, 0.5 mg/kg q24h second week, 0.5 mg/kg q48h third and fourth weeks
- Continue exercise restriction for 6 to 8 weeks after last melarsomine injections

Day 120: Test for presence of microfilariae
- If positive, treat for microfilariae with additional 30-day regimen of doxycycline and retest in 4 weeks
- Establish year-round heartworm prevention

Day 271: Antigen test 6 months after completion; screen for microfilariae

*2014 American Heartworm Society Recommendations (www.heartwormsociety.org).
†Follow manufacturer's instructions closely for all melarsomine injections.

Coughing or (less often) dyspnea after treatment can be related to the HWD itself (pneumonitis), inflammatory reaction in the lungs and pulmonary vasculature secondary to worm die-off, or dead worm fragments causing PTE. In general, these reactions are steroid responsive and can be mitigated by administration of antiinflammatory prednisone course concurrently with melarsomine. Most clinical signs noted in dogs treated with melarsomine have been behavioral (e.g., tremors, lethargy, unsteadiness and ataxia, restlessness); respiratory (e.g., panting, shallow breathing, labored respirations, crackles); or injection-site related (e.g., edema, redness, tenderness, vocalization, increased aspartate aminotransferase and creatine kinase activities). Injection site reactions are generally mild to moderate and resolve within 4 (to 12) weeks. Occasionally these reactions are severe. The manufacturer reports that firm nodules might persist indefinitely at the sites. General signs of lethargy, depression, and anorexia occur in about 15% or fewer dogs; other adverse effects, including fever, vomiting, and diarrhea, occur occasionally. Adverse effects generally are mild at recommended doses. Hepatic and renal changes have not proved clinically relevant in animals receiving recommended doses of melarsomine. Overall, melarsomine causes less systemic toxicity than its predecessor, thiacetarsamide. Nevertheless, melarsomine has a low margin of safety. Overdose may cause collapse, severe salivation, vomiting, respiratory distress resulting from pulmonary inflammation and edema, stupor, and death.

Strict exercise restriction should be enforced for 4 to 6 weeks after each dose of adulticide therapy to reduce the effects of adult worm death and PTE. The rest period for working dogs should probably be longer because increased pulmonary blood flow in response to exercise exacerbates pulmonary capillary bed damage and subsequent fibrosis.

HW Ag testing (with concurrent microfilaria testing) is recommended 6 months after the final adulticide injection; results should be negative with successful treatment. Many dogs are HW Ag-negative by 3 to 4 months after adulticide therapy. Persistent antigenemia 6 months after three-dose melarsomine protocol may occur due to latent worm die-off, persistence of a small number of live worms postadulticide, or reinfection if monthly preventative was not given consistently. The Ag test should be repeated again 6 months later. A positive Ag test 12 months posttreatment despite adherence to a monthly preventative schedule suggests persistent infection. Because the three-dose melarsomine protocol kills 98% of worms, some dogs will remain Ag positive after treatment due to presence of a small number of residual worms. The decision to repeat adulticide therapy is guided by the patient's overall health, performance expectations, and age. Complete worm kill is probably not necessary; even if a few adult HWs survive, pulmonary arterial disease improves considerably after adulticide therapy.

Thiacetarsamide is an older arsenical agent that previously was the only adulticide available. It had no advantages and greater toxicity potential compared with melarsomine and is no longer used. Likewise, the use of other drugs such as levamisole or stibophen as adulticides is not recommended. Levamisole does not consistently kill adult HWs, although it is somewhat effective against male worms and may sterilize adult female worms.

The use of a flexible alligator forceps with fluoroscopic or transesophageal echocardiographic guidance has been advocated as a way to reduce the worm burden in accessible segments of the main or branch pulmonary arteries before adulticide therapy, even in dogs without caval syndrome. Removing as many worms as feasible reduces the risk for postadulticide PTE in heavily infected dogs. However, this procedure is not routinely performed due to requirements for imaging equipment and technical expertise, the need for sedation or anesthesia, and the potential for worm breakage with exacerbated pulmonary reaction.

POSTADULTICIDE PULMONARY THROMBOEMBOLIC COMPLICATIONS

Pulmonary arterial disease worsens from 5 to 30 days after adulticide therapy and can be especially severe in previously symptomatic dogs. Dead and dying worms promote thrombosis and pulmonary artery obstruction, with exacerbation of platelet adhesion, myointimal proliferation, villous hypertrophy, granulomatous arteritis, perivascular edema, and hemorrhage. Severe ventilation-perfusion mismatch may result from pulmonary hypoperfusion, hypoxic vasoconstriction and bronchoconstriction, pulmonary inflammation, and fluid accumulation. PTE is most likely to occur 7 to 10 days after adulticide therapy but can occur up to 4 weeks later. As expected, the caudal and accessory lung lobes are most commonly and severely affected. Pulmonary blood flow obstruction and increased vascular resistance further strain the RV and increase oxygen demand. Poor cardiac output and hypotension can result.

Depression, fever, tachycardia, tachypnea or dyspnea, and cough are common clinical signs. Hemoptysis, right-sided CHF, collapse, or death can also occur. Interstitial and alveolar pulmonary inflammation and fluid accumulation cause pulmonary crackles on auscultation. Focal lung consolidation can cause areas of muffled lung sounds. Thoracic radiographs show patchy alveolar infiltrates with air bronchograms, especially near the caudal lobar arteries. Thrombocytopenia or neutrophilia with a left shift may be seen on CBC.

Treatment of PTE (whether it occurs before or after adulticide therapy) includes strict rest (i.e., cage confinement) and glucocorticoid therapy to reduce pulmonary inflammation (e.g., prednisone, 0.5 mg/kg PO q12h for a week, then decreasing to 0.5 mg/kg q24h for a week, then decreasing again to 0.5 mg/kg q48h for 1 to 2 additional weeks). Supplemental oxygen therapy is recommended to reduce hypoxia-mediated pulmonary vasoconstriction, and sildenafil (1-3 mg/kg PO q8-12h) is indicated to decrease pulmonary vascular resistance. Antiplatelet therapy (clopidogrel or aspirin), as well as anticoagulant therapy (unfractionated heparin or low-molecular-weight heparin), may be considered for severe cases of thromboembolism. A bronchodilator (e.g., oral theophylline, 10 mg/kg q12h); judicious fluid

therapy (if there is evidence of cardiovascular shock); and cough suppressants could be useful. Antibiotics are of questionable benefit unless there is evidence of concurrent bacterial infection. Endothelial changes in survivors regress within 4 to 6 weeks after an adulticide. Pulmonary hypertension and arterial disease, along with radiographic changes, diminish over the next several months. Eventually, pulmonary arterial pressure and the contour of the proximal pulmonary arteries normalize, although some fibrosis may remain.

Treatment of Dogs With Complicated Heartworm Disease

PULMONARY COMPLICATIONS

Allergic or eosinophilic pneumonitis develops in a minority of dogs with HWD. It tends to develop early in the disease process and is thought to involve an immune-mediated reaction to dying larvae in the pulmonary microvasculature. Clinical manifestations of HW pneumonitis include a progressively worsening cough, crackles heard on auscultation, tachypnea or dyspnea, and sometimes cyanosis, weight loss, and anorexia. Eosinophilia, basophilia, and hyperglobulinemia are inconsistent findings. HW Ag tests are usually positive, but many cases do not have circulating microfilaria. Diffuse interstitial and alveolar infiltrates, especially in the caudal lobes, are common on radiographs; these can be similar to those in dogs with pulmonary edema, PTE, blastomycosis, or metastatic hemangiosarcoma. There is often no clinically relevant cardiomegaly or pulmonary lobar artery enlargement. Tracheal wash cytology usually reveals a sterile eosinophilic exudate with variable numbers of well-preserved neutrophils and macrophages. Therapy with a glucocorticoid (e.g., prednisone, 0.5 mg/kg PO q12h) usually results in rapid and marked improvement. Prednisone may be continued as needed, in gradually tapered doses (to 0.5 mg/kg every other day) and does not appear to adversely affect the adulticide efficacy of melarsomine.

Pulmonary eosinophilic granulomatosis is an uncommon syndrome that has been associated with HWD, although some affected dogs have negative HW tests. Its pathogenesis is thought to involve a hypersensitivity reaction to HW Ag or immune complexes, or both. Pulmonary granulomas are composed of a mixed cell population, with predominantly eosinophils and macrophages. A proliferation of bronchial smooth muscle within granulomas and an abundance of alveolar cells in the surrounding area are typical. Lymphocytic and eosinophilic perivascular infiltrates may also occur. Eosinophilic granulomas involving the lymph nodes, trachea, tonsils, spleen, gastrointestinal (GI) tract, and the liver or kidneys may occur concurrently. The clinical signs of pulmonary eosinophilic granulomatosis are similar to those of eosinophilic pneumonitis. Clinicopathologic findings variably include leukocytosis, neutrophilia, eosinophilia, basophilia, monocytosis, and hyperglobulinemia. In some cases, an exudative, primarily eosinophilic pleural effusion develops. Radiographic findings include multiple pulmonary nodules of varying size and location with mixed alveolar and interstitial pulmonary infiltrates; hilar and mediastinal lymphadenopathy may also be present. Eosinophilic granulomatosis is treated initially with prednisone (1-2 mg/kg PO q12h); however, additional cytotoxic therapy (e.g., cyclophosphamide or azathioprine) may be necessary as well. Not all dogs respond completely, and relapses are common, especially when therapy is reduced or discontinued. The response to immunosuppressive drugs after relapse may be poor. Surgical removal of a severely affected lung lobe is a strategy sometimes used. Therapy for adult HWs is given when pulmonary disease improves.

Severe pulmonary arterial disease, including PAH and PTE, is more common in dogs with long-standing HW infection, in those with many adult worms, and in active dogs. Severe cough, exercise intolerance, tachypnea or dyspnea, episodic weakness, syncope, weight loss, fever, and pallor are common clinical signs; sudden death sometimes occurs. Typical radiographic findings include markedly enlarged, tortuous, and blunted pulmonary arteries with or without pulmonary interstitial and alveolar infiltrates; signs usually are more severe in the caudal lobes. Marked hypoxemia occurs in some cases. Thrombocytopenia and sometimes hemolysis can occur in dogs with severe pulmonary arterial disease and thromboembolism; DIC develops in some dogs. As for postadulticide PTE, treatment with oxygen, sildenafil, prednisone, strict cage rest, and sometimes a bronchodilator (e.g., theophylline) is indicated to improve oxygenation and reduce pulmonary artery pressures. Caution is indicated to avoid systemic hypotension. Antiplatelet therapy (clopidogrel or aspirin) or anticoagulant therapy (unfractionated heparin or low-molecular-weight heparin) could be considered, although benefit of anticoagulation must be weighed against risk of bleeding, particularly in patients with thrombocytopenia or hemoptysis.

After the animal's condition is stabilized, the typical HW treatment protocol can commence as recommended by the American Heartworm Society (macrocyclic lactone and doxycycline; 3-injection melarsomine protocol after 2 months).

RIGHT-SIDED CONGESTIVE HEART FAILURE

Severe pulmonary arterial disease and PAH can cause right-sided CHF. Jugular venous distention or pulsation, ascites, syncope, exercise intolerance, and arrhythmias are typical signs; other physical and auscultatory signs secondary to severe PAH might also occur (see p. 191). Although ascites is the most common manifestation of right-sided CHF in dogs, pleural or pericardial effusion can occur as well. Cardiogenic pulmonary edema is not expected. Treatment is the same as for dogs with severe PAH (sildenafil 1-3 mg/kg PO q8-12h), with the addition of abdominocentesis or thoracocentesis as needed, furosemide (e.g., 1-2 mg/kg PO q12h or as needed), pimobendan (0.2-0.3 mg/kg PO q12h), an ACEI (e.g., enalapril or benazepril 0.5 mg/kg PO q12h), and moderate dietary salt restriction. Clopidogrel or aspirin could be considered, because PTE is one of the major mechanisms of

PAH in HWD. An additional diuretic (spironolactone or hydrochlorothiazide) could be helpful in refractory cases, if renal function is adequate. Dogs that develop right-sided CHF before adulticide therapy should be treated for heart failure while beginning initial American Heartworm Society treatment guidelines (macrocyclic lactone and doxycycline). If dogs respond well to heart failure treatment and remain clinically stable, they may receive the three-dose melarsomine protocol after the typical 2-month waiting period.

CAVAL SYNDROME

The (vena) caval syndrome occurs when venous inflow to the heart is obstructed by a mass of worms, leading to low-output cardiovascular shock. Other terms for this condition include *postcaval syndrome, acute hepatic syndrome, liver failure syndrome, dirofilarial hemoglobinuria,* and *vena cava embolism.* It is an uncommon but devastating complication in heavily infected animals. As the HW burden increases, adult worms migrate from their preferred location in the distal pulmonary arteries "backward" or "upstream" into the RV, right atrium (RA), and caudal vena cava. Dogs with more than 40 worms or with more severe PAH have increased risk for developing caval syndrome. Caval syndrome occurs more often in geographic areas where HWD is enzootic.

Most dogs that develop caval syndrome are males. Often no history of HW-related signs exists. Acute collapse is common, often accompanied by anorexia, weakness, tachypnea or dyspnea, pallor, and hemoglobinuria. Dogs with caval syndrome invariably have severe PAH and concurrent right-sided CHF, so additional clinical signs and findings typical of these syndromes can occur as well (see p. 201).

Intravascular hemolysis (from red blood cell trauma) results in Coombs-negative fragmentation hemolytic anemia, hemoglobinemia, and hemoglobinuria. Hemoglobinuria is considered a hallmark sign of caval syndrome. Other clinicopathologic findings are similar to other presentations of severe HWD (see p. 197)

Thoracic radiographs indicate right heart and pulmonary artery enlargement, consistent with severe HWD. The ECG usually suggests RV enlargement. Ventricular or supraventricular premature complexes are common. Echocardiography reveals a mass of worms entangled at the tricuspid valve and in the RA and/or venae cavae (see Fig. 10.3). Characteristic echocardiographic changes associated with severe PAH (RV dilation and hypertrophy, paradoxical septal motion, tricuspid insufficiency, and a small LV) are also seen.

Without aggressive treatment, most dogs die within between 24 and 72 hours as a result of cardiogenic shock complicated by metabolic acidosis, DIC, and anemia. Worms must be surgically removed from the vena cava and RA as soon as possible. The dog is sedated (preferred) or anesthetized. A right jugular venotomy, with the dog restrained in left lateral recumbency, is the usual approach. Local anesthesia is used after the right jugular region is shaved and surgically prepped. The jugular vein is isolated, and loops of moist umbilical tape or suture material are used to control bleeding once the vein is incised. Long alligator forceps (or another endoscopic retrieval instrument) are used to grasp and withdraw the HWs through the jugular vein incision. The instrument is gently passed down the vein through the cranial vena cava into the RA; repositioning of the animal's head and neck may be necessary to pass the instrument beyond the thoracic inlet. Fluoroscopic or echocardiographic guidance is helpful. The goal is to retrieve as many worms as possible without causing worm breakage; generally, five to six unsuccessful attempts in sequence is the end point. Resistance to instrument withdrawal from the vein may occur if too many worms are grasped at once or a cardiovascular structure is grabbed by forceps. The jugular vein is ligated proximally and distally, and then the subcutis and skin are closed routinely. Survival rates of 50% to 80% have been reported for dogs undergoing this procedure.

Other supportive care given during and after surgical worm removal might include IV fluid therapy, particularly in cases presenting with cardiovascular shock; however, most dogs with caval syndrome concurrently have right-sided CHF, and fluid therapy will exacerbate venous congestion. A hypotonic crystalloid solution (such as half-strength saline) is preferred, with fluid rate determined by the individual case. Depending on the degree of anemia, blood transfusion (fresh whole blood or packed red blood cells) might be required. Adjunctive therapy after HW extraction is similar to recommendations for the other complications of severe HWD. Treatment includes prednisone, sildenafil, and clopidogrel or aspirin (for pulmonary inflammation, PAH, and PTE); pimobendan (for right-sided congestive heart failure [R-CHF]); and initiation of doxycycline and macrocyclic lactone (as with any other HW-positive dog). Additional treatments for R-CHF, including furosemide and ACEIs, generally are delayed until the dog's clinical condition stabilizes and may not be required if venous congestion improves dramatically after worm removal. In the acute setting, monitoring for anemia, thrombocytopenia, DIC, and organ dysfunction is important; treatment is given as indicated. Severe PTE and renal or hepatic failure are associated with poor outcome. Assuming clinical stabilization after worm extraction, adulticide therapy can be started after the typical 2-month period to eliminate remaining worms.

Heartworm Prevention

HW prophylaxis is indicated for all dogs living in endemic areas. The American Heartworm Society recommends year-round administration of an HW preventive drug to prevent HWD, increase compliance, and control pathogenic and/or zoonotic parasites. The time of year in which infection can occur is limited in many geographic areas because sustained warm and moist conditions are necessary for transmission of the disease. Transmission usually occurs only during a few months in the most northern parts of the United States and Canada, and generally in fewer than 6 months per year north of the Virginia–North Carolina border; however, local microclimates may allow larval development in mosquitoes for a much longer period. Year-round transmission is likely in the southern continental United States. Although

monthly preventive therapy may be most important only during June through November in the majority of the United States, continuous chemoprophylaxis throughout the year may be more practical, not only for animals living in locations where transmission is likely during more than half the year but also for those that travel to warmer regions. If seasonal prophylaxis is elected for financial or other reasons, prevention should begin 1 month before the anticipated HW transmission season and continue for 6 months after the season's end. Puppies should begin HW prevention as early as feasible after weaning, by 8 weeks of age at the latest. HW Ag and microfilaria testing is recommended before the initial dose of preventive medication in dogs 6 months of age and older. For all age dogs, if accidental lapse in HW preventive drug administration occurs, continuous prophylaxis should be restarted as soon as possible and Ag test repeated 6 months and 12 months after the lapse. Owner education about the potential seriousness of HW infection and need for consistent administration of preventive medication as directed is important.

Several macrocyclic lactone (macrolide) drugs are currently available for HWD prevention, including the avermectins (ivermectin, selamectin) and the milbemycins (milbemycin oxime, moxidectin). DEC is no longer commercially available; this HW preventative required daily dosing and could be given only to amicrofilaremic dogs. Macrocyclic lactones induce neuromuscular paralysis and death in nematode (and arthropod) parasites by interacting with membrane chloride channels. They are effective against third- and fourth-stage larvae during the 2 months after infection, as well as microfilariae and in some cases adult worms. Ivermectin, used continuously for more than 30 months, is effective against adult *D. immitis;* selamectin also has adulticidal effect with chronic administration. Retroactive preventive efficacy ("reachback") with these agents lasts at least 1 and possibly more than 2 months after a single dose. These agents are quite safe in mammals when used as directed; all commercially available macrocyclic lactones at preventive doses are safe in sensitive Collies and other P-glycoprotein-deficient dogs. Cases of clinical toxicity usually have been related to dosage miscalculation using a concentrated livestock preparation.

Macrocyclic lactones available for monthly oral administration include ivermectin (6-12 μg/kg; Heartgard, Iverhart, Tri-Heart) and milbemycin oxime (0.5-1 mg/kg; Interceptor, Sentinel, Trifexis). Products available for monthly topical administration (applied to the skin between the shoulder blades, at dose ranges of 6-12 mg/kg) include selamectin (Revolution) and moxidectin/imidacloprid (Advantage Multi); efficacy is not affected if bathing or swimming is delayed at least 2 hours after application. A slow-release formulation of moxidectin in a liposomal formulation (ProHeart 6) is given by SC injection; its effect lasts 6 months. Some of these agents are effective against other parasites at the doses used for HW prevention (e.g., hookworms with milbemycin; fleas, ear mites, and ticks with selamectin). These drugs are sometimes marketed in combination with other antiparasitic agents for broader protection against endoparasites and ectoparasites.

Lack of efficacy (LOE) of HW preventives has been reported, particularly in the Mississippi Delta. Reasons for LOE include owner noncompliance (failure to administer HW prevention as directed), patient factors (failure of ingestion or absorption of HW preventative), or true parasite resistance. In the vast majority of cases, LOE of macrocyclic lactones can be attributed to owner noncompliance, highlighting the importance of client education and monthly reminder systems. However, in a few cases, genetic polymorphisms have been documented that suggest true resistance of HW microfilariae or adult worms to various macrocyclic lactones. Despite these rare and isolated instances of HW resistance, efficacy of HW preventatives remains extremely high, and veterinarian efforts should be directed toward educating clients of the importance of monthly year-round prevention. Reports of LOE have not altered the American Heartworm Society's guidelines for diagnosis, prevention, or treatment of HWD.

Effective HW prevention, particularly in heavily endemic areas, also involves limiting mosquito exposure. This includes removal or treatment of standing water sources, use of mosquito repellants or traps, and keeping pets indoors during peak mosquito hours.

HEARTWORM DISEASE IN CATS

Cats are an atypical host of HWD. HWs mature more slowly, fewer numbers of infective larvae mature to adults, and the adult life span is shorter in cats. However, live worms can persist for 2 to 4 years. HW-infected cats generally have fewer than six adult worms in the RV and pulmonary arteries, and most cats with mature HW infection have only one or two worms. Nevertheless, in terms of host versus parasite biomass, a cat infected with two or three worms is still considered heavily infected, and even one adult worm can cause death. Unisex infection is common. Most cats with both male and female worms have no or only a brief period of microfilaremia, so cats rarely serve as important reservoirs of infection. Aberrant worm migration is also more common in cats than dogs and complicates necropsy confirmation of infection. Aberrant sites have included the brain, subcutaneous nodules, body cavities, and occasionally a systemic artery.

HW infection where the parasites never reach maturity because of the host's inflammatory response is thought to be much more common than mature HWD in cats. This HW "exposure" with early parasite destruction has been called "pulmonary larval dirofilariasis" or "heartworm-associated respiratory disease" (HARD).

Pathophysiology

The pathophysiologic changes associated with HW infection in cats can be considered to occur in two stages, with most infections only reaching the first. Approximately 3 to 4 months after infection, immature worms arrive in the

pulmonary arteries, and most die from an acute host inflammatory reaction involving pulmonary intravascular macrophage activation. These specialized phagocytic cells are located in the pulmonary capillary beds of cats but not dogs. Activation of these macrophages by the presence of the parasites leads to acute eosinophilic and neutrophilic inflammation, and proliferative lesions in the pulmonary arteries, as well as in lung tissue and bronchioles. Increased pulmonary vascular permeability can promote edema formation, and the more extensive alveolar type 2 (surfactant-producing) cell hyperplasia seen in cats (compared with dogs) also can interfere with alveolar O_2 exchange. This initial HARD phase can mimic signs of feline allergic airway disease (asthma) and can lead to acute respiratory distress in cats 3 to 9 months after infection. Although many cats recover, this phase is fatal in others. Sudden death can occur.

In cats that survive, the acute inflammation subsides and any remaining worms continue to mature. Vascular injury leads to myointimal proliferation, muscular hypertrophy, luminal narrowing, tortuosity, and thrombosis in affected pulmonary arteries. Because HWD in cats usually involves only a few worms and worm life span is relatively short, pulmonary arterial lesions tend to be localized; as a result, clinically relevant pulmonary hypertension, secondary RV hypertrophy, and right-sided CHF are uncommon in cats. In cats that do develop CHF, pleural effusion (modified transudate or chylous), ascites, or both can develop. As in dogs, the bronchopulmonary collateral circulation helps protect against pulmonary infarction.

The host often tolerates mature HWs, but dying and degenerating worms cause recrudescence of pulmonary inflammation and thromboembolism that can be fatal. Disease is most severe in the caudal lung lobes. Caudal lobar arterial obstruction can be caused by villous proliferation, thrombi, or dead HWs. Adult worms are more likely to obstruct the pulmonary arteries of cats (compared with dogs) by virtue of their relative size.

Vomiting is common in cats with HWD. The mechanism for this may involve central stimulation (of the chemoreceptor trigger zone) by inflammatory mediators. Antiinflammatory doses of a glucocorticoid often control this sign.

Clinical Features

Most reported cases have occurred in cats 3 to 6 years of age, although cats of any age are susceptible. Although outdoor lifestyle is a risk factor for HW exposure in cats, those living strictly indoors account for approximately 25% of feline HW infections. Unlike in dogs, haircoat length does appear to affect HW prevalence in cats; longhaired cats are infected less frequently than shorthaired cats. Many exposed cats could clear the infection without ever showing clinical signs. Some clinicians have noted an increase in feline HWD diagnosis during fall and winter, presumably after infection in the spring, but others have found fewer cases in the latter part of the year.

Clinical signs are variable and can be transient or nonspecific. Respiratory signs mimicking feline asthma occur in more than half of symptomatic cats, including tachypnea, paroxysmal cough, and/or increased respiratory effort. Other client complaints include lethargy, anorexia, weight loss, vomiting (including hemoptysis), syncope, neurologic signs, or sudden death. Vomiting, usually unrelated to eating, is common and may be the only sign in some infected cats. Severe clinical signs usually are associated with the arrival of immature worms in the pulmonary arteries (HARD) or with the death of one or more adult worms. The sudden onset of neurologic signs, with or without anorexia and lethargy, is common during aberrant worm migration. Such signs include seizures, dementia, apparent blindness, ataxia, circling, mydriasis, and hypersalivation. Only rarely do cardiopulmonary and neurologic signs coexist. Although HWs can cause marked pulmonary disease, some cats have no clinical signs.

Auscultation might reveal pulmonary wheezes or crackles, muffled lung sounds (either from pulmonary consolidation or pleural effusion), tachycardia, and sometimes a cardiac gallop sound or murmur. Pleural effusion or ascites caused by right-sided CHF, as well as syncope, are less common in cats than in dogs with HWD. Pneumothorax occurs rarely. There are sporadic reports of caval syndrome in cats.

Diagnosis

Definitive diagnosis is more difficult in cats than dogs. A combination of serologic testing, thoracic radiographs, and echocardiography is used. Microfilaria testing is only occasionally helpful.

TESTS FOR HEARTWORM DISEASE IN CATS

Serologic tests

Antigen tests. The HW Ag tests are highly specific in detecting adult (female) HW infection, but their sensitivity depends on the sex, age, and number of worms; therefore Ag tests often are negative in cats. Ag test results are negative during the first 5 months of infection, the time period when clinical signs from HARD are common. Ag tests can be variably positive at 6 to 7 months; infections with mature female worms should be detected after 7 months. Feline-specific Ag tests are reported to have increased sensitivity for detecting HWD in cats compared with canine tests. False-negative HW Ag test results are more likely in cats because worm burden is typically low; also, a longer time is required for cats to become Ag-positive. Up to 50% of cats with mature HWs could have a negative Ag test, and acute death and severe clinical signs can occur in Ag-negative cats. False-negative tests can occur because of Ag-Ab complexation, similar to dogs; heating the samples before testing can improve test accuracy in cases with a high index of suspicion for HWD. Occasionally, a positive Ag test result occurs, but no worms are found on postmortem examination. Spontaneous worm death, worms overlooked during pulmonary evaluation, and ectopic infection are likely reasons for this finding. Postmortem diagnosis is difficult if the worms are located in distal pulmonary arteries or aberrant sites.

Antibody tests. HW antibody (Ab) tests are used to screen for feline HW exposure. They are relatively sensitive but not specific for adult HWs. The Ab tests detect circulating Abs against a surface protein of male or female L_4 larvae. These Ab tests have minimal to no cross-reactivity with GI parasitic infections. Ab tests provide greater sensitivity than Ag tests because larvae of either sex can provoke a host immune response, and Ab tests become positive during the time frame when cats typically experience clinical signs of HARD. Serum Ab is detected as early as 60 days after infection, although different Ab tests vary in sensitivity to different larval stages. A positive Ab test indicates exposure to migrating larvae and adults, not necessarily the presence of adult HWs. It is estimated that approximately 50% of Ab-positive but Ag-negative cats develop HARD, whereas only 10% to 20% develop a mature HW infection. When an Ab test is positive, other evidence should be sought to support a diagnosis of mature HW infection (and thus true HWD). This can include a positive HW Ag test or findings consistent with HWD on thoracic radiography or echocardiography. The concentration of Ab does not appear to correlate well with an individual cat's worm burden nor with the severity of clinical disease or radiographic signs, although high Ab titers are associated with HW death. Antibodies persist for 6 to 12 months and decrease as HWs mature, such that a cat with an adult HW that has persisted over 12 months may be Ag-positive and Ab-negative. HW Abs are not protective against future HW infection.

False-negative Ab tests also occur fairly frequently (up to 10%-15% of cases). Therefore a negative HW Ab test suggests one of the following: (1) the cat has not been exposed to HWs, (2) the cat has a HW infection less than 60 days old, or (3) the cat produced a concentration of IgG Ab against the Ag used in making the test that is too low to be detected. When clinical findings suggest HWD or HARD but the Ab test is negative, serologic testing should be repeated using a different Ab test and an HW Ag test. Thoracic radiographs and an echocardiogram also are recommended. The Ab test could be repeated in a few months, as well.

Radiography

Radiographic findings that suggest HWD are similar to those seen in dogs, including pulmonary artery enlargement with or without visible tortuosity and pruning, RV or generalized cardiac enlargement, and diffuse or focal pulmonary bronchointerstitial infiltrates (Fig. 10.4). Pulmonary hyperinflation sometimes is evident, similar to cats with asthma. The pulmonary artery and right heart changes typically are more subtle in cats than in dogs. Radiographic abnormalities occur in approximately 50% of cats with HWD, and may not correlate with severity of clinical signs or results of serologic tests. Pulmonary artery distention may be greatest within the first 7 months of infection. Caudal lobar arteries are most frequently abnormal, and are seen best on the DV view. The right caudal lobar artery can be more prominent; however, a left caudal pulmonary artery greater than or equal to 1.6 times the width of the ninth rib at the ninth intercostal space reportedly is the most discriminating radiographic finding for separating HW-infected from noninfected cats. The main pulmonary artery segment is not usually visible on DV or ventrodorsal views in cats because its location is more medial than it is in dogs. Marked right heart enlargement is more likely when signs of right-sided CHF (e.g., pleural effusion) exist. Ascites, which is a rare manifestation of CHF secondary to the common feline cardiomyopathies, occurs in some cats with HWD.

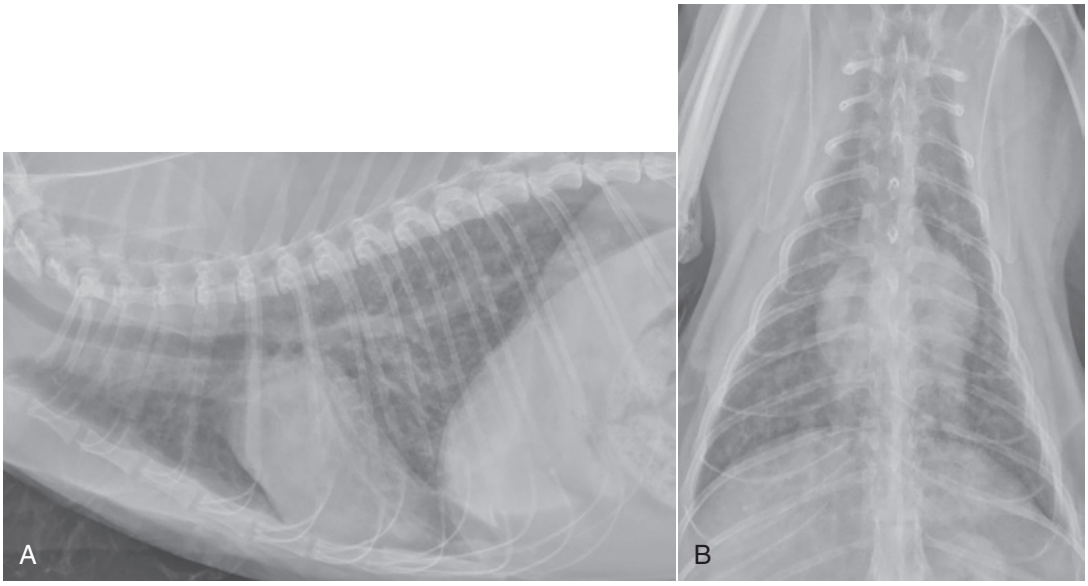


FIG 10.4
Lateral **(A)** and dorsoventral **(B)** radiographs from a cat with heartworm disease. There are interstitial infiltrates throughout the lung fields and enlarged pulmonary arteries seen on both views.

HW-associated pneumonitis and PTE result in pulmonary infiltrates. Focal perivascular and interstitial opacities are more common than diffuse infiltrates but are nonspecific. Radiographs tend to be normal in cats without clinical signs.

ECHOCARDIOGRAPHY

Echocardiographic findings can be normal unless worms are located in the heart, main pulmonary artery segment, or proximal left and right pulmonary arteries. Echocardiography is more sensitive for HW screening in cats versus dogs because worms are physically larger compared with the cat's body size; worms are therefore more likely to extend into the main PA or RV from their preferred location in the distal PAs. On two-dimensional echocardiograms, HWs appear as bright, double-line (parallel) echodensities; they are visible in up to 75% of infected cats. Higher numbers of worms increase the likelihood of identification with echocardiography. Because worms are seen more often in the pulmonary arteries than in right heart chambers, an index of suspicion and careful interrogation of these structures are important.

ELECTROCARDIOGRAPHY

ECG findings are often normal. Severely affected cats with HW-induced CHF can have changes suggesting RV enlargement and axis deviation. Arrhythmias appear to be uncommon, although advanced pulmonary arterial disease and CHF are more likely to cause ventricular tachyarrhythmias.

OTHER TESTS

Between one and two thirds of infected cats have peripheral eosinophilia, usually from 4 to 7 months after infection. Otherwise the eosinophil count often is normal; basophilia is uncommon. About one third of the cases have mild nonregenerative anemia. Advanced pulmonary arterial disease and thromboembolism might be accompanied by neutrophilia (sometimes with a left shift), monocytosis, thrombocytopenia, or DIC. Hyperglobulinemia, the most common biochemical abnormality, occurs inconsistently. The prevalence of glomerulopathies in cats with HWD is unknown, but it does not appear to be high.

Tracheal wash or bronchoalveolar lavage specimens can show an eosinophilic exudate that suggests allergic or parasitic disease, similar to that found with feline asthma or pulmonary parasites. This finding usually occurs between 4 and 8 months after infection. Later in the disease, tracheal wash findings can be unremarkable or indicate nonspecific chronic inflammation. Pleural effusion resulting from HW-induced CHF generally is a modified transudate, although chylothorax occasionally develops.

At around 6.5 to 7 months after infection, a transient (1-2 months in duration), low-grade microfilaremia occurs in about half of cats with mature infections. Therefore microfilaria concentration tests usually are negative. Nevertheless, a concentration test could still prove valuable in some individual cats. Between 3 and 5 mL, rather than 1 mL, of blood should be used to increase the probability of detecting microfilariae.

Treatment of Cats With Heartworm Disease

MEDICAL THERAPY AND COMPLICATIONS

Adulticide therapy is not recommended in most cases because the likelihood of severe complications in this species is high. Also, spontaneous cure can occur in cats because of the shorter HW life span, and cats do not act as reservoirs for HWD transmission to other animals.

The recommended approach for infected cats is to initiate monthly HW preventative (if not already begun) and to use prednisone as needed for respiratory signs and radiographically evident pulmonary interstitial infiltrates. Clinical utility of doxycycline in cats with HWD is not yet established; however, given the effects of doxycycline on HW viability and reproductive capacity in dogs, it is reasonable to treat cats with doxycycline in the same manner (10 mg/kg PO q12h for 4 weeks beginning at time of diagnosis). If cats develop GI adverse effects at this dose, the dose can be lowered to 5 mg/kg q12h. Serologic tests (for HW Ab and Ag in tandem) are obtained every 6 to 12 months to monitor infection status. Ag-positive cats usually become negative within 4 to 5 months of worm death; Ab tests can remain positive at least 6 to 12 months. Serial thoracic radiographs and echocardiograms also can be useful for monitoring cats that have had abnormal findings. Interstitial pulmonary infiltrates usually respond to prednisone (e.g., 1-2 mg/kg PO q24h, reduced gradually over 2 weeks to 0.5 mg/kg q48h, then discontinued after 2 more weeks). Prednisone therapy could be repeated periodically if respiratory signs recur.

The possibility of severe respiratory distress and death is always present, especially after worm death. PTE is more likely to produce a fatal outcome in cats than dogs. Clinical findings with PTE include fever, cough, dyspnea, hemoptysis, pallor, pulmonary crackles, tachycardia, and hypotension. Radiographic signs include poorly defined, rounded or wedge-shaped interstitial opacities that obscure associated pulmonary vessels. Alveolar infiltrates are seen in some cases. Cats with acute disease are given supportive care, including supplemental oxygen, a glucocorticoid (dexamethasone at 0.2 mg/kg IM or IV), a bronchodilator (such as terbutaline), and fluid support as needed. Sildenafil (1-2 mg/kg PO q8-12h) is indicated if severe PAH is documented. Antiplatelet drugs (clopidogrel or aspirin) or anticoagulants (heparins) can be considered in cats with PTE. Diuretics are not indicated unless right-sided CHF is present.

Right-sided CHF develops occasionally in cats with severe pulmonary arterial disease and PAH. Dyspnea (caused by pleural effusion) and jugular venous distention or pulsation are common. Radiographic and ECG findings usually suggest RV enlargement. Therapy is directed at decreasing pulmonary arterial pressure and controlling the signs of heart failure. This includes thoracocentesis as needed, cage rest, sildenafil, furosemide, an ACEI, and pimobendan. The cat's clinical progress and clinicopathologic abnormalities are used to guide supportive therapy.

SURGICAL THERAPY

Caval syndrome occurs rarely in cats. Successful removal of adult worms through a jugular venotomy is possible, as in dogs. Prior echocardiographic confirmation of worm location is important. A right jugular venotomy can be used to reach worms in the RA, vena cava, and possibly the RV with small alligator forceps, endoscopic grasping or basket retrieval forceps, or another device. Worm removal via thoracotomy and right atriotomy, ventriculotomy, or pulmonary arteriotomy also has been done successfully. A potentially fatal anaphylactic reaction associated with worm breakage could occur during such procedures. Presurgical treatment with a glucocorticoid and antihistamine has been suggested.

MICROFILARICIDE THERAPY

Microfilaricide therapy is rarely necessary because microfilaremia is brief. The combination of monthly HW preventative and doxycycline are sufficient to kill any microfilaria present.

HEARTWORM PREVENTION

HW prophylaxis is recommended for cats in endemic areas, including those living "indoors" only. Monthly preventative should be initiated 1 month before the beginning of regional HW transmission season and continued until at least 1 month after the season has ended. However, year-round prevention has advantages, including improved compliance, retroactive activity ("reachback") in case of missed doses, and activity against GI parasites. Oral HW prevention products for cats include ivermectin (Heartgard for Cats) and milbemycin oxime (Interceptor Flavor Tabs for Cats); topical options include selamectin (Revolution) and a moxidectin/imidacloprid combination (Advantage Multi for Cats). Selamectin is used at the same dose as for dogs (6 mg/kg, topically); it is also useful for controlling fleas and ear mites, as well as hookworm and roundworm infections in cats. Ivermectin is administered orally at 24 μg/kg monthly (four times the dose used in dogs). The minimum recommended dose for oral milbemycin is 2 mg/kg (about twice the dose used in dogs). Moxidectin is used at 1 mg/kg, applied topically. All these agents are safe in kittens 6 weeks or older, and all preventative agents are safe for use in seropositive cats. Serologic testing before preventive use can be useful for purposes of identifying local HW prevalence, as well as individual cat risk for HARD or adult HWD. However, the usefulness of serologic testing for individual cats before initiating monthly preventative is less than dogs.

ANGIOSTRONGYLOSIS

Infection with metastrongylid nematode *Angiostrongylus vasorum* in dogs, also known as the "French heartworm," can cause pulmonary vascular disease similar to dirofilariasis. Angiostrongylosis is regionally endemic in parts of Western and Northern Europe and the United Kingdom, as well as in Turkey, Brazil, Colombia, Uganda, and the maritime provinces of Canada. The natural definitive host of *Angiostrongylus vasorum* is the wild fox. Similar to dirofilariasis, domestic dogs can serve as a definitive host and shed L_1 larvae in feces; worms can mature in experimentally infected cats, but no larvae are produced. The life cycle requires a gastropod intermediate host (marine or freshwater snail or slug). L_1 larvae are ingested by the gastropod host during feeding on fox or dog feces and undergo two molting stages within the snail or slug to develop into infective L_3 larvae. Dogs become infected by eating either the gastropod or a paratenic host (frog). Once ingested, L_3 larvae penetrate through the intestinal mucosa and migrate to abdominal lymph nodes. Immature worms then travel via the portal circulation to the pulmonary arteries, where they mature, mate, and produce eggs. Immature worms reach the pulmonary arteries by approximately 30 to 35 days postinfection. Eggs lodge and develop in pulmonary capillaries; when L_1 larvae hatch, they break into airspaces and are coughed up and swallowed to pass in the feces of infected hosts. The overall prepatent period for *A. vasorum* is approximately 5 to 8 weeks. Life span of the adult worms is at least 2 years and can last the lifetime of the canine host, leading to lifelong intermittent shedding of larvae in feces.

Pathophysiologic consequences of angiostrongylosis are similar to HWD in dogs. Worms cause an inflammatory response in the pulmonary arteries that can cause pneumonitis, interstitial pneumonia, or pulmonary granulomatosis. Pulmonary vascular lesions include villous arteritis and intimal proliferation. Incidence of PTE and PAH appear to be less than in canine HWD, possibly due to recruitment of pulmonary arteriovenous shunts. Only approximately 15% of dogs diagnosed with *A. vasorum* in the United Kingdom have moderate to severe PAH; right-sided CHF is therefore a rare complication. Coagulopathies such as thrombocytopenia and DIC can occur, and hemorrhage is a relatively frequent complication compared with HWD. Aberrant migration of adult worms has been reported, including to sites such as the eye, left heart, and femoral artery. Aberrant migration of L_1 larvae is common, including to the brain, spinal cord, eye, kidney, liver, or other abdominal organs.

Clinical presentation of dogs with angiostrongylosis is variable and based on disease severity but generally mimics HWD. Dogs could present for cough, dyspnea, anorexia, exercise intolerance, or syncope. Sudden death has been reported. Coagulopathic (hemorrhagic) presentations are common as well, including mucosal or subcutaneous hemorrhage, melena, or hemoptysis. Common clinicopathologic findings are similar to those in dogs with HWD, and include eosinophilia, neutrophilia, thrombocytopenia, mild anemia, and hyperglobulinemia. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are often prolonged. Thoracic radiographs typically reveal a patchy alveolar-interstitial pattern in peripheral lung areas and, occasionally, mild pleural effusion; pulmonary vascular lesions (enlarged and tortuous pulmonary arteries) are less

common. Echocardiography can be used to identify right heart remodeling and quantify PAH, if present.

Definitive diagnosis of *A. vasorum* infection involves visualization of L_1 larvae in feces of an infected dog. The Baermann technique is more sensitive than direct fecal smear. However, fecal shedding can be intermittent; serial examination is recommended, and negative fecal examinations do not rule out angiostrongylosis. Larvae also can be identified by airway cytology, such as with bronchoalveolar lavage. *A. vasorum* larvae can be differentiated from other nematode larvae by tail morphology.

Recently, serologic testing has become available for *A. vasorum*. An ELISA is available for detection of an Ag produced by adult female worms, similar to the HW Ag test. The test becomes positive approximately 5 to 9 weeks postinfection, and has high sensitivity and specificity (minimal cross-reaction with other parasites, including *D. immitis*). A cage-side test also is available (Angio Detect, IDEXX Laboratories). This test is highly specific (100%) although less sensitive (85%) and becomes positive later in the disease process (9-11 weeks).

Treatment options for adult worm infections include fenbendazole (25-50 mg/kg PO q24h for 7-21 days), milbemycin oxime (0.5 mg/kg PO once weekly for 4 weeks), or moxidectin (single topical dose of 2.5 mg/kg). Additional supportive care could include glucocorticoids for pulmonary inflammation, exercise restriction, oxygen therapy, and blood product transfusions in cases of coagulopathy and hemorrhage. Several macrolide anthelmintics have shown efficacy in prevention of *A. vasorum* infections, although to date none are currently licensed for this practice. Imidocloprid/moxidectin (Advantage Multi, Advocate); spinosad/milbemycin oxime (Trifexis, Milbemax); or afoxolaner/milbemycin oxime (NexGard) can be considered as monthly preventatives in endemic regions. Additional prevention strategies include prompt disposal of dog feces, and reducing contact with intermediate hosts (snails and slugs) when possible. Standard practices for screening, treatment, and prevention of this emerging parasite have yet to be established.

Suggested Readings

Pulmonary Hypertension

Adams DS, et al. Associations between thoracic radiographic changes and severity of pulmonary arterial hypertension diagnosed in 60 dogs via Doppler echocardiography: a retrospective study. *Vet Radiol Ultrasound*. 2017;58:454–462.

Atkinson KJ, et al. Evaluation of pimobendan and N-terminal pro-brain natriuretic peptide in the treatment of pulmonary hypertension secondary to degenerative mitral valve disease in dogs. *J Vet Intern Med*. 2009;23:1190–1196.

Bach JF, et al. Retrospective evaluation of sildenafil citrate as a therapy for pulmonary hypertension in dogs. *J Vet Intern Med*. 2006;20:1132–1135.

Brown AJ, Davison E, Sleeper MM. Clinical efficacy of sildenafil in treatment of pulmonary arterial hypertension in dogs. *J Vet Intern Med*. 2010;24:850–854.

Guglielmini C, et al. Serum cardiac troponin I concentration in dogs with precapillary and postcapillary pulmonary hypertension. *J Vet Intern Med*. 2010;24:145–152.

Johnson L, Boon J, Orton EC. Clinical characteristics of 53 dogs with Doppler-derived evidence of pulmonary hypertension: 1992-1996. *J Vet Intern Med*. 1999;13:440–447.

Kellihan HB, MacKie BA, Stepien RL. NT-proBNP, NT-proANP, and cTnI concentrations in dogs with pre-capillary pulmonary hypertension. *J Vet Cardiol*. 2011;13:171–182.

Kellihan HB, Stepien RL. Pulmonary hypertension in dogs: diagnosis and therapy. *Vet Clin North Am Small Anim Pract*. 2010;40:623–641.

Kellihan HB, et al. Acute resolution of pulmonary alveolar infiltrates in 10 dogs with pulmonary hypertension treated with sildenafil citrate: 2005-2014. *J Vet Cardiol*. 2015;17:182–191.

Kellum HB, Stepien RL. Sildenafil citrate therapy in 22 dogs with pulmonary hypertension. *J Vet Intern Med*. 2007;21:1258–1264.

Mazzotta E, et al. Red blood cell distribution width, hematology, and serum biochemistry in dogs with echocardiographically estimated precapillary and postcapillary pulmonary arterial hypertension. *J Vet Intern Med*. 2016;30:1806–1815.

Pariaut R, et al. Tricuspid annular plane systolic excursion (TAPSE) in dogs: reference values and impact of pulmonary hypertension. *J Vet Intern Med*. 2012;26:1148–1154.

Schober KE, Baade H. Doppler echocardiographic prediction of pulmonary hypertension in West Highland White Terriers with chronic pulmonary disease. *J Vet Intern Med*. 2006;20:912–920.

Soydan LC, et al. Accuracy of Doppler echocardiographic estimates of pulmonary artery pressures in a canine model of pulmonary hypertension. *J Vet Cardiol*. 2015;17:13–24.

Stepien RL. Pulmonary arterial hypertension secondary to chronic left-sided cardiac dysfunction in dogs. *J Small Anim Pract*. 2009;50:34–43.

Tidholm A, et al. Diagnostic value of selected echocardiographic variables to identify pulmonary hypertension in dogs with myxomatous mitral valve disease. *J Vet Intern Med*. 2015;29:1510–1517.

Visser LC, et al. Diagnostic value of right pulmonary artery distensibility index in dogs with pulmonary hypertension: comparison with Doppler echocardiographic estimates of pulmonary arterial pressure. *J Vet Intern Med*. 2016;30:543–552.

Heartworm Disease in the Dog

American Heartworm Society. Current canine guidelines for the diagnosis, prevention, and management of heartworm (Dirofilaria immitis) infection in dogs (revised July 2014). Available at: www.heartwormsociety.org. Accessed May 29, 2017.

Atkins CE. Canine and feline heartworm disease. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 8th ed. St Louis: Elsevier; 2017:1316–1343.

Atkins CE. Comparison of results of three commercial heartworm antigen test kits in dogs with low heartworm burdens. *J Am Vet Med Assoc*. 2003;222:1221–1223.

Atkins CE, Keene BW, McGuirk SM. Pathophysiologic mechanism of cardiac dysfunction in experimentally induced heartworm caval syndrome in dogs: an echocardiographic study. *Am J Vet Res*. 1988;49:403–410.

Atkins CE, Miller MW. Is there a safer (better) way to administer heartworm adulticidal therapy? *Vet Med*. 2003;98:310–317.

Atkins CE, et al. Heartworm 'lack of effectiveness' claims in the Mississippi delta: computerized analysis of owner compliance – 2004-2011. *Vet Parasitol*. 2014;206:106–113.

Bazzocchi C, et al. Combined ivermectin and doxycycline treatment has microfilaricidal and adulticidal activity against Dirofilaria immitis in experimentally infected dogs. *Int J Parasitol*. 2008;12:1401–1410.

Blagburn BL, et al. Comparative efficacy of four commercially available heartworm preventive products against the P3 laboratory strain of Dirofilaria immitis. *Vet Parasitol*. 2011;176:189–194.

Bourguinat C, et al. Correlation between loss of efficacy of macrocyclic lactone heartworm anthelmintics and P-glycoprotein genotype. *Vet Parasitol*. 2011;176:374–381.

Bove CM, et al. Outcome of minimally invasive surgical treatment of heartworm caval syndrome in dogs: 42 cases (1999-2007). *J Am Vet Med Assoc*. 2010;236:187–192.

Bowman D, et al. Prevalence and geographic distribution of Dirofilaria immitis, Borrelia burgdorferi, Ehrlichia canis, and Anaplasma phagocytophilum in dogs in the United States: results of a national clinic-based serologic survey. *Vet Parasitol*. 2009;160:138–148.

Dillon AR, et al. Activity of pulmonary intravascular macrophages in cats and dogs with and without adult Dirofilaria immitis. *Vet Parasitol*. 2008;158:171–176.

Drake J, et al. False negative antigen tests in dogs infected with heartworm and placed on macrocyclic lactone preventatives. *Parasit Vectors*. 2015;8:68.

Hettlich BF, et al. Neurologic complications after melarsomine dihydrochloride treatment for Dirofilaria immitis in three dogs. *J Am Vet Med Assoc*. 2003;223:1456–1461.

Hopper K, Aldrich J, Haskins SC. Ivermectin toxicity in 17 collies. *J Vet Intern Med*. 2002;16:89–94.

Kotani T, Powers KG. Developmental stages of Dirofilaria immitis in the dog. *Am J Vet Res*. 1982;43:2199–2206.

Kramer L, et al. Evaluation of lung pathology in Dirofilaria immitis—Experimentally infected dogs treated with doxycycline or a combination of doxycycline and ivermectin before administration of melarsomine hydrochloride. *Vet Parasitol*. 2011;176:357–360.

Litster A, et al. Radiographic cardiac size in cats and dogs with heartworm disease compared with reference values using the vertebral heart scale method: 53 cases. *J Vet Cardiol*. 2005;7:33–40.

Maxwell E, et al. Outcome of a heartworm treatment protocol in dogs presenting to Louisiana State University from 2008 to 2011: 50 cases. *Vet Parasitol*. 2013;206:71–77.

McCall JW, et al. Heartworm and Wolbachia: therapeutic implications. *Vet Parasitol*. 2008;158:204–214.

McCall JW, et al. Effects of doxycycline on heartworm embryogenesis, transmission, circulating microfilaria, and adult worms in microfilaremic dogs. *Vet Parasitol*. 2014;206:5–13.

Rawlings CA, et al. Pulmonary thromboembolism and hypertension after thiacetarsemide vs melarsomine dihydrochloride treatment of Dirofilaria immitis infection in dogs. *Am J Vet Res*. 1993;54:920–925.

Rohrbach BW, Odoi A, Patton S. Risk factors associated with failure of heartworm prophylaxis among members of a national hunting dog club. *J Am Vet Med Assoc*. 2011;238:1150–1158.

Snyder DE, et al. Ivermectin and milbemycin oxime in experimental adult heartworm (Dirofilaria immitis) infection of dogs. *J Vet Intern Med*. 2011;25:61–64.

Velasquez L, et al. Increased prevalence of Dirofilaria immitis antigen in canine samples after heat treatment. *Vet Parasitol*. 2014;206:67–70.

Venco L, et al. Efficacy of long-term monthly administration of ivermectin on the progress of naturally acquired heartworm infections in dogs. *Vet Parasitol*. 2004;124:259–268.

Yoon WK, et al. Comparison of two retrieval devices for heartworm removal in 52 dogs with heavy worm burden. *J Vet Intern Med*. 2013;27:469–473.

Heartworm Disease in the Cat

American Heartworm Society. Current feline guidelines for the diagnosis, prevention, and management of heartworm (Dirofilaria immitis) infection in cats (revised October 2014). Available at: www.heartwormsociety.org. Accessed May 29, 2017.

Atkins CE, et al. Heartworm infection in cats: 50 cases (1985-1997). *J Am Vet Med Assoc*. 2000;217:355–358.

Berdoulay P, et al. Comparison of serologic tests for the detection of natural heartworm infection in cats. *J Am Anim Hosp Assoc*. 2004;40:376–384.

Borgarelli M, et al. Surgical removal of heartworms from the right atrium of a cat. *J Am Vet Med Assoc*. 1997;211:68–69.

Browne LE, et al. Pulmonary arterial disease in cats seropositive for Dirofilaria immitis but lacking adult heartworms in the heart and lungs. *Am J Vet Res*. 2005;66:1544–1549.

DeFrancesco TC, et al. Use of echocardiography for the diagnosis of heartworm disease in cats: 43 cases (1985-1997). *J Am Vet Med Assoc*. 2001;218:66–69.

Dillon AR, et al. Feline heartworm disease: correlations of clinical signs, serology, and other diagnostics–results of a multi-center study. *Vet Ther*. 2000;1:176–182.

Dillon AR, et al. Effect of pre-cardiac and adult stages of Dirofilaria immitis in pulmonary disease in cats: CBC, bronchial lavage cytology, serology, radiographs, CT images, bronchial reactivity, and histopathology. *Vet Parasitol*. 2014;206:24–37.

Levy JK, et al. Seroprevalence of heartworm infection, risk factors for seropositivity, and frequency of prescribing heartworm preventatives for cats in the United States and Canada. *J Am Vet Med Assoc*. 2017;250:873–880.

Morchon R, et al. Specific IgG antibody response against antigens of Dirofilaria immitis and its Wolbachia endosymbiont bacterium in cats with natural and experimental infections. *Vet Parasitol*. 2004;125:313–321.

Small MT, et al. Use of a nitinol gooseneck snare catheter for removal of adult Dirofilaria immitis in two cats. *J Am Vet Med Assoc*. 2008;233:1441–1445.

Snyder PS, et al. Performance of serologic tests used to detect heartworm infection in cats. *J Am Vet Med Assoc*. 2000;216:693–700.

Venco L, et al. Clinical evolution and radiographic findings of feline heartworm infection in asymptomatic cats. *Vet Parasitol*. 2008;158:232–237.

Canine Angiostrongylosis

Boag AK, et al. Radiographic findings in 16 dogs infected with Angiostrongylus vasorum. *Vet Rec*. 2004;154:426–430.

Bohm C, et al. Assessment of the combination of spinosad and milbemycin oxime in preventing the development of canine Angiostrongylus vasorum infections. *Vet Parasitol*. 2014;199:272–277.

Borgeat K, et al. Retrospective evaluation of moderate-to-severe pulmonary hypertension in dogs naturally infected with Angiostrongylus vasorum. *J Small Anim Pract*. 2015;56:196–202.

Chapman PS, et al. Angiostrongylus vasorum infection in 23 dogs (1999-2002). *J Small Anim Pract*. 2004;45:435–440.

Lebon W, et al. Monthly administrations of milbemycin oxime plus afoxolaner chewable tablets to prevent Angiostrongylus vasorum infection in dogs. *Parasit Vectors*. 2016;9:485.

Matos JM, et al. Recruitment of arteriovenous pulmonary shunts may attenuate the development of pulmonary hypertension in dogs experimentally infected with Angiostrongylus vasorum. *J Vet Cardiol*. 2012;14:313–322.

Morgan E, Shaw S. Angiostrongylus vasorum infection in dogs: continuing spread and developments in diagnosis and treatment. *J Small Anim Pract*. 2010;51:616–621.

Schnyder M, et al. Larvicidal effect of imidacloprid/moxidectin spot-on solution in dogs experimentally inoculated with Angiostrongylus vasorum. *Vet Parasitol*. 2009;166:326–332.

Schnyder M, et al. Evaluation of a rapid device for serological in-clinic diagnosis of canine angiostrongylosis. *Parasit Vectors*. 2014;7:72.

CHAPTER 11

Systemic Arterial Hypertension



GENERAL CONSIDERATIONS

Systemic hypertension refers to the sustained elevation of systemic arterial blood pressure (BP). Over time, marked increase in arterial BP can cause serious clinical consequences. Multiple studies have attempted to define BP levels in normal dogs and cats; the largest studies suggest average systolic BP of approximately 130 mm Hg in dogs and 120 mm Hg in cats. However, various factors influence values obtained for systolic, diastolic, and mean arterial BP in healthy, as well as diseased, animals. Variations related to age, sex, reproductive status, and other factors might contribute minimally, whereas breed differences in normal values can be more pronounced. For example, BP can be 10 to 20 mm Hg higher in normal Greyhounds and some other sighthounds compared with mixed-breed dogs, although this could reflect an increased and sustained level of anxiety in the hospital setting ("white-coat" effect). Lesser differences in normal BPs have been reported for some other dog breeds as well. Variation in measured BP could be related to technique (direct and various noninvasive methods) and patient anxiety. Use of a consistent protocol for BP measurement in the clinic can help reduce variability related to environmental factors and technique. The demarcation between acceptable and "abnormally high" arterial BP is not clear-cut. Furthermore, although some dogs and cats clearly have clinical disease caused by hypertension, many with "abnormally high" BP have no evidence of related pathology. In addition, systolic BP can exceed 180 mm Hg in some stressed normal animals. Repeated BP measurements over time along with careful clinical evaluation are indicated when considering a diagnosis of hypertension.

Classification of abnormal BP in dogs and cats is based on risk for damage to so-called *target organs* (see p. 212). Animals with BP less than 150/95 mm Hg (systolic/diastolic) have minimal risk (Risk Category I). In general, this level is the therapeutic goal for patients receiving antihypertensive medications. Repeatable BP measurements of 150 to 159 mm Hg systolic and 95 to 99 mm Hg diastolic constitute mild hypertension, as well as mild risk for future target organ disease (Category II). Moderate hypertension (Category III) is associated with BPs between 160 and 179 mm Hg systolic and 100 and 119 mm Hg diastolic. Arterial pressures greater than 180/120 mm Hg indicate severe hypertension, with severe risk for target organ damage (Category IV). An additional 20 mm Hg is allowed for specific breed differences (e.g., for sighthounds).

Animals with mild hypertension (Category II) usually are not given antihypertensive therapy, although any underlying disease should be addressed. Some surveys of normal animals show BPs in this range, and it is likely that anxiety ("white-coat" hypertension) plays a role in mild BP elevation. Animals with moderate hypertension (Category III) could benefit from specific antihypertensive therapy, especially if there is evidence for target organ damage or treatment for underlying disease does not normalize BP. However, animals with BP closer to 160 mm Hg or where the white-coat effect is thought likely usually are not treated unless the clinician's assessment of the case dictates otherwise. Patients with severe hypertension (Category IV) should be treated to prevent or reduce target-organ damage. When possible, BP measurement is repeated to confirm presence of severe hypertension. On occasion, marked patient anxiety or technical error in BP recording can produce this degree of BP elevation, although this is uncommon. Some animals require urgent antihypertensive therapy because of rapidly progressing signs (see p. 213). When antihypertensive therapy is used, close monitoring for efficacy, adverse effects, and deterioration of underlying conditions is warranted. In all cases, predisposing disease should be treated, as possible.

Etiology

Hypertension in dogs and cats usually is associated with other diseases (Box 11.1) rather than being a primary condition (idiopathic or essential hypertension). The most common associations in cats are chronic kidney disease (CKD) and hyperthyroidism. Reported prevalence of hypertension in these disease conditions ranges from 25% to 75%. In dogs, the most common conditions associated with hypertension are renal disease (especially glomerular disease) and hyperadrenocorticism, with prevalence of hypertension reported to be up to 30% to 80% for each disease. Diabetes

BOX 11.1

Diseases Associated With Hypertension

Documented or Suspected Causes in Dogs and Cats

Renal disease (especially glomerular)
Hyperadrenocorticism
Hyperthyroidism
Pheochromocytoma
Diabetes mellitus
Hyperaldosteronism
Intracranial lesions (↑ intracranial pressure)
High-salt diet (?)
Obesity

Other Diseases Associated With Hypertension in People*

Acromegaly
Inappropriate antidiuretic hormone secretion
Hyperviscosity/erythrocytosis
Renin-secreting tumors
Hypercalcemia
Hypothyroidism with atherosclerosis
Hyperestrogenism
Coarctation of the aorta
Pregnancy
Central nervous system disease

*Essential (idiopathic) hypertension is often associated with family history, high salt intake, smoking, or obesity.

mellitus also can be associated with higher BP in dogs. Other less common diseases associated with high prevalence of systemic hypertension include pheochromocytoma and primary hyperaldosteronism (Conn's syndrome). Because of the increased risk for hypertension in patients with such conditions, BP should be measured when the disease is diagnosed and periodically thereafter. Similarly, hypertension discovered during a routine examination could be an early marker of underlying diseases associated with hypertension, so additional testing is indicated. Certain drugs such as glucocorticoids, mineralocorticoids, nonsteroidal antiinflammatory agents, phenylpropanolamine, sodium chloride, and even topical ocular phenylephrine can increase BP. Inherited idiopathic (essential) hypertension has been documented in dogs and cats, although it is uncommon. Idiopathic hypertension is considered a diagnosis of exclusion. Primary cardiac disease is not a recognized cause of systemic hypertension in dogs and cats.

Pathophysiology

BP is the product of cardiac output and systemic vascular resistance. BP is increased by conditions that raise cardiac output (by increasing heart rate, stroke volume, and/or blood volume) or by those that increase peripheral vascular resistance. Arterial BP is normally maintained within narrow bounds by the actions of the autonomic nervous system (e.g., via arterial baroreceptors); various hormonal systems (e.g., the renin-angiotensin system [RAAS], aldosterone, vasopressin/antidiuretic hormone, and natriuretic peptides); blood volume regulation by the kidney; and other factors.

Modulation of these systems by various disease conditions can lead to chronic elevation of arterial BP. For example, hypertension can result from increased sympathetic activity or responsiveness (e.g., with hyperthyroidism or hyperadrenocorticism), increased catecholamine production (e.g., with pheochromocytoma), or volume expansion caused by increased sodium retention (e.g., decreased glomerular filtration and reduced sodium excretion in renal failure, hyperaldosteronism, or hyperadrenocorticism). RAAS activation, with subsequent salt and water retention and vasoconstriction, can result from intrarenal disease (e.g., glomerulonephritis, chronic interstitial nephritis), enhanced production of angiotensinogen (e.g., hyperadrenocorticism), or extrarenal diseases that increase sympathetic nervous activity or interfere with renal perfusion (e.g., hyperthyroidism, renal artery obstruction). Impaired production of vasodilator substances (e.g., prostaglandins, kallikreins) and effects related to secondary hyperparathyroidism could be involved in chronic renal failure.

High perfusion pressure can damage capillary beds. In most tissues, capillary pressure is regulated by vasoconstriction of arterioles that feed the capillaries, although this control could be inadequate because of underlying organ disease. The continued arteriolar constriction secondary to chronic hypertension leads to hypertrophy and other vascular remodeling changes that can further increase vascular resistance. These structural changes and vascular spasm can cause capillary hypoxia, tissue damage, hemorrhage, and infarction, which can lead to organ dysfunction (Box 11.2).

Organs that are particularly vulnerable to damage from chronic hypertension are the eye, kidney, heart, and brain. These structures often are referred to as *target organs* or *end organs* damaged by systemic hypertension. In the eye, hypertension often causes focal perivascular edema, hemorrhage, and ischemia, especially in the retina and choroid layers. Bullous or total retinal detachment is common. Hyphema, vitreal hemorrhage, and optic neuropathy also can occur. Renal glomerular hypertension occurs when afferent arteriolar autoregulation is disrupted. The resulting glomerular hyperfiltration can lead to glomerulosclerosis, renal tubular degeneration, and fibrosis. These changes contribute to deterioration of renal function and increases in vascular resistance, thus chronic hypertension tends to perpetuate itself. Proteinuria is an important manifestation of renal damage and has been associated experimentally with severity of hypertension in cats and dogs. Reduction in proteinuria can indicate that therapeutic benefit is being achieved, especially in cats. BP is not directly correlated with serum creatinine concentrations, and hypertension can develop before azotemia, particularly in glomerular disease. Increased systemic arterial pressure and vascular resistance increase the afterload stress on the heart and stimulate left ventricular (LV) hypertrophy and dilation of the ascending aorta. Increased cerebral vascular pressure can promote edema formation, raise intracranial pressure, and cause hemorrhage.

BOX 11.2

Complications of Hypertension

Ocular

Retinopathy (edema, vascular tortuosity, hemorrhage, focal ischemia, atrophy)
Choroidopathy (edema, vascular tortuosity, hemorrhage, focal ischemia)
Retinal detachment (bullous or total)
Hemorrhage (retinal, vitreal, hyphema)
Papilledema
Blindness
Glaucoma
Secondary corneal ulcers

Neurologic

Cerebral edema, ↑ intracranial pressure
Hypertensive encephalopathy (lethargy, behavioral changes)
Cerebrovascular accident (focal ischemia, hemorrhage)
Seizures
Other acute neurologic deficits

Renal

Glomerulosclerosis/proliferative glomerulitis
Renal tubular degeneration and fibrosis
Progression of chronic kidney disease
Worsening proteinuria
Polyuria/polydipsia

Cardiac

Left ventricular hypertrophy
Murmur or gallop sound
Aortic dilation
Aortic aneurysm or dissection (rare)
Left-sided congestive heart failure (rare)

Other

Epistaxis

Clinical Features

Clinically recognized systemic hypertension usually occurs in middle-aged to older dogs and cats, presumably because of the associated disease conditions. Cats with severe end-organ disease secondary to hypertension tend to be geriatric. Signs of hypertension relate either to underlying disease or end-organ damage caused by the hypertension itself.

Ocular signs are the most common presenting issue, especially sudden blindness, which usually results from acute retinal hemorrhage or detachment. Although the retina may reattach, sight often does not return. Ocular fundic changes associated with hypertension include bullous to complete effusive retinal detachment, intraretinal edema, and hemorrhage. Vascular tortuosity, hyperreflective scars, retinal atrophy, papilledema, and perivasculitis are other signs of hypertensive retinopathy. Hemorrhage in the anterior or posterior chamber or sclera, closed-angle glaucoma, and corneal ulceration can occur also. Ocular damage is more likely at systolic BPs greater than 180 mm Hg, although it can develop at lower pressures.

Another common complaint is polyuria and polydipsia, which can be associated with renal disease, hyperadrenocorticism (in dogs), or hyperthyroidism (in cats). Furthermore, hypertension itself causes a so-called pressure diuresis. Hypertensive encephalopathy can result from cerebral edema or hemorrhage and can cause lethargy, seizures, abnormal mentation, collapse, or other neurologic or nonspecific signs. Paresis and other focal defects can occur as a result of cerebrovascular accident (stroke) caused by hypertensive arteriolar spasm or hemorrhage. Epistaxis can result from vascular rupture in the nasal mucosa. A soft, systolic cardiac murmur is heard on auscultation in many animals with hypertension. A gallop sound might also be present, especially in cats. Clinical left-sided congestive heart failure is uncommon.

Diagnosis

BP measurements are indicated in the following patient populations: (1) patients with suspected target organ damage (such as retinal detachment or LV hypertrophy); (2) patients diagnosed with a disease known to be associated with systemic hypertension (such as hyperthyroidism, protein losing nephropathy, or CKD); or (3) as a screening test in older dogs and cats. BP measurement at age 5 to 7 can be useful to establish the patient's baseline values. Annual BP measurement is recommended in dogs and cats beginning at ~8 years of age given the increased prevalence of renal and other predisposing diseases with age. A diagnosis of systemic hypertension should be confirmed by measuring BP multiple times and (ideally) on different days. A fundic examination, as well as routine laboratory database (complete blood count [CBC]; serum biochemical profile; and urinalysis with a urine protein-to-creatinine ratio [UPC]), is indicated in all hypertensive patients. Not all hypertensive patients with underlying CKD are azotemic. Other tests are done as needed to rule out possible underlying diseases or complications. These might include various endocrine tests, thoracic and abdominal radiographs, echocardiography, abdominal ultrasound, and serologic tests.

Thoracic radiographs can show some degree of cardiomegaly in patients with chronic hypertension. Cats especially can have a prominent aortic arch and an undulating (wavy) appearance to the thoracic aorta, although these findings might be present in normal geriatric cats and are not exclusive to hypertension.

LV hypertrophy is the classic echocardiographic finding in animals with systemic hypertension. However, the degree of LV hypertrophy is generally mild. Mean LV wall thickness measurements in hypertensive cats are higher than in normal cats but often remain within reference range. LV wall and septal hypertrophy can be symmetric or asymmetric. Proximal aortic dilation is another echocardiographic finding in some animals with systemic hypertension. A ratio of proximal ascending aortic diameter–to–aortic valve annulus diameter of greater than or equal to 1.25 is a common finding in hypertensive cats. Other echocardiographic findings could

include mild LA enlargement and sometimes mild mitral or aortic regurgitation. Systolic BP could be estimated during an echocardiographic examination in animals with mitral valve insufficiency by measuring the peak velocity of the mitral regurgitation jet using continuous-wave Doppler imaging; the modified Bernoulli equation (see p. 30) then is used to estimate the pressure gradient between the LV and LA. However, this method can underestimate BP and correlates only moderately with indirect BP measurements.

BLOOD PRESSURE MEASUREMENT

Several methods can be used to measure systemic arterial BP in the clinic. High pressures should be confirmed by repeated measurement sessions before a diagnosis of hypertension is made. Anxiety related to the clinical setting can falsely increase BP in some animals (i.e., the white-coat effect), and BP measurements can decrease with acclimation. Using as little restraint as possible in a quiet environment and allowing time (e.g., 5-15 minutes) for acclimatization is best for awake animals. It is often helpful to have the owner present. Use of consistent technique and cuff sizing (for indirect methods) is important. The technical skill and experience of the individual who obtains the BP measurements are also highly relevant to achieving consistent results.

Direct Blood Pressure Measurement

Arterial pressure can be measured directly by a needle or catheter placed into an artery and connected to a pressure transducer. Direct arterial pressure measurement is considered the gold standard, but it requires greater technical skill; moreover, in awake animals the physical restraint and discomfort associated with arterial puncture may falsely increase BP. Direct arterial pressure measurement is more accurate than indirect methods in hypotensive animals.

For arterial pressure monitoring over a period of time, an indwelling arterial catheter is often the best approach. The dorsal metatarsal artery is commonly used for this technique. An electronic pressure monitor provides continuous measurement of systolic and diastolic pressures and calculated mean pressure. With fluid-filled systems, the pressure transducer must be placed at the level of the patient's right atrium (RA) to prevent a false increase or decrease of the measured pressure related to the effects of gravity on the fluid within the connecting tubing.

When occasional BP measurement is necessary, a small-gauge needle attached directly to a pressure transducer may be used to puncture the dorsal metatarsal or femoral artery. To prevent hematoma formation, direct pressure should be applied to the arterial puncture site for several minutes after removing the catheter or needle used for BP measurement.

Indirect Blood Pressure Measurement

Several noninvasive methods are available to measure BP indirectly. These techniques involve the use of an inflatable cuff placed around a limb to occlude blood flow, usually over the brachial, radial, or saphenous artery, or the median caudal artery of the tail. Controlled release of cuff pressure is monitored to detect the return of blood flow. A standardized protocol for noninvasive BP measurement in dogs and cats has been described. The patient is gently restrained in sternal or lateral recumbency, with the cuff's vertical position close to the level of the RA during BP measurement. In lateral recumbency, the nondependent limb is used for BP measurements. A sitting position is not recommended due to poor repeatability and systematic overestimation of BP.

Doppler ultrasonic flow detection and oscillometric methods are used most often. Both techniques produce measurements that correlate somewhat well with direct BP measurement but are not exactly predictive of it; falsely high or low values occur. Calculating the average of several measurements (generally five to seven) in succession is recommended to increase accuracy. Often the first reading, or the highest and lowest, is discarded. If there is more than 20% variability in systolic pressure readings among successive measurements, the cuff placement or limb may need to be changed to obtain more consistent readings. If the accuracy of the BP measurements is in doubt, the process should be repeated at a later time, when the patient (hopefully) is better acclimated and more relaxed. Indirect methods are most reliable in normotensive and hypertensive animals. The BP device used should be calibrated semiannually to maximize accuracy.

Other methods such as auscultation and arterial palpation are not recommended for estimating BP. The auscultatory method (used to detect Korotkoff sounds in people) is technically impractical because of the limb conformation of dogs and cats. Direct arterial palpation is not reliable for estimating BP because pulse strength depends on the pulse pressure (systolic minus diastolic arterial pressure), not the absolute level of systolic or mean pressure. Pulse strength is also influenced by body conformation and other factors.

Cuff size and placement. A wide selection of cuff sizes, including human pediatric- and infant-size cuffs, is available for indirect BP measurement in dogs and cats. The cuff must be the correct size for the patient. The width of the cuff should be about 40% of the circumference of the extremity it surrounds for dogs (30%-40% for cats). The length of the inflatable balloon (bladder) within the cuff should cover at least 60% of this circumference. Cuffs that are too large can cause falsely low BP readings, whereas cuffs that are too small can cause falsely high BP readings. Some of the cuff inflation pressure goes toward tissue compression. Cuffs that are too narrow are more affected by this phenomenon and produce falsely increased pressure readings; cuffs that are too wide may underestimate BP. Intra-individual differences in BP between forelimb and hindlimb measurement sites have been reported. For these reasons, the cuff size and specific placement site used should be noted in the animal's record for consistency when repeating BP measurements over time. The cuff bladder should be centered over the target artery. Common cuff locations are midway between the elbow and carpus, in the tibial region, or at the base of the tail; skeletal prominences are avoided. The cuff should encircle the limb snugly without being excessively tight. Tape (not just Velcro on the cuff) can be used to secure the cuff in position.

Oscillometric method. The indirect oscillometric method uses an automated system for detecting and processing cuff pressure oscillation signals. With these systems, the flow occlusion cuff is inflated to a pressure above the systolic pressure and then slowly deflated in small pressure decrements. The microprocessor measures and averages the resulting pressure oscillations characteristic of systolic, diastolic, and/or mean pressures (depending on the system). Accurate results with oscillometric methods depend on careful adherence to the directions for use and an immobile subject. Because muscle contraction can produce oscillations, the limb used should not be bearing weight. At least five readings should be obtained; the lowest and highest are discarded, and the remaining measurements are averaged. The oscillometric method may be difficult to use effectively in small dogs and cats; poor agreement in systolic BP values (specifically underestimation) compared with direct measurements has been reported with various oscillometric devices.

Doppler ultrasonic method. This method employs the frequency change between emitted ultrasound and returning echoes (from moving blood cells or vessel wall) to detect blood flow in a superficial artery. This frequency change, the so-called Doppler shift, is converted to an audible signal. One system commonly used in animals is designed to determine systolic pressure by detecting blood cell flow (Ultrasonic Doppler Flow Detector, Model 811, Parks Medical Electronics, Inc, Aloha, OR).

Effective locations for pressure measurement include the dorsal metatarsal, palmar common digital (forelimb), and median caudal (tail) arteries. The probe is placed distal to the occluding cuff. A small area of hair is clipped over the artery for probe placement. Ultrasonic coupling gel is applied to the flat Doppler flow probe to obtain air-free contact with the skin. The probe is positioned so that a clear flow signal is heard but not held so tightly that it occludes flow. The probe must remain still to minimize noise; it can be taped in place. A low-volume setting on the Doppler unit or a headset is used to minimize patient anxiety caused by loud audio signals.

The flow-occluding cuff is attached to a sphygmomanometer and inflated to about 20 to 30 mm Hg above the point at which arterial flow ceases and no audible signals are heard. The cuff is slowly deflated (by a few mm Hg per second). During deflation, characteristic pulsatile flow signals from blood cell (or arterial wall) motion return during systole. The systolic pressure is the pressure at which blood flow first recurs (indicated by brief swishing sounds). A change in the flow sound from short and pulsatile to a longer, more continuous swishing often can be detected as cuff pressure diminishes; the pressure at which this change occurs approximates the diastolic pressure. However, Doppler estimation of diastolic BP is less accurate because of its subjective nature. The change in flow sound is not always detectable, especially with small or stiff vessels. As with the oscillometric method, it may be difficult to obtain measurements in small or hypotensive animals with the Doppler method. Patient movement also interferes with measurement. Overall, Doppler is considered the preferred method for systolic BP measurement in cats and small dogs.

Treatment and Prognosis

Antihypertensive therapy definitely is indicated for animals with severe hypertension, animals with clinical signs presumed to be caused by hypertension, and animals with evidence of target-organ damage. It is unclear whether all asymptomatic dogs and cats with moderate hypertension (e.g., repeatable systolic pressures of 160-180 mm Hg) benefit from specific antihypertensive treatment. Nevertheless, patients with high BP that persists after treatment for the primary disease should generally be treated. The goal of therapy is to reduce the BP to below 150/95 mm Hg. The expense and time commitment required for long-term (usually life-long) antihypertensive therapy and monitoring, as well as the potential for adverse medication effects, are considerations and should be explained clearly to the owner. Although some cases constitute hypertensive emergencies that require immediate therapy and intensive monitoring (discussed in more detail later), most hypertensive animals can be managed more conservatively (Box 11.3). Gradual reduction in BP could be safer in patients with long-standing hypertension. Chronically high BP leads to vascular adaptations in the cerebral autoregulatory process; if BP is suddenly reduced, cerebral perfusion may be adversely affected.

Several drugs are used as antihypertensive agents in dogs and cats (Table 11.1). Usually one drug is administered initially, at a low to moderate dose, if there is not a hypertensive crisis; then the BP is rechecked in 7 to 10 days to assess efficacy. The dose of the initial agent can be increased within recommended guidelines, if needed; if this is not sufficiently effective a second antihypertensive agent can be added. The drugs used most often are angiotensin-converting enzyme inhibitors (ACEIs), the Ca^{++}-blocker amlodipine, and (less commonly) the β-adrenergic blocker atenolol. Therapy with a single agent is effective in some cases, but combination therapy may be necessary for adequate BP control in others. An ACEI is recommended as the antihypertensive drug of first choice for all dogs. If the ACEI does not provide adequate BP reduction even at maximum recommended dosage, amlodipine is added. Amlodipine is not recommended as the sole antihypertensive therapy in dogs, because amlodipine administration in dogs activates the RAAS (and thus requires concurrent ACEI). In cats, amlodipine often is recommended as the initial antihypertensive drug, unless hyperthyroidism is the underlying cause, in which case atenolol could be considered first or in combination with amlodipine. However, an ACEI also has been recommended as initial therapy for cats with renal disease and proteinuria as the suspected underlying cause of hypertension. Other strategies are indicated in certain other specific conditions, such as sympathetic antagonists for pheochromocytoma or an aldosterone antagonist (e.g., spironolactone) for hyperaldosteronism.

Ancillary strategies might be helpful in patients with hypertension, although alone they are unlikely to markedly

BOX 11.3

Approach to the Patient With Hypertension

Suspect Hypertension or Disease Associated With Hypertension (see Box 11.2, text)

- Measure BP (see text).
- Use quiet environment.
- Allow at least 5 to 10 minutes for patient to acclimate to environment (if animal is easily stressed, have owner present when possible).
- Measure limb circumference, and use appropriate-size cuff (use same cuff size for subsequent measurements as well).
- Use consistent measurement technique.
- Take at least five BP readings; discard highest and lowest, average the remaining readings.
- Repeat BP measurements at other (one to three) times, preferably on different days, to confirm diagnosis of hypertension, except:
- If acute, hypertension-induced clinical signs (e.g., ocular hemorrhage, retinal detachment, neurologic signs) are present, begin therapy immediately (see p. 217; Table 11.1).
- Screen for underlying disease(s) (see Box 11.1).
- Obtain CBC, serum biochemistry tests, urinalysis, urine protein-to-creatinine ratio.
- Obtain other data depending on individual presentation: endocrine testing, thoracic and abdominal radiographs, ocular examination, ECG, echocardiography, other tests as indicated.

If Hypertension Confirmed:

- Manage underlying disease(s).
- Avoid drugs that can increase BP, if possible.
- Consider mildly to moderately reduced-sodium diet.
- Use weight-reduction diet if patient is obese.
- Begin initial antihypertensive drug therapy (see Table 11.1).
- Dogs: ACEI
- Cats with proteinuric renal disease: ACEI
- Cats with hyperthyroidism: atenolol ± amlodipine
- Other cats: amlodipine
- If pheochromocytoma suspected, see p. 219
- If emergent therapy needed, see p. 218
- Provide client education about the patient's disease(s) and potential complications, medication and reevaluation schedules, potential adverse effects of medication(s), and dietary concerns.

Patient Reevaluation

- Recheck BP in 7 to 10 days for clinically stable patients.
- Earlier reevaluation is advised for unstable patients, but full effects of antihypertensive drugs might not yet be realized.
- Obtain other tests as individually indicated.
- If BP control is not achieved with initial agent, try combination therapy (add ACEI or amlodipine).
- Further control can be achieved with dose escalation of amlodipine.
- Continue weekly to biweekly BP monitoring and underlying disease management. When BP (and underlying disease) is controlled, gradually increase time between recheck examinations.
- Recheck at least every 3 to 4 months because medication requirements may change.
- Recheck baseline laboratory data every 6 months or as individually indicated.

ACEI, Angiotensin-converting enzyme inhibitor; *BP,* arterial blood pressure; *CBC,* complete blood count; *ECG,* electrocardiogram.

reduce BP. Dietary salt restriction is controversial. A high-salt diet could contribute to development of hypertension in some cats, although salt intake does not generally affect BP in normal animals (as is the case in people). Neurohormonal activation can occur in animals fed a very low-sodium diet; this can also increase potassium excretion, especially in cats with renal dysfunction. However, moderate dietary salt reduction (e.g., ≤0.22%-0.25% sodium on a dry matter basis) could be useful in some cases. Although not expected to normalize BP by itself, salt restriction might enhance antihypertensive drug effectiveness. Weight reduction usually is advised for obese animals. It is prudent to avoid prescribing drugs that can potentiate vasoconstriction (e.g., phenylpropanolamine and other α_1-adrenergic agonists). Glucocorticoids and progesterone derivatives should also be avoided when possible because steroid hormones can increase BP. A diuretic (thiazide or furosemide; see Chapter 3) might help by reducing blood volume in patients with volume expansion (this is a common approach to antihypertensive treatment in people); however, a diuretic alone rarely is effective in hypertensive animals. Diuretics should be avoided in animals with renal disease because they can cause dehydration and exacerbate azotemia.

The ability to monitor BP is important when antihypertensive drugs are prescribed. Serial measurements are necessary to assess treatment efficacy and prevent hypotension. Adverse effects of antihypertensive therapy usually relate to hypotension, manifested by lethargy or ataxia, or reduced appetite. Attaining initial BP control may take several weeks. Monitoring can be done every 7 to 10 days to assess the efficacy of antihypertensive treatment in nonurgent cases. The dosage of antihypertensive drug(s) can be increased if control has not been achieved or reduced if systolic BP is less than ~110 mm Hg. Once satisfactory regulation is achieved, BP should be measured every 1 to 4 months, depending on patient stability. Some animals become refractory to therapy that was initially effective. Increased antihypertensive dosage, adjunctive therapy, or a change of antihypertensive drug can

TABLE 11.1

Drugs Used to Treat Hypertension

DRUG	DOG	CAT
ACEIs (see Chapter 3)		
Enalapril	0.5 mg/kg PO q12h	0.5 mg/kg PO q24h
Benazepril	0.5 mg/kg PO q12h	Same
Ramipril	0.125-0.25 mg/kg PO q24h	0.125 mg/kg PO q24h
Captopril	0.5-2 mg/kg PO q8-12h	0.5-1.25 mg/kg PO q(8-)24h
Calcium Channel Blocker		
Amlodipine	0.1-0.3 (up to 0.5) mg/kg PO q24(-12)h	0.625 mg/cat (or 0.1-0.2 [up to 0.5] mg/kg) PO q(-12)24h
β-Adrenergic Blockers (see Chapter 4)		
Atenolol	0.2-1 mg/kg PO q12(-24)h (start low)	6.25-12.5 mg/cat PO q12(-24)h
Propranolol	0.1-1 mg/kg PO q8h (start low)	2.5-10 mg/cat PO q8-12h
α_1-Adrenergic Blockers		
Phenoxybenzamine	0.25 mg/kg PO q8-12h or 0.5 mg/kg q24h	2.5 mg/cat PO q8-12h or 0.5 mg/kg q12-24h
Prazosin	0.05-0.2 mg/kg PO q8-12h	0.25-0.5 mg/cat PO q12-24h
Drugs for Hypertensive Crisis		
Amlodipine	0.1-0.3 (up to 0.5) mg/kg PO q24(-12)h	0.625 mg/cat (or 0.1-0.2 [up to 0.5] mg/kg) PO q(-12)24h
Hydralazine (see Chapter 3)	0.5-2 mg/kg PO q12h (start low, titrate up to effect); or 0.1-0.2 mg/kg, IV or IM, repeat q2h as needed	Same (or 2.5 [up to 10] mg/cat PO q12h)
Nitroprusside (see Chapter 3)	0.5-1 mcg/kg/min CRI (initial) to 5-15 mcg/kg/min CRI	0.5-1 mcg/kg/min CRI (initial), to 5 mcg/kg/min CRI
Esmolol	25-75 (up to 200) mcg/kg/min CRI	Same
Propranolol	0.02 mg/kg (initial) to max of 0.1 mg/kg slow IV	Same
Acepromazine	0.05-0.1 mg/kg (up to 3 mg total) IV	0.01-0.05 mg/kg IV
Phentolamine	0.02-0.1 mg/kg IV bolus, followed by CRI to effect	Same

ACEI, Angiotensin-converting enzyme inhibitor; *CRI,* constant-rate infusion; *IV,* intravenous; *PO,* by mouth.

be tried. Continued attention to the underlying disease process is important. Routine CBC, serum biochemistry profile, and urinalysis (with UPC) are also recommended every 6 months. Other tests are done as indicated. Decreasing the magnitude of proteinuria associated with hypertension is a desired treatment outcome, as degree of proteinuria is a negative prognostic factor in cats with CKD.

The long-term prognosis for animals with hypertension reflects prognosis for the underlying disease, which may be chronic and progressive. Unfortunately, hypertension often persists even with adequate treatment or control of the underlying disease, particularly in dogs with hyperadrenocorticism and cats with hyperthyroidism. In addition, therapy for some primary diseases (such as fluid therapy, steroids, and erythropoietin) can exacerbate hypertension or complicate its control. Target-organ damage from systemic hypertension could improve or reverse once patients become normotensive. Retinal hemorrhage generally resolves and detached retinas may reattach, although prognosis for vision remains guarded. Reverse remodeling of LV hypertrophy can occur. Adequate control of BP also is thought to decrease the rate of progression of CKD.

ANTIHYPERTENSIVE DRUGS

The ACEIs (e.g., enalapril, benazepril) reduce angiotensin II production, thereby reducing vascular resistance and volume retention (see p. 67). These agents also selectively dilate the glomerular efferent arteriole and thus decrease

intraglomerular pressure and proteinuria. ACEI are relatively weak antihypertensive medications, leading to BP reduction in the realm of 10% to 20%, even at relatively high doses. The efficacy of these agents likely is greater in patients with glomerular hypertension (proteinuric renal disease) and in patients with significant RAAS activation. ACEIs are the recommended first-line treatment for systemic hypertension in dogs, as well as in cats with proteinuric renal disease. In dogs, q12h dosing is recommended for optimal RAAS suppression, whereas q24h dosing is adequate in cats. If BP remains elevated despite ACEI administration at a typical dose (0.5 mg/kg PO q12h for dogs, q24h for cats), it is unlikely that dose escalation will further reduce BP, and amlodipine is generally added. ACEI are generally very well tolerated, although GI upset, electrolyte disturbances, and hypotension are potential concerns. Worsening azotemia is possible in patients with CKD because efferent arteriolar dilation reduces glomerular filtration rate (GFR).

Angiotensin receptor blockers (ARBs), such as telmisartan, losartan, and irbesartan, inhibit the RAAS system "downstream" from ACEI by selectively antagonizing the AT_1 receptor to which angiotensin II binds. In experimental studies, ARBs appear to lower BP more effectively than ACEI, although reported BP reduction with ARBs is only in the realm of 20 to 25 mm Hg. As with ACEI, these agents are also used for treatment of proteinuria and are likely to be particularly useful for systemic hypertension associated with glomerular disease or in patients with RAAS activation. No studies have compared efficacy of ACEI to ARBs in clinical patients with systemic hypertension. Telmisartan appears to be the most effective ARB in dogs and cats, and has been studied at doses of 1 to 3 mg/kg PO q24h in both dogs and cats. Losartan is not recommended due to inferior BP control, likely due to failure of hepatic conversion to the active metabolite in dogs.

Amlodipine besylate is a long-acting dihydropyridine Ca^{++}-blocker that causes vasodilation without appreciable cardiac effects. It is a more effective antihypertensive agent than ACEIs or ARBs. The drug usually is dosed once daily, although q12h administration can be used in patients that do not respond sufficiently to the lower dose. Amlodipine dilates the glomerular afferent arterioles and can thereby act synergistically with ACEI to reduce glomerular hypertension. In dogs, amlodipine administration alone has been shown to activate the RAAS. In cats with CKD, amlodipine does not alter serum creatinine concentration, although RAAS activation specifically has not been studied.

Amlodipine is an effective antihypertensive in both dogs and cats. In cats, amlodipine monotherapy is effective in controlling hypertension secondary to various causes. Amlodipine is initially dosed in cats as 0.625 mg/cat (one quarter of a 2.5-mg tablet) q24h; this dose can be increased to q12h (or to 1.25 mg/cat) if needed, based on rechecked BP. Cats with higher BP at diagnosis (>200 mm Hg) often require a higher dose of amlodipine for eventual BP control. In hypertensive dogs, amlodipine is added to the treatment regimen when ACEI monotherapy fails to achieve adequate BP control; amlodipine should not be used as an antihypertensive monotherapy in dogs. A low dose is started initially and titrated upward as needed. Amlodipine's half-life is about 30 hours in dogs; maximal effects occur 4 to 7 days after initiating therapy. Oral bioavailability is high, and peak plasma concentrations are reached 3 to 8 hours after administration; plasma concentrations increase with chronic therapy. The drug undergoes hepatic metabolism, but there is not extensive first-pass elimination; caution is warranted when liver function is poor. The drug is excreted through the urine and feces. In both dogs and cats, combination therapy of amlodipine plus an ACEI can control BP while yielding a balanced effect on glomerular pressure and GFR through equal dilation of afferent and efferent arterioles.

β-adrenergic blockers potentially could reduce BP by decreasing heart rate, cardiac output, and renal renin release. Atenolol and propranolol have been used most often (see p. 94). A β-blocker can be considered for cats with hyperthyroid-induced hypertension, as increased activity of the sympathetic nervous system could underlie hypertension in this disease; furthermore, β-blockers can inhibit peripheral conversion of T_4 to active T_3. However, atenolol therapy causes no change in BP in normotensive cats and only decreases BP by ~15 mm Hg in hypertensive hyperthyroid cats. In general, β-blockers are ineffective as a sole antihypertensive agent in cats; adjunct amlodipine usually is required.

α_1-adrenergic antagonists oppose the vasoconstrictive effects of α-receptors. Their main use is for hypertension caused by pheochromocytoma. Phenoxybenzamine is a noncompetitive α_1- and α_2-blocker used most often for pheochromocytoma-induced hypertension. Treatment is initiated with a low dose titrated upward as needed. The selective α_1-blocker prazosin is another option. After α-blocker dosing is begun, adjunctive therapy with a β-blocker can help control reflex tachycardia or arrhythmias. In cases of pheochromocytoma, β-blockade should not be initiated before α-blockade, because use of a β-blocker as the sole agent in this setting leaves α_1-receptors unopposed and is likely to exacerbate hypertension.

Hypotension is a potential adverse effect of any antihypertensive drug. Hypotension usually is manifested as periods of lethargy or ataxia. Reduced appetite could be another adverse effect. Conversely, rebound hypertension can occur if antihypertensive therapy is suddenly discontinued. This especially is of concern when using β- or α_2-blockers. If therapy with such agents is to be terminated, the dosage should be gradually tapered down first.

HYPERTENSIVE EMERGENCY

Urgent antihypertensive therapy is indicated when new or progressive signs of severe hypertension are identified. Examples include acute retinal detachment and hemorrhage, encephalopathy, intracranial hemorrhage, acute renal failure, aortic aneurysm, or acute left-sided congestive heart failure. The animal should be hospitalized until BP and other acute signs are controlled.

Oral amlodipine can be effective in quickly decreasing BP, especially in cats, and has less risk of inducing hypotension than more potent vasodilators. Oral amlodipine is initiated at the typical dose of 0.625 mg/cat, and BP rechecked q2h. Maximal effect of amlodipine after a single oral dose in cats occurs at 4 to 6 hours. If BP is not adequately controlled in 4 to 6 hours, an additional 0.625 mg/cat PO can be given, and dose continued q12h.

Direct-acting vasodilator agents (e.g., nitroprusside, hydralazine) can produce faster reduction in BP; arterial pressure should be closely monitored to prevent hypotension. Nitroprusside is dosed to effect by constant intravenous (IV) infusion (see Table 11.1). Hydralazine (IV or PO) is an alternative, especially for dogs. An IV β-blocker (esmolol, propranolol) or acepromazine (see Table 11.1) can also be used. One of these agents can be added to oral amlodipine therapy if BP is not adequately reduced within 12 hours. BP rechecks within 1 to 3 days are recommended in patients with serious or rapidly progressive signs.

When a hypertensive crisis is related to pheochromocytoma or other cause of catecholamine excess, the α-blocker phentolamine can be used intravenously (see Table 11.1) and titrated to effect. Addition of a β-blocker can help mitigate pheochromocytoma-induced tachyarrhythmias, but it should not be administered alone or before an α-blocker is given, for reasons previously discussed. Antihypertensive treatment is recommended for 2 to 3 weeks before surgery for pheochromocytoma excision, if possible. For inoperable pheochromocytoma, therapy is continued orally to prevent hypertensive emergencies.

Suggested Readings

Acierno MJ, et al. Agreement between directly measured blood pressure and pressures obtained with three veterinary-specific oscillometric units in cats. *J Am Vet Med Assoc*. 2010;237:402–406.

Atkins CE, et al. The effect of amlodipine and the combination of amlodipine and enalapril on the renin-angiotensin-aldosterone system in the dog. *J Vet Pharmacol Ther*. 2007;30:394–400.

Belew AM, Barlett T, Brown SA. Evaluation of the white-coat effect in cats. *J Vet Intern Med*. 1999;13:134–142.

Bijsmans ES, et al. Factors influencing the relationship between the dose of amlodipine required for blood pressure control and change in blood pressure in hypertensive cats. *J Vet Intern Med*. 2016;30:1630–1636.

Bodey AR, Sanson J. Epidemiological study of blood pressure in domestic cats. *J Small Anim Pract*. 1998;39:567–573.

Bright JM, Dentino M. Indirect arterial blood pressure measurement in nonsedated Irish Wolfhounds: reference values for the breed. *J Am Anim Hosp Assoc*. 2002;38:521–526.

Brown S, et al. Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. ACVIM Consensus Statement. *J Vet Intern Med*. 2007;21:542–558.

Buranakarl C, Mathur S, Brown SA. Effects of dietary sodium chloride intake on renal function and blood pressure in cats with normal and reduced renal function. *Am J Vet Res*. 2004;65:620–627.

Chetboul V, et al. Spontaneous feline hypertension: clinical and echocardiographic abnormalities, and survival rate. *J Vet Intern Med*. 2003;17:89–95.

Chetboul V, et al. Comparison of Doppler ultrasonography and high-definition oscillometry for blood pressure measurements in healthy awake dogs. *Am J Vet Res*. 2010;71:766–772.

Coleman AE, et al. Attenuation of the pressor response to exogenous angiotensin by angiotensin-receptor blockers in normal dogs [abstract]. *J Vet Intern Med*. 2014;28:977.

Elliot J, et al. Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases. *J Small Anim Pract*. 2001;42:122–129.

Finco DR. Association of systemic hypertension with renal injury in dogs with induced renal failure. *J Vet Intern Med*. 2004;18:289–294.

Hanzlicek AS, Baumwart RD, Payton ME. Systolic arterial blood pressure estimated by mitral regurgitation velocity, high definition oscillometry, and Doppler ultrasonography in dogs with naturally occurring degenerative mitral valve disease. *J Vet Cardiol*. 2016;18:226–233.

Henik RA, Stepien RL, Bortnowski HB. Spectrum of M-mode echocardiographic abnormalities in 75 cats with systemic hypertension. *J Am Anim Hosp Assoc*. 2004;40:359–363.

Henik RA, et al. Efficacy of atenolol as a single antihypertensive agent in hyperthyroid cats. *J Feline Med Surg*. 2008;10:577–582.

Huhtinen M, et al. Randomized placebo-controlled clinical trial of a chewable formulation of amlodipine for the treatment of hypertension in client-owned cats. *J Vet Intern Med*. 2015;29:786–793.

Jackson BL, Adin DB, Lehmkuhl LB. Effect of atenolol on heart rate, arrhythmias, blood pressure, and dynamic left ventricular outflow tract obstruction in cats with subclinical hypertrophic cardiomyopathy. *J Vet Cardiol*. 2015;17:S296–S305.

Jacob F, et al. Association between initial systolic blood pressure and risk of developing a uremic crisis or of dying in dogs with chronic renal failure. *J Am Vet Med Assoc*. 2003;222:322–329.

Jenkins TL, et al. Attenuation of the pressor response to exogenous angiotensin by angiotensin receptor blockers and benazepril hydrochloride in clinically normal cats. *Am J Vet Res*. 2015;76:807–813.

Jepson RE, et al. Effect of control of systolic blood pressure on survival in cats with systemic hypertension. *J Vet Intern Med*. 2007;21:402–409.

Lalor SM, et al. Plasma concentrations of natriuretic peptides in normal cats and normotensive and hypertensive cats with chronic kidney disease. *J Vet Cardiol*. 2009;11(suppl 1):S71–S79.

LeBlanc NL, Stepien RL, Bentley E. Ocular lesions associated with systemic hypertension in dogs: 65 cases (2005-2007). *J Am Vet Med Assoc*. 2011;238:915–921.

Maggio F, et al. Ocular lesions associated with systemic hypertension in cats: 69 cases (1985-1998). *J Am Vet Med Assoc*. 2000;217:695–702.

Marino CL, et al. White-coat effect on systemic blood pressure in retired racing Greyhounds. *J Vet Intern Med*. 2011;25:861–865.

Misbach C, et al. Echocardiographic and tissue Doppler imaging alterations associated with spontaneous canine systemic hypertension. *J Vet Intern Med*. 2011;25:1025–1035.

Nelson OL, et al. Echocardiographic and radiographic changes associated with systemic hypertension in cats. *J Vet Intern Med*. 2002;16:418–425.

Payne JR, Brodbelt DC, Luis Fuentes V. Blood pressure measurements in 780 apparently healthy cats. *J Vet Intern Med*. 2017;31:15–21.

Rattez EP, et al. Within-day and between-day variability of blood pressure measurement in healthy conscious Beagle dogs using a new oscillometric device. *J Vet Cardiol*. 2010;12:35–40.

Reusch CE, Schellenberg S, Wenger M. Endocrine hypertension in small animals. *Vet Clin North Am Small Anim Pract*. 2010;40: 335–352.

Rondeau DA, Mackalonis ME, Hess R. Effect of body position on indirect measurement of systolic arterial blood pressure in dogs. *J Am Vet Med Assoc*. 2013;252:1523–1527.

Sakatani A, Miyagawa Y, Takemura N. Evaluation of the effect of an angiotensin-converting enzyme inhibitor, alacepril, on drug-induced renin–angiotensin–aldosterone system activation in normal dogs. *J Vet Cardiol*. 2016;18:248–254.

Sansom J, Rogers K, Wood JL. Blood pressure assessment in healthy cats and cats with hypertensive retinopathy. *Am J Vet Res*. 2004;65:245–252.

Scansen BA, et al. Comparison of forelimb and hindlimb systolic blood pressures and proteinuria in healthy shetland sheepdogs. *J Vet Intern Med*. 2014;28:277–283.

Schellenberg S, Glaus TM, Reusch CE. Effect of long-term adaptation on indirect measurements of systolic blood pressure in conscious untrained beagles. *Vet Rec*. 2007;161:418–421.

Snyder PS, Sadek D, Jones GL. Effect of amlodipine on echocardiographic variables in cats with systemic hypertension. *J Vet Intern Med*. 2001;15:52–56.

Stepien RL. Feline systemic hypertension: diagnosis and management. *J Feline Med Surg*. 2011;13:35–43.

Stepien RL, et al. Comparative diagnostic test characteristics of oscillometric and Doppler ultrasound methods in the detection of systolic hypertension in dogs. *J Vet Intern Med*. 2003;17: 65–72.

Syme HM, et al. Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation. *J Am Vet Med Assoc*. 2002;220:1799–1804.

Taylor SS, et al. ISFM consensus guidelines on the diagnosis and management of hypertension in cats. *J Feline Med Surg*. 2017;19: 288–303.

Tissier R, Perrot S, Enriquez B. Amlodipine: one of the main antihypertensive drugs in veterinary therapeutics. *J Vet Cardiol*. 2005;7:53–58.

Uechi M, Imamoto S, Ishikawa Y. Dose-dependent inhibition of angiotensin converting enzyme by enalapril in cats. *J Vet Med Sci*. 2002;64:385–387.

Wernick MB, et al. Comparison of arterial blood pressure measurements and hypertension scores obtained by use of three indirect measurement devices in hospitalized dogs. *J Am Vet Med Assoc*. 2012;240:962–968.

CHAPTER 12

Thromboembolic Disease



GENERAL CONSIDERATIONS

Thromboembolic (TE) disease involves either a locally formed (in situ) aggregation of platelets and other blood elements (thrombus), or a thrombus or other aggregate that breaks away from its origination site (embolus) and is carried downstream by blood flow. Both thrombi and emboli can partially or completely obstruct blood flow, either in a vessel or in the heart. TE disease can occur whenever normal hemostatic mechanisms are disturbed. Most clinically recognized TE events involve the distal aorta, pulmonary arteries, heart, or cranial vena cava. (For additional information on the pathogenesis of thromboembolism, see Chapter 87.)

The clinical sequelae of TE disease depend mainly on the size and location of the thrombus/thrombi. These factors determine how much functional compromise occurs and in which organs and tissues. Acute, profound clinical signs of pain and organ dysfunction result from some thromboemboli. Others cause subclinical tissue damage and varying degrees of pathology. TE disease is sometimes suspected antemortem; in other cases, it is discovered at necropsy (or not at all).

NORMAL HEMOSTATIC MECHANISMS

There is normally interplay among the different factors that promote coagulation, inhibit coagulation, and promote fibrinolysis. A proper balance of these factors maintains blood fluidity and minimizes loss when vessels are damaged. Platelets, the vascular endothelium, coagulation proteins, and the fibrinolytic system are all involved in normal hemostasis. Injury to the vascular endothelium quickly induces several reactions that cause vasoconstriction, hemostatic plug formation, and attempts at vascular repair to prevent blood loss.

Intact endothelium exerts anticoagulant properties via several mechanisms. First, the endothelium represents a physical barrier that is negatively charged, discouraging and repelling platelet adhesion. Second, the arrangement of phospholipids in healthy cell membranes inhibits coagulation. In normal endothelial cells and platelets, the outer membrane of the lipid bilayer contains neutral phospholipids; the more reactive phospholipids, phosphatidylserine (PTS) and phosphatidylethanolamine (PEA), are localized to the inner membrane. This asymmetry in the lipid bilayer is maintained by active transport of phospholipids by the ATP-dependent enzymes flippase and floppase. After cell injury, the enzyme scramblase shuffles phospholipids between the inner and outer membranes, resulting in PTS and PEA expression on the outer membrane. Membranes with exposed PTS provide a substrate that supports and catalyzes coagulation reactions, whereas such reactions occur very slowly on membranes lacking PTS. Finally, healthy endothelium actively produces substances that inhibit both platelet adhesion and coagulation. Antiplatelet substances produced by vascular endothelium include nitric oxide, prostacyclin, and adenosine diphosphatase (ADPase). Anticoagulant substances synthesized by intact endothelium include thrombomodulin, protein S, heparin sulfated proteoglycans (HSPGs), and tissue factor pathway inhibitor (TFPI).

Damaged endothelial cells promote thrombus formation. Although this reduces blood loss in the event of vascular damage, in other settings TE disease results. Endothelial damage contributes to thrombus formation in several ways. First, injured endothelial cells release endothelin, which promotes vasoconstriction and slows local blood flow, allowing more time for blood components to interact with the vessel wall. Second, as previously discussed, presence of PTS on the outer lipid membrane of damaged cells dramatically increases speed of coagulation reactions. Perhaps most importantly, damaged endothelium exposes cells expressing tissue factor (TF or thromboplastin), which is the key step to initiate thrombus formation.

Traditional models of hemostasis involve a temporal and functional division of thrombus formation into *primary hemostasis* (formation of the primary platelet plug), *secondary hemostasis* (coagulation proteins creating cross-linked fibrin), and *fibrinolysis* (thrombus breakdown). Secondary hemostasis has been further modeled as a "cascade" of coagulation proteins involving sequential cleavage of proenzymes, each step activating the next coagulation factor in the series. This cascade was historically divided into *extrinsic*

(outside the blood, TF-dependent) and *intrinsic* (within the blood, contact-dependent), considered to be two alternative pathways for eventual activation of factor Xa (FXa). FXa activation then initiates the final "common pathway": activation of prothrombin to thrombin, followed by cleavage of fibrinogen to fibrin. Although the cascade model historically explained many aspects of coagulation in vitro, more recent models have been proposed that highlight the role of cell membranes in the process of hemostasis in vivo.

The currently advocated *cell-based model* of hemostasis is divided into three sequential but overlapping phases: initiation, amplification, and propagation. During *initiation*, vascular injury exposes subendothelial cells expressing TF, which binds to factor VIIa (FVIIa) in circulating blood. The complex of TF-FVIIa activates FXa to produce small amounts of thrombin (FIIa), which attracts and activates nearby platelets. In the *amplification* phase, platelet activation by thrombin results in platelet shape change, platelet degranulation, and expression of platelet surface receptors. Platelet granules release substances that attract and activate other platelets (including thromboxane A_2, serotonin, adenosine diphosphate [ADP], calcium, and fibrinogen). Different types of platelet receptors bind to subendothelial von Willebrand factor (glycoprotein [GP] I_b-IX) or to other platelets via fibrinogen ($GP\alpha_{IIb}$ β_3, formerly known as $GPII_b$-III_a). This recruitment and aggregation creates a "plug" of fibrinogen-linked platelets. The platelet plug helps limit blood loss through small vessels; more importantly, however, the activated platelet membranes (with exposed PTS) create a substrate for the *propagation* phase of hemostasis. In the propagation phase, activated coagulation factors react on the activated platelet surface in a series of steps to generate more activated FXa, which along with its co-factor FVa cleaves prothrombin into thrombin (FIIa). Formation of large amounts of thrombin is the "final step" in the cell-based model of coagulation. Thrombin converts fibrinogen into fibrin monomers, which polymerize to soluble fibrin, which is then cross-linked by the action of thrombin-activated FXIII (or fibrin-stabilizing factor). This insoluble fibrin stabilizes the clot.

After a thrombus forms, several mechanisms limit its extent and promote its breakdown. Thrombolysis requires plasmin. Its inactive precursor, plasminogen, is converted to plasmin by tissue plasminogen activator (t-PA) when fibrin is present. During activation of the coagulation cascade, endothelial cells simultaneously release t-PA. Several other substances also can act as plasminogen activators. Plasmin degrades fibrinogen and soluble (noncross-linked) fibrin to yield fibrinogen/fibrin degradation products (FDPs). Plasmin also cleaves cross-linked fibrin in stabilized clots into large fragments (x-oligomers) that are further broken down into D-dimers and other fragments. D-dimers are produced only with active coagulation and subsequent fibrinolysis. There also are negative feedback constraints on fibrinolysis (e.g., plasminogen activator inhibitors [PAI], α_2-antiplasmin, thrombin-activated fibrinolytic factor). Defective fibrinolysis is thought to play a role in pathologic thrombosis.

There are multiple physiologic mechanisms that limit the extent of thrombus formation in addition to the fibrinolytic system. As previously discussed, inherent properties of healthy vascular endothelium effectively localize coagulation only to sites of injury. Antithrombin (AT), a small protein produced by the liver, is responsible for most of the anticoagulant effect of plasma. Along with its co-factor heparan sulfate, AT binds to and inactivates many coagulation proteins, including thrombin; FIXa, FXa, FXIa, and FXIIa; and kallikrein. Protein C (and its co-factor Protein S) are vitamin K–dependent glycoproteins that inactivate FVa and FVIIIa. Proteins C and S are stimulated by thrombin (via formation of the thrombin-thrombomodulin complex), thus acting as a negative feedback loop during the coagulation process. Endothelial-derived TFPI also limits hemostasis by inhibiting FVIIa and TF. Malfunction of one or more of these control systems promotes thrombosis.

Pathophysiology

TE disease is more likely when changes in normal hemostatic processes create conditions that favor clot formation or impair fibrinolysis. Three general situations (so-called "Virchow's triad") promote pathologic thrombosis: abnormal endothelial structure or function, slowed or static blood flow, and a hypercoagulable state (from either increased procoagulant substances or decreased anticoagulant or fibrinolytic substances). A number of common diseases produce such conditions (Box 12.1).

Diseases that induce severe or widespread endothelial injury promote thrombosis via loss of the antiplatelet, anticoagulant, and fibrinolytic functions of normal endothelium. Injured endothelium also releases TF and antifibrinolytic factors. Subendothelial tissue, exposed because of endothelial cell damage, promotes thrombosis by acting as a substrate for clot formation and stimulating platelet adherence and aggregation. Systemic release of inflammatory cytokines (e.g., tumor necrosis factor [TNF], various interleukins, platelet activating factor, nitric oxide) can cause widespread endothelial injury, induce TF expression, and inhibit anticoagulant mechanisms. This occurs in patients with sepsis and likely other systemic inflammatory conditions as well. Neoplastic invasion, vascular disruption resulting from other disease, and postischemic injury also induce endothelial damage. Microparticles, small membrane-bound vesicles derived from platelets or other cell types in certain disease states, can provide a procoagulant phospholipid membrane surface for pathologic thrombosis. Mechanical trauma to the vascular endothelium (as with catheterization) can also precipitate TE disease, especially when other predisposing conditions exist. Pulmonary artery endothelial injury resulting from heartworm disease (HWD) is well known (see Chapter 10). The inflammatory reaction to dead or dying worms and worm fragments exacerbates the endothelial damage and prothrombotic conditions.

Stagnant blood flow promotes thrombosis by impeding the dilution and clearance of coagulation factors, as well as increasing time for blood components to contact vessel

BOX 12.1

Diseases Potentially Associated With Thromboembolism

Endothelial Disruption

Sepsis
Systemic inflammatory disease
Heartworm disease
Neoplasia
Massive trauma
Shock
Intravenous catheterization
Injection of irritating substance
Atherosclerosis
Arteriosclerosis
Hyperhomocysteinemia

Abnormal Blood Flow

Vascular obstruction (e.g., mass lesion, adult heartworms, catheter or other device)
Heart disease (especially cardiomyopathy in cats)
Cardiovascular neoplasia
Endocarditis
Shock
Hypovolemia/dehydration
Prolonged recumbency
Hyperviscosity (e.g., polycythemia, leukemia, hyperglobulinemia)
Hypoviscosity (anemia)
Anatomic abnormality (e.g., aneurysm, AV fistula)

Increased Coagulability

Glomerular disease/protein-losing nephropathy
Hyperadrenocorticism
Immune-mediated hemolytic anemia (±thrombocytopenia)
Pancreatitis
Protein-losing enteropathy
Sepsis/infection
Neoplasia
Disseminated intravascular coagulation
Heart disease

walls. Poor flow also can promote local tissue hypoxia and endothelial injury. Abnormal turbulence has also been associated with thrombus formation because it can mechanically injure the endothelial surface.

Hypercoagulability can develop secondary to various systemic diseases in dogs and cats. Multiple mechanisms are thought to be involved. AT deficiency is a common cause of hypercoagulability. Excessive loss, increased consumption, or possibly inadequate hepatic synthesis all can lead to AT deficiency. Decreased protein C activity and other mechanisms (including hyperfibrinogenemia and increases in factors II, V, VII, VIII, IX, X, or XII) also can contribute to hypercoagulability. Increased platelet aggregability, another mechanism of hypercoagulability, has been associated with neoplasia, some heart diseases (including hypertrophic cardiomyopathy [HCM] in cats), diabetes mellitus, and nephrotic syndrome in some animals. Thrombocytosis alone, without an increase in platelet aggregability, is not thought to increase the risk for thrombosis. Defective fibrinolysis can promote pathologic thrombosis by preventing efficient breakdown of physiologic clots. This can result from either reduced levels of fibrinolytic substances (e.g., t-PA, plasminogen, urokinase) or increased production of PAIs; the latter is a major mechanism of TE disease in humans with hypertension. Finally, any severe systemic disease that progresses to the systemic inflammatory response syndrome (SIRS; e.g., pancreatitis, sepsis, neoplasia, heatstroke, immune-mediated disease) can lead to gross thrombosis, as well as disseminated intravascular coagulopathy (DIC). DIC involves massive activation of thrombin and plasmin, with generalized consumption of coagulation factors and platelets. DIC produces extensive thrombosis and hemorrhage in the microcirculation, resulting in widespread tissue ischemia and multiorgan failure (see p. 1400).

The most common, although not the only, cause of TE disease in cats is myocardial disease (see Chapter 8). Cats with cardiomyopathy are at risk for intracardiac thrombus formation and subsequent arterial embolization. Mechanisms involved include poor intracardiac blood flow and blood stasis, especially within an enlarged left atrium (LA). Cats with HCM have increased platelet expression of P-selectin and platelet-endothelial cell adhesion molecules, as well as increased plasma concentrations of fibrinogen, thrombin-antithrombin-complex, and D-dimers, suggesting a possible role for systemic hypercoagulability as well. Additionally, abnormal turbulence from mitral regurgitation or dynamic outflow tract obstruction could be a factor. Some cats with TE disease have decreased plasma arginine and vitamin B_6 and B_{12} concentrations; hyperhomocysteinemia might be a factor in some cases. Hyperhomocysteinemia and low plasma vitamin B concentrations are risk factors for thromboembolism in people. It is not known if hypercoagulability induced by a genetic abnormality exists in some cats, as it does in people.

Three common systemic diseases associated with TE disease in dogs are protein-losing nephropathy, immune-mediated hemolytic anemia (IMHA), and hyperadrenocorticism. Protein-losing nephropathy (resulting from glomerulonephritis, renal amyloid deposition, or hypertensive injury) can lead to marked AT deficiency. Because of its small size, AT is lost through damaged glomeruli more easily than most procoagulant proteins, which predisposes to thrombosis. Protein-losing enteropathies also cause AT deficiency, but concurrent loss of larger proteins tends to maintain a balance between procoagulant and anticoagulant factors. Other factors also could contribute to TE disease in animals with protein-losing nephropathies, such as increased platelet aggregation secondary to hypoalbuminemia.

Thrombosis associated with IMHA also is thought to be multifactorial, with the systemic inflammatory (immune-mediated) response playing a large role. Thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia have been identified as risk factors for TE disease. The role of high-dose

corticosteroid therapy in pathologic thrombosis is unclear. However, TE disease is relatively common in animals receiving exogenous corticosteroids and in those with hyperadrenocorticism (see next paragraph). Other predisposing factors usually coexist in these cases as well.

TE disease occurs in some dogs with spontaneous hyperadrenocorticism. This endocrinopathy has been associated with decreased fibrinolysis (resulting from increased PAI activity) and high levels of several coagulation factors. Corticosteroids result in hypercoagulable thromboelastography (TEG) tracings in normal dogs. Diabetes mellitus is occasionally associated with TE disease in dogs. Platelet hyperaggregability and possibly hypofibrinolysis are thought to be involved. Greyhounds appear to be predisposed to TE disease despite lack of detectable hemostatic or cardiovascular abnormalities; one proposed mechanism is abnormalities of homocysteine metabolism (hyperhomocysteinemia). Occasionally, a patient with clinically relevant TE disease does not have any detectable abnormality that can result in hypercoagulability.

PULMONARY THROMBOEMBOLISM

Pulmonary thromboemboli (PTE) in dogs are associated with HWD, IMHA, neoplasia, DIC, sepsis, hyperadrenocorticism, protein-losing nephropathy, pancreatitis, trauma, hypothyroidism, and right atrial (RA) thrombi related to infection or neoplasia.

Pulmonary TE disease appears to be rare in cats compared with dogs, except in those with HWD (see Chapter 10). Nevertheless, PTE have been associated with a variety of systemic and inflammatory disorders in cats, including neoplasia, HWD, anemia (probably immune-mediated), pancreatitis, glomerulonephritis, encephalitis, pneumonia, heart disease, sepsis, glucocorticoid administration, protein-losing enteropathy, and hepatic lipidosis.

Pulmonary TE disease is an important cause of precapillary pulmonary hypertension, and can lead to right ventricular hypertrophy and even right-sided congestive heart failure (CHF). See Chapters 19 and 25 for further information about pulmonary thromboembolism and pulmonary hypertension.

SYSTEMIC ARTERIAL THROMBOEMBOLISM IN CATS

Cardiomyopathy, mainly HCM, is the most common underlying disease in cats with arterial thromboembolism (ATE) (see Chapter 8). Thrombi initially form in the left heart, usually in an enlarged LA or auricle, and can become quite large. Neoplastic and systemic inflammatory disease occasionally are associated with systemic thromboemboli in cats. Pulmonary carcinoma is the most common neoplasm to cause ATE, potentially because tumor emboli from the lungs have direct access to pulmonary veins and, thereby, the left heart. Hyperthyroidism could be a risk factor for ATE in cats independent of its cardiac effects. A rare cause of ATE could occur in cats with atrial septal defect, if a venous embolus crossed from RA to LA. In some cases of feline ATE, no predisposing condition is identified.

Systemic arterial emboli usually lodge at the aortic trifurcation (so-called "saddle thrombus" or, more correctly, "saddle embolus"; Fig. 12.1), but iliac, femoral, renal, brachial, and other arteries can be affected depending on embolus size and flow path. Besides obstructing flow in the affected artery, thromboemboli release vasoactive substances that induce vasoconstriction and compromise collateral blood flow around the obstructed vessel. Tissue ischemia results and causes further damage and inflammation, including ischemia-reperfusion injury after blood flow to the area is restored. An ischemic neuromyopathy occurs in the affected limb(s), with peripheral nerve dysfunction and degeneration, as well as pathologic changes in associated muscle tissue. Coronary thromboembolism with myocardial necrosis has occurred in cats with cardiac disease, especially severe HCM or infective endocarditis, as well as from carcinoma emboli.

Clinical Features

Arterial TE in cats usually causes acute and dramatic clinical signs secondary to tissue ischemia (Fig. 12.2). Male cats appear to be at higher risk for ATE, but this gender bias appears to be related to the prevalence of HCM. Common physical examination findings of cats with ATE can be summarized with the mnemonic "5 Ps": pain, pallor (pale coloration of affected pawpad[s]), paresis or plegia (of affected limb[s]), pulselessness (weak or absent pulse in affected limb[s]), and poikilothermia (decreased temperature of affected compared with unaffected limb[s]). Additional clinical abnormalities are summarized in Box 12.2.

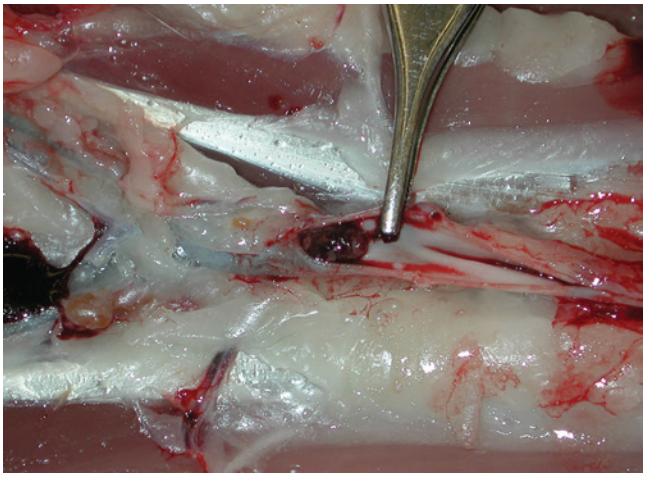


FIG 12.1
Postmortem image with opened distal aorta, from a cat with cardiomyopathy. A thromboembolus (just left of the forceps tip) is lodged at the aortic trifurcation. The rear limbs are to the left in the image; cranial is to the right.

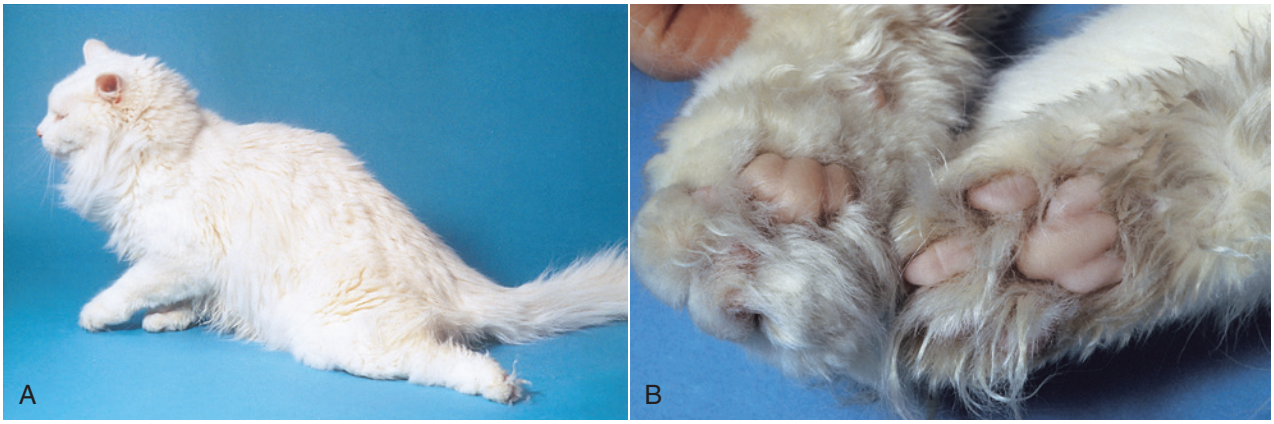


FIG 12.2
(A) Cat with thromboembolism to the distal aorta. The left rear limb was dragged behind as the cat tried to walk; there was slightly better function in the right rear limb. **(B)** The pads of the left rear paw (right side of image) in this cat were paler as well as cooler compared with the left forepaw (left side of image).

Signs of poor systemic perfusion usually are present. Hypothermia and azotemia are common. A heart murmur, gallop sound, or arrhythmia often is identified, but these signs are not always evident even with underlying heart disease. Clinical signs of heart disease before the ATE event are absent in many cases. Tachypnea and open-mouth breathing are common in cats with acute arterial embolization. Although these signs often relate to the onset of CHF, they also occur in cats without overt CHF. These respiratory signs could represent a pain response or result from increased pulmonary venous pressure. Thoracic radiographs should be obtained as soon as possible, because it is important to determine whether pulmonary edema underlies the respiratory signs.

Peripheral limb functional deficits depend on the area embolized, as well as the extent and duration of arterial blockage. However, distal aortic embolization occurs in most cases, so bilateral hindlimb deficits are most common. Acute hindlimb paresis without palpable femoral pulses is typical. Motor function in the rear limbs is minimal to absent in most cases, although the cat can usually flex and extend the hips. Sensation to the lower limbs is poor. Hindlimb deficits can be asymmetric. Emboli occasionally are small enough to lodge more distally in only one limb, which causes paresis of the lower limb alone. Embolization of an axillary or the more distal brachial artery produces (usually right) forelimb monoparesis. Intermittent claudication (see pp. 230–231) occurs rarely. Thromboemboli within the renal or mesenteric arterial circulation can result in failure of these organs and death. Emboli to the brain could induce seizures or various neurologic deficits. Clinical signs related to other predisposing disease may be evident in cats without cardiomyopathy.

Diagnosis

Feline ATE usually is diagnosed clinically based on a combination of acute onset paraparesis and absent femoral pulses on physical examination. If the diagnosis is not straightforward, obtaining a small amount of peripheral blood from an affected limb might be helpful. Blood glucose values are lower, whereas lactate values are higher, in blood from limbs affected by ATE compared with unaffected limbs or centrally obtained samples. Abdominal ultrasound can confirm the presence of a thrombus in the distal aorta.

Thoracic radiography is used to screen for evidence of cardiomyopathy, including cardiomegaly (and especially LA enlargement), and to determine whether CHF is present. Signs of CHF include pulmonary venous distension, pulmonary edema, and/or pleural effusion. Thoracic radiographs also could suggest the presence of other diseases potentially associated with ATE (e.g., pulmonary carcinoma, HWD). A few affected cats have no radiographic abnormalities.

Echocardiography depicts the type of myocardial disease, and sometimes the presence of an intracardiac thrombus as well (see Fig. 8.4). Echocardiography also can reveal cavitary effusions (pleural or pericardial effusion) suggestive of CHF. Some degree of LA enlargement is seen the majority (>90%) of cats with ATE. An LA dimension of greater than 20 mm (measured from the two-dimensional, long-axis, four-chamber view) may increase the risk for ATE, though only approximately half of cats with ATE have this degree of LA dilation.

Cats with ATE often have azotemia. This can be prerenal, resulting from poor systemic perfusion or dehydration; primary renal, resulting from embolization of the renal arteries or preexisting kidney disease; or a combination of both. Metabolic acidosis, DIC, electrolyte abnormalities (especially low serum sodium, calcium, potassium, and elevated phosphorus), and stress hyperglycemia are common. Hyperkalemia can develop secondary to ischemic muscle damage and reperfusion. Skeletal muscle damage and necrosis are accompanied by rapid elevation in CK; ALT and AST activities become elevated within 12 hours of the ATE event and peak by 36 hours. Myoglobinuria may also occur

BOX 12.2

Common Clinical Findings in Cats With Systemic Arterial Thromboembolism

- Acute limb paresis
  - Posterior paresis
  - Monoparesis
  - ±Intermittent claudication
- Characteristics of affected limb(s)
  - Painful
  - Cool distal limbs
  - Pale footpads
  - Cyanotic nailbeds
  - Absent arterial pulse
  - Contracture of affected muscles (especially gastrocnemius and cranial tibial)
- Tachypnea/dyspnea
  - Rule out congestive heart failure versus pain or other pulmonary disease
- Vocalization (pain and distress)
- Hypothermia
- Anorexia
- Lethargy/weakness
- Signs of heart disease (inconsistent)
  - Systolic murmur
  - Gallop sounds
  - Arrhythmias
  - Cardiomegaly
- Signs of congestive heart failure
  - Pulmonary edema
  - Cavitary effusions
- Hematologic and biochemical abnormalities
  - Azotemia
  - Increased creatine kinase activity
  - Increased aspartate aminotransferase activity
  - Increased alanine aminotransferase activity
  - Increased lactate dehydrogenase activity
  - Increased cardiac biomarkers (Troponin I, NT-proBNP)
  - Hyperglycemia (stress)
  - Lymphopenia (stress)
  - Disseminated intravascular coagulation

secondary to widespread muscle injury. Cats with ATE usually have normal coagulation parameters (PT and PTT), though fibrinogen and D-dimers might be elevated. Laboratory tests can reveal abnormalities associated with other underlying disease as well, such as eosinophilia from HWD. Thyroxine (T_4) levels should be measured in older cats to screen for hyperthyroidism.

Other causes of acute posterior paresis to be considered include intervertebral disk disease, spinal neoplasia (e.g., lymphoma), trauma, fibrocartilaginous infarction, diabetic neuropathy, and possibly myasthenia gravis.

Treatment and Prognosis

The goals of treatment are to prevent extension of the embolus and additional thrombus formation, promote collateral circulation, and manage concurrent CHF and arrhythmias (if present). Other supportive care is given to improve and maintain adequate tissue perfusion, minimize further endothelial damage and blood stasis, optimize organ function, and allow time for collateral circulation development. (Box 12.3). The treatment of CHF in cats is outlined in Chapter 8 and Box 8.1. General supportive care in acute ATE includes active external warming for hypothermia, rotation of position and recumbency (if nonambulatory), assistance with litter box posturing or bladder expression, and physical therapy once the patient is stable.

An analgesic is indicated for cats with ATE, especially for the first 24 to 36 hours after the embolic event, because this is a painful condition. For caudal arterial obstruction, analgesic administration into a more cranial site is recommended to improve absorption (e.g., IV into the cephalic vein or IM into the cranial lumbar area). Drugs that are most useful include μ-opioids such as fentanyl citrate (IV bolus followed by infusion), buprenorphine HCl, hydromorphone, methadone, oxymorphone, or morphine (see Box 12.3). A fentanyl patch (25 μg/h size) applied to a shaved area of skin can be used for pain relief for up to 3 days, but because this formulation takes about 12 hours to become effective, another analgesic is used simultaneously during this initial period. Respiratory depression and reduced gastrointestinal (GI) motility are potential adverse effects of opioids. Narcotics sometimes cause dysphoria in cats. Acepromazine is not recommended for animals with ATE, despite its vasodilatory α-adrenergic receptor–blocking effects. Improved collateral flow has not been documented, and hypotension and exacerbation of dynamic ventricular outflow obstruction (in cats with hypertrophic obstructive cardiomyopathy) are potential adverse effects.

Antiplatelet therapy is used to inhibit platelet aggregation and to reduce production of vasoconstrictive substances released from activated platelets. Platelet inhibitors are considered especially important for inhibiting thrombus formation within arteries, where blood flows under high shear rates and platelet adhesion via von Willebrand factor is critical for clot formation. Clopidogrel (Plavix) has replaced aspirin as the standard of care for antiplatelet therapy in cats with ATE. Clopidogrel is a second-generation thienopyridine with antiplatelet effects that are more potent than aspirin. A double-blind randomized controlled trial in 75 cats (Feline Arterial Thromboembolism: Clopidogrel versus Aspirin Trial; FATCAT) (Hogan, 2015) demonstrated that clopidogrel was superior to aspirin for secondary prevention of ATE and resulted in longer survival times post-ATE.

The thienopyridines inhibit ADP-binding at platelet receptors and subsequent ADP-mediated platelet aggregation. Clopidogrel irreversibly antagonizes platelet membrane ADP_{2Y12} receptors, which inhibit a conformational change of the $GP\alpha_{IIb}\ \beta_3$ complex, resulting in reduced binding to fibrinogen and von Willebrand factor. Clopidogrel also impairs platelet release of serotonin, ADP, and other vasoconstrictive and platelet-aggregating substances. Clopidogrel's antiplatelet effects occur after the drug is transformed in the liver to an active metabolite. Similar to humans, there

BOX 12.3

Therapy for Acute Thromboembolic Disease

Initial Diagnostic Tests

Complete physical examination and history
Thoracic radiographs (rule out signs of congestive heart failure, other infiltrates, pleural effusion)
CBC, serum biochemical profile, urinalysis
±Comparative blood glucose and blood lactate from affected vs. unaffected limbs
±Coagulation and D-dimer tests

Analgesia as Needed (Especially for Systemic Arterial Thromboembolism)

Fentanyl citrate
- Dog: 0.002-0.005 mg/kg IV bolus, followed by 0.002-0.005 mg/kg/h infusion
- Cat: 0.002-0.005 mg/kg IV bolus, followed by 0.002-0.005 mg/kg/h infusion

or Buprenorphine
- Dog: 0.01-0.03 mg/kg IM, IV, SC q6-8h
- Cat: 0.01-0.03 mg/kg IM, IV, SC q6-8h; can give PO for transmucosal absorption

or Hydromorphone
- Dog: 0.05-0.2 mg/kg IM, IV, SC q4-6h
- Cat: 0.05-0.2 IM, IV, SC q4-6h

or Oxymorphone
- Dog: 0.05-0.2 mg/kg IM, IV, SC q2-4h
- Cat: 0.05-0.2 mg/kg IM, IV, SC q2-4h

or Morphine
- Dog: 0.2-0.4 mg/kg IM, IV, SC q4-6h
- Cat: 0.1 mg/kg IM, IV, SC q4-6h

Supportive Care

Provide supplemental O_2 if respiratory signs exist.
Monitor for and correct azotemia and electrolyte abnormalities.
Manage congestive heart failure if present (see Chapters 3 and 8).
Provide external warming if hypothermia persists after rehydration.
Identify and manage underlying disease(s).
Administer intravenous fluid if indicated (and if not in congestive heart failure).
Provide nutritional support if anorexia persists.

Further Diagnostic Testing

Complete cardiac evaluation, including echocardiogram
±Abdominal ultrasound to confirm presence of thrombus/embolus in distal aorta
Other tests as indicated (based on initial findings and cardiac examination) to rule out predisposing conditions

Inhibit Extension of Existing Clot and New Thromboembolic Events

Antiplatelet therapy

Clopidogrel
- Dog: 2-4 mg/kg PO q24h
- Cat: loading dose of 75 mg PO once, then 18.75 mg/cat PO q24h

Aspirin (in cats, consider only if clopidogrel not tolerated or available)
- Dog: 0.5-1.0 mg/kg PO q24h
- Cat: 81 mg/cat q72h

Anticoagulant therapy

Sodium heparin (unfractionated)*
- Dog: 100-300 IU/kg IV, followed by 100-300 IU/kg SC q8h (or CRI of 600 IU/kg/day) for 2-4 days or as needed
- Cat: 100 IU/kg IV, followed by 200 IU/kg SC q8h (or CRI of 600-800 IU/kg/day) for 2-4 days or as needed

or Enoxaparin*
- Dog: 1.5 mg/kg SC q12-24h
- Cat: 1.5 mg/kg SC q12-24h

or Dalteparin sodium*
- Dog: 50-100 U/kg SC q12-24h
- Cat: 100 U/kg SC q12-24h

Thrombolytic therapy (pursue only with caution, see text)

rt-PA
- Dog: 1.4 mg/kg IV total as front-loaded 90-minute protocol:
  0.2 mg/kg IV bolus
  0.7 mg/kg IV over 30 minutes
  0.5 mg/kg IV over 1 hour
- Cat: 5 mg/cat IV total as front-loaded 90-minute protocol:
  0.75 mg IV bolus
  2.5 mg IV over 30 minutes
  1.75 mg over 1 hour

Cats: Draw blood samples for LMWH peak anti-Xa activity at 2-3 hours postdose.
Dogs: Draw blood samples for LMWH peak anti-Xa activity at 3-4 hours postdose.
IM, Intramuscularly; *IV,* intravenously; *PO,* by mouth; *rt-PA,* recombinant tissue plasminogen activator; *SC,* subcutaneously; *TE,* thromboembolic.
*Anti-Xa monitoring is recommended. One laboratory providing this service for cats and dogs is the Cornell Comparative Coagulation laboratory, http://ahdc.vet.cornell.edu/Sects/Coag/.

may be pharmacogenomic differences in individual cats' ability to biotransform clopidogrel, resulting in clopidogrel "nonresponders"; the clinical implications of this finding remain unclear. The recommended oral dose is 18.75 mg/cat once daily (or 2-4 mg/kg once daily); maximal antiplatelet effects occur within 72 hours and disappear about 7 days after drug discontinuation. A loading dose of 75 mg/cat given as soon as possible after an acute ATE event might also confer vasomodulating effects that improve collateral blood flow, and short-term administration of this dose appears to be well tolerated. Clopidogrel does not cause GI ulceration, as aspirin can; however, a single cat receiving clopidogrel in the FATCAT trial developed a reversible icterus. Vomiting does occur in some cats, and the tablets taste very bitter. This can be ameliorated by giving the drug with food or in a gelatin capsule.

Aspirin (acetylsalicylic acid) previously was employed to block platelet activation and aggregation in cats with, or at risk for, ATE. Aspirin irreversibly inhibits cyclooxygenase, which reduces prostaglandin and thromboxane A_2 synthesis and therefore could reduce subsequent platelet aggregation, serotonin release, and vasoconstriction. Because platelets cannot synthesize additional cyclooxygenase, this reduction of procoagulant prostaglandins and thromboxane persists for the platelet's life span (7-10 days). Endothelial production of prostacyclin (also via the cyclooxygenase pathway) is reduced by aspirin but only transiently as endothelial cells synthesize additional cyclooxygenase. Adverse effects of aspirin tend to be mild, unless overdosed, and usually relate to signs of GI upset or ulceration, mainly as anorexia and vomiting. The optimal dose is unclear. Cats lack an enzyme (glucuronyl transferase) necessary to metabolize aspirin, so less frequent dosing is required compared with dogs. Aspirin's efficacy at clinical doses in acute ATE is unknown. In cats with experimental aortic thrombosis, high-dose aspirin (100 mg/kg) inhibited platelet aggregation and improved collateral circulation, but this dose would be toxic in a clinical setting. The commonly used dose of 10 to 25 mg/kg (81 mg/cat) q72h does inhibit platelet aggregation in vitro, but the clinical benefit for treatment or prevention of ATE has not been established. In cats with ATE, there was no difference in outcome for cats receiving low-dose aspirin (5 mg/cat q72h) compared with more typical doses (40-81 mg/cat q48h), and fewer GI side effects were seen at the lower dose. However, given the superiority of clopidogrel (18.75 mg/cat q24h) compared with aspirin (81 mg/cat q72h) in the FATCAT trial, clopidogrel now should be the first-line antiplatelet for treatment or prevention of ATE in cats. Aspirin could be used for cats that fail to tolerate clopidogrel, or possibly as an adjunct antiplatelet in addition to clopidogrel.

Several new antiplatelet medications have been developed recently for use in people. These include later-generation P_{2Y12} platelet inhibitors, such as prasugrel (a third-generation thienopyridine) and ticagrelor (a nonthienopyridine), as well as the $GP\alpha_{IIb}\ \beta_3$ receptor antagonists abciximab and eptifibatide. Prasugrel and ticagrelor have yet to be evaluated in veterinary patients. Abciximab was shown to improve arterial flow in cats with experimentally induced arterial thrombosis but interestingly did not reduce platelet aggregation in vitro. Eptifibatide effectively reduced platelet aggregation in vitro but caused cardiovascular collapse and death when given systemically to cats. Further research is needed before these new drugs are added to the veterinary repertoire.

In addition to antiplatelet therapy, anticoagulation with heparin is used in treatment of acute ATE. Heparin is indicated to limit extension of existing thrombi and prevent additional thrombus formation; it does not promote thrombolysis. Unfractionated heparin and a number of low-molecular-weight heparin (LMWH) products are available. Heparin's main anticoagulant effect occurs through AT activation, which in turn inhibits FIXa, FXa, FXIa, FXIIa, and FIIa (thrombin). Unfractionated heparin binds thrombin and AT. Optimal dosing protocols for animals are not known. For acute ATE, unfractionated heparin is usually given as an initial IV bolus (often 100 U/kg) followed by either a continuous rate infusion or SC injections (see Box 12.3). Heparin is not given IM because of the risk for hemorrhage at the injection site. Unfractionated heparin treatment is continued until the patient is stable and has been on antiplatelet therapy for a few days.

Monitoring the patient's activated partial thromboplastin time (aPTT) has been recommended, although results may not accurately predict serum heparin concentrations; pretreatment coagulation testing is done for comparison, and the goal is to prolong the aPTT to 1.5 to 2.0 times baseline. Monitoring of anti-Xa activity could be a more accurate means of assessing heparin therapy. Hemorrhage is the major complication of heparin therapy. Protamine sulfate can be used to counteract heparin-induced bleeding; however, an overdose of protamine can paradoxically cause irreversible hemorrhage. Dosage guidelines for protamine sulfate are as follows: 1 mg/100 U of heparin is given slowly IV if the heparin was given within the previous 30 minutes; 0.5 mg/100 U of heparin is given if the heparin was given more than 30 but fewer than 60 minutes earlier; and 0.25 mg/100 U of heparin is given if more than 1 hour has elapsed since heparin was administered. Fresh-frozen plasma might be necessary to replenish AT in cases of heparin overdose.

For long-term treatment, LMWH is a safer and more practical alternative to unfractionated heparin. LMWH products are a diverse group of depolymerized heparin that vary in size, structure, and pharmacokinetics. Their smaller size prevents simultaneous binding to thrombin and AT. LMWH products have more specific effect against factor Xa and have minimal ability to inhibit thrombin, thus are less likely to cause bleeding. LMWH products have greater bioavailability and a longer half-life than unfractionated heparin when given subcutaneously because of lesser binding to plasma proteins, as well as endothelial cells and macrophages. However, LMWH products do not markedly affect coagulation times, so aPTT cannot be used to monitor LMWH. LMWH effect can be monitored indirectly

by anti-Xa activity (see Box 12.3). Optimal anti-Xa activity level in cats is not known; the target range in people is reported as 0.5 to 1 U/mL, although 0.3 to 0.6 U/mL has also been used.

The LMWH products have differences in biologic and clinical effects and are not interchangeable. The most effective dosage for the various LMWH products is not clearly established in dogs and cats. Commonly used dosages of dalteparin sodium and enoxaparin (see Box 12.3) have been extrapolated from human use. Although enoxaparin produces anti-Xa activity close to target range at 4 hours postdose in cats, activity is generally undetectable 8 hours later. This finding led to the presumption that higher and more frequent doses should be used to maintain anti-Xa levels closer to human target range. However, this rationale is disputed because it does not appear necessary to maintain peak or target anti-Xa levels throughout the dosing period. Indeed, an experimental study of enoxaparin in a modified venous stasis model in healthy cats showed no correlation between antithrombotic effect and anti-Xa levels; in this model, antithrombotic effect of enoxaparin lasted >12 hours. The optimal therapeutic range in cats and the most effective dosage in cats with ATE remain unknown. LMWHs are relatively expensive and require owner compliance to administer SC injections every 12 to 24 hours.

Warfarin was historically the most common long-term anticoagulant treatment for cats with ATE. However, due to serious risk of bleeding, requirement for frequent monitoring, and availability of alternative anticoagulants (including LMWH), warfarin is now rarely used in cats. Warfarin is still sometimes used in large dogs with systemic TE (see pg. 232) if other agents are cost-prohibitive.

A number of new anticoagulant drugs have been developed for human use and are becoming available for veterinary patients. In people, these drugs offer similar or improved antithrombotic efficacy compared with warfarin, with fewer side effects. Synthetic factor Xa inhibitors (e.g., rivaroxaban, apixiban, fondaparinux) potentiate effects of AT without affecting thrombin or platelet function. Their effect is monitored via anti-Xa activity measurement because they do not affect results of routine coagulation tests. Fondaparinux is given SC, whereas apixaban and rivaroxaban are both oral. Doses for rivaroxaban, apixaban, and fondaparinux in cats have been published based on pharmacokinetics and anti-Xa activity in healthy cats; however, clinical efficacy in cats with ATE has yet to be investigated. Dabigatran etexilate is an oral direct thrombin inhibitor; use of this medication has not been reported in veterinary medicine.

All treatments for ATE discussed thus far are supportive rather than directed therapy; the common approach is essentially to support the cat while the patient's own intrinsic fibrinolytic system breaks down the embolus, rather than pursuing treatment specifically aimed at dissolving the clot. However, thrombolytic drugs that directly promote clot lysis are available. These medications increase conversion of plasminogen to plasmin, thus facilitating fibrinolysis. The most commonly used thrombolytic agent in veterinary medicine is human recombinant tissue plasminogen activator (rt-PA). rt-PA is a single-chain polypeptide serine protease with a higher specificity for fibrin within thrombi and a low affinity for circulating plasminogen. The risk of hemorrhage is therefore less with rt-PA than with nonspecific plasminogen activators such as streptokinase and urokinase. However, there remains the potential for serious bleeding, reperfusion injury, and neurologic adverse effects. rt-PA also is potentially antigenic in animals because it is a human protein.

Veterinary experience with rt-PA is limited, it is relatively expensive, and the optimal dosage is not known; the most commonly used dose is 5 mg per cat, generally given as a front-loaded IV infusion over 1 to 2 hours (see Box 12.3). In a case series of 11 cats with ATE, rt-PA administration was associated with improved limb function and return of pulses; however, there was a high rate of adverse effects related to reperfusion injury (azotemia, hyperkalemia, and neurologic signs), and mortality was high. Thus although rt-PA can effectively break down clots, a clear survival advantage has not been shown. If used, this therapy is best instituted within 3 to 4 hours of vascular occlusion. An intensive care setting, including frequent monitoring of serum potassium concentration, acid-base status, and electrocardiogram (ECG), is important to detect reperfusion-induced hyperkalemia and metabolic acidosis. The risk-to-benefit profile of thrombolytic treatment may be more favorable in patients with brain, renal, or splanchnic thromboembolism. Other thrombolytics, including the nonspecific plasminogen activators streptokinase and urokinase, are associated with even more severe side effects and higher mortality, and are not currently recommended.

Surgical thromboembolus removal is typically not advised in cats. The surgical risk is high, and significant neuromuscular ischemic injury is likely to have already occurred by the time of surgery. Percutaneous clot removal using an embolectomy catheter has not been effective in cats.

In general, the prognosis for cats with ATE is poor. Many cats are euthanized on presentation (approximately ⅓ of cats in reports from tertiary care facilities, and nearly ⅔ of cats in a primary care setting). Of cats where treatment is attempted, approximately half survive the initial ATE episode regardless of therapy chosen (conservative or thrombolytic). Survival is better if only one limb is involved and/or if some motor function is preserved at presentation. Hypothermia and CHF at presentation are both associated with poor survival in cats. Other negative factors can include hyperphosphatemia, progressive hyperkalemia or azotemia, bradycardia, persistent lack of motor function, progressive limb injury (continued muscle contracture after 2-3 days, necrosis), severe LA enlargement, presence of intracardiac thrombi or spontaneous contrast ("swirling smoke") on echocardiogram, DIC, and history of previous ATE. Significant embolization of the kidneys, intestines, or other organs carries a grave prognosis.

Barring complications, limb function should begin to return within days to a week. Some cats become clinically normal within 1 to 2 months, although residual deficits can

persist for a variable time. Tissue necrosis might require wound management and skin grafting. Permanent limb deformity develops in some cats, and amputation is occasionally necessary. Repeated ATE events are common, as is progressive CHF. Overall, median long-term survival is approximately 6 to 9 months.

PROPHYLAXIS AGAINST ARTERIAL THROMBOEMBOLISM IN CATS

Prophylactic therapy with an antiplatelet or anticoagulant drug is commonly used in cats thought to be at increased risk for ATE. This includes cats with history of ATE, as well as cats with cardiomyopathy and moderate to severe LA enlargement, decreased LA or auricular function, or intracardiac spontaneous echo-contrast or thrombus on echocardiography, However, the efficacy of thromboprophylaxis is unknown, and a strategy that consistently prevents ATE has not been identified.

Drugs used for ATE prophylaxis include platelet inhibitors (clopidogrel or aspirin), LMWH, warfarin, and factor Xa antagonists. The antiplatelet drugs are prescribed most commonly, both because they target platelet adhesion (the most critical factor for thrombus formation in high-shear states), and because platelet inhibitors present a low risk for serious hemorrhage and require minimal monitoring. Clopidogrel is preferred over aspirin based on its superior clinical effect in prevention of secondary ATE in cats, although a comparison of clopidogrel versus aspirin for prevention of *primary* ATE has not been undertaken. Warfarin rarely is used because of increased bleeding risk, frequent monitoring required, and lack of demonstrated survival benefit. LMWH is expensive and must be given by SC injection, but some owners are motivated to do this. Platelet inhibitors can be used concurrently with LMWH in cats that are not thrombocytopenic. No studies have evaluated the efficacy of antiplatelet or anticoagulant drugs in prevention of ATE in cats. Therefore empiric decisions about thromboprophylaxis are clinician-dependent judgments based on risk stratification: cats with HCM and severe LA often receive clopidogrel alone, whereas cats with spontaneous echo-contrast, an intracardiac thrombus, or history of ATE might receive clopidogrel in combination with LMWH or a factor Xa inhibitor.

SYSTEMIC ARTERIAL THROMBOSIS IN DOGS

Arterial thrombotic disease in dogs is relatively uncommon compared with cats. However, the true prevalence is unknown and may be underrecognized in dogs because of differences in pathogenesis and clinical presentation. The distal aorta is the most commonly reported location, and in dogs usually results from primary (in situ) thrombus formation, rather than an acute distant embolic event as in cats. The development of clinical signs in these dogs is usually more vague and chronic. Aortic thrombosis in dogs has been associated with many conditions, including systemic and endocrine diseases leading to hypercoagulability, neoplasia, aortic disease, and some cardiovascular diseases. However, in many cases (up to half of dogs with aortic thrombosis in some reports) no predisposing abnormality can be found. Aortic thrombosis appears more prevalent in male compared with female dogs. It is unclear whether any true breed predisposition exists, although Greyhounds, Cavalier King Charles Spaniels, and Labradors might be overrepresented.

The most common cause of aortic thrombosis in dogs is protein-losing nephropathy, in which urinary loss of AT leads to a hypercoaguable state. Similarly, protein-losing enteropathy could predispose dogs to aortic thrombosis via alimentary loss of AT. Other procoagulant conditions commonly associated with aortic thrombosis in dogs include hyperadrenocorticism (or recent steroid administration), hypothyroidism, and diabetes mellitus. Neoplasia can result in TE disease either via tumor embolism or by inducing a paraneoplastic hypercoagulable state. Common neoplasms associated with aortic thrombosis include hemangiosarcoma, pulmonary carcinoma, osteosarcoma, intravascular lymphoma, and adrenal tumors. Diseases directly affecting the aorta, including aortitis, aortic intimal fibrosis, atherosclerosis, aortic dissection, or aortic tumors, can also cause aortic thrombosis.

Unlike in cats, common primary structural cardiac diseases of dogs (cardiomyopathy or degenerative valve disease) rarely cause thrombosis. The most common cardiac diseases associated with systemic thrombotic disease in dogs are vegetative endocarditis and cardiac neoplasia. Other cardiovascular conditions occasionally associated with canine thrombotic disease include patent ductus arteriosus (thrombosis at the surgical ligation site), arteritis, LA rupture, or granulomatous inflammatory erosion into the LA. In the presence of a right-to-left shunting atrial or ventricular septal defect, fragments originating from venous thrombosis could cross the defect to cause systemic arterial embolization.

Atherosclerosis is uncommon in dogs, but it has been associated with thrombotic disease in this species, as it has in people. Endothelial disruption in areas of atherosclerotic plaque, hypercholesterolemia, increased PAI-1, and possibly other mechanisms could be involved in thrombus formation. Atherosclerosis may develop with profound hypothyroidism, hypercholesterolemia, or hyperlipidemia. The aorta, coronary arteries, and other medium to large arteries are affected. Myocardial and cerebral infarctions occur in some cases, and there is a high rate of interstitial myocardial fibrosis in affected dogs. Vasculitis related to infectious, inflammatory, immune-mediated, neoplastic, or toxic disease can underlie thrombosis or embolic events. Arteritis of immune-mediated pathogenesis is described in some young Beagles and other dogs.

Clinical Features

The distal aorta is the most common location for clinically recognized TE disease in dogs. Affected dogs typically present for intermittent rear limb lameness or paresis

(claudication) and have weak femoral pulses on the affected side. In contrast to cats, most dogs have more chronic clinical signs (>2 weeks before presentation). Less than a quarter of dogs have peracute paralysis without prior signs of lameness. These species differences support the notion that aortic thrombi in dogs form in situ in the caudal aorta, rather than embolizing from a distant location as in cats. Clinical signs in dogs include unilateral or bilateral hindlimb lameness or paresis (which may be progressive or intermittent), exercise intolerance, pain, and self-trauma or hypersensitivity of the affected limb(s) or lumbar area. Most dogs are ambulatory on presentation. Intermittent claudication, common in people with peripheral occlusive vascular disease, can be a manifestation of distal aortic TE disease. This involves pain, weakness, and lameness that develop during exercise. Inadequate perfusion during exercise leads to lactic acid accumulation and cramping. These signs intensify until walking becomes impossible and they then disappear with rest.

Key physical examination findings in dogs with aortic thrombosis include absent or weak femoral pulses and hindlimb neuromuscular dysfunction. Cool extremities, hindlimb pain, loss of sensation in the digits, hyperesthesia, and cyanotic nailbeds are variably present. Occasionally, a brachial or other artery is embolized. TE disease involving an abdominal organ causes abdominal pain, with clinical and laboratory evidence of damage to the affected organ.

Coronary artery thromboembolism usually results in arrhythmias, as well as ST segment and T-wave changes on ECG. Ventricular (or other) tachyarrhythmias are common, although if the atrioventricular (AV) nodal area is injured, conduction block may result. Clinical signs of acute myocardial infarction/necrosis can mimic those of pulmonary TE disease; these include weakness, dyspnea, and collapse. Patients might have a heart murmur, tachycardia, and weak pulses. Respiratory difficulty can develop as a result of left-sided CHF (depending on degree of myocardial dysfunction) or concurrent pulmonary abnormalities, including pulmonary thromboembolism. Coronary artery thromboembolism also can cause sudden death; the associated acute ischemic myocardial injury might not be detectable on routine histopathology.

Diagnosis

Definitive diagnosis requires direct visualization of the thrombus. Typically, abdominal ultrasonography is used to identify an intraluminal or mural mass in the distal aorta (or other vessels). Doppler studies can demonstrate partial or complete obstruction to blood flow in some cases. Computed tomography (CT) with contrast or angiography can also demonstrate presence of the thrombus and vascular occlusion. Contrast imaging can be valuable in cases where ultrasound is inconclusive, to demonstrate collateral circulation, or if concurrent CT imaging of other body areas is desired.

Once the diagnosis of aortic thrombosis is confirmed, additional testing is indicated to look for an underlying cause. Thoracic radiography provides an initial screen for cardiac abnormalities. Evidence for CHF or pulmonary abnormalities associated with TE disease (e.g., neoplasia, HWD, other infections) may also be found. Echocardiography is indicated to identify and characterize heart disease (if present), particularly vegetative endocarditis or cardiac neoplasia. Thrombi within the left or right heart chambers and proximal great vessels can be readily seen with two-dimensional echocardiography. In dogs with coronary TE disease, the echocardiographic examination might indicate reduced myocardial contractility with or without regional dysfunction. Spontaneous echo-contrast ("swirling smoke") could be seen in one or both ventricles; similar to cats, this finding is thought to indicate increased risk for TE disease.

Routine laboratory test results depend largely on the disease process underlying the TE event(s). Azotemia and proteinuria are common, because protein-losing nephropathy is the most common disease causing aortic thrombosis. Systemic arterial TE disease also produces elevated muscle enzyme activities from skeletal muscle ischemia and necrosis, including CK, AST, and ALT.

Coagulation test results in dogs with thrombotic disease are variable. The concentration of FDPs or D-dimers may be increased, but this can occur in patients with inflammatory disease and is not specific for a TE event or DIC. Modestly increased D-dimer concentrations also can occur in diseases associated with procoagulant states, such as neoplasia, liver disease, and IMHA, as well as in body cavity hemorrhage (due to increased fibrin formation). Elevation of D-dimers is therefore a sensitive but nonspecific test for pathologic thromboembolism. It is important to interpret D-dimer results in the context of other clinical and test findings. Assays for circulating AT and proteins C and S are available for dogs and cats also. Deficiencies of these proteins are associated with increased risk of thrombosis.

TEG provides an easy point-of-care method of assessing global hemostasis and can be used to demonstrate hypercoagulability in patients with TE disease. However, in most Greyhounds and other sighthounds with aortic thrombosis, results of TEG are within normal limits for the breed.

Treatment and Prognosis

Although the clinical presentation often is more subtle and chronic in canine aortic thrombosis compared with feline ATE, the goals of therapy are the same: stabilize the patient by supportive treatment as indicated, prevent extension of the existing thrombus and additional TE events, and restore perfusion. Supportive care is given to improve and maintain adequate tissue perfusion, minimize further endothelial damage and blood stasis, and optimize organ function, as well as to allow time for collateral circulation development. Correcting or managing underlying disease(s), to the extent possible, is important. Antiplatelet and anticoagulant therapies are used to reduce platelet aggregation and growth of existing thrombi (see p. 232 and Box 12.3). Coagulation testing, including TEG if available, should be used to monitor response to anticoagulants in patients with TE disease.

Management strategies used for TE disease in dogs are outlined in Box 12.3. Although fibrinolytic therapy is available, its use is limited by dosage uncertainties, the need for intensive care, and the potential for serious complications. Systemic thrombolysis with rt-PA and streptokinase have been reported in dogs, with variable success. Locally directed thrombolysis (catheter delivery of rt-PA directly to the side of thrombosis) is feasible in dogs and may reduce systemic effects of thrombolytics. Interventional radiology techniques can also be used to break down or remove thrombi percutaneously via catheter-directed thrombectomy and embolectomy. These techniques have not been effective in cats with ATE but might hold promise in dogs of larger size. Arterial stenting has been used successfully in some dogs with aortic thromboembolism. The consequences of reperfusion injury and distal embolization of clot fragments remain serious concerns with any form of thrombolytic therapy.

Fluid therapy is used (in patients without CHF) to expand vascular volume, support blood pressure, and correct electrolyte and acid/base abnormalities depending on individual patient needs. Hypothermia that persists after circulating volume is restored can be addressed with external warming. Concurrent CHF is rarely a concern because cardiac disease is an uncommon cause of aortic thrombosis in dogs; acute respiratory signs are more likely to signal pain or pulmonary thromboembolism. In cases where heart disease is present, treatment for CHF or arrhythmias is provided as indicated (see Chapters 3 and 4 and other relevant chapters).

Analgesic therapy is important in cases of acute ATE, which is particularly painful especially for the first 24 to 36 hours (see Box 12.3). Chronic in situ aortic thrombosis is less painful, and analgesics may or may not be indicated. Loosely bandaging the affected limb(s) to prevent self-mutilation might be necessary. Renal function, serum electrolyte concentrations, and ECG rhythm are monitored frequently to help detect acute hyperkalemia associated with reperfusion (see Chapter 2, p. 47).

Antiplatelet and anticoagulant therapies are indicated to prevent growth of the existing clot and decrease additional thrombus formation. Drug options are the same as in cats, and no standard therapeutic protocol has been established. Given that aortic thrombi in dogs generally develop in situ in the distal aorta (an area of high-shear blood flow), platelet inhibitors are thought to be particularly important. As in cats, clopidogrel and aspirin are the most commonly used antiplatelet medications. There are few studies evaluating efficacy of antiplatelet drugs in dogs, and none specifically in dogs with aortic thrombosis. In dogs with IMHA, a disease known to predispose dogs to TE disease (though more commonly pulmonary thromboemboli), a retrospective study suggested that dogs that received ultra–low-dose aspirin (0.5 mg/kg PO q24h) in addition to other therapies had improved survival compared with dogs that did not receive aspirin. Although this study does not prove efficacy of aspirin in preventing TE disease, it did establish safety of ultra–low-dose aspirin in a patient population concurrently receiving immunosuppressive doses of glucocorticoids. Clopidogrel (at a dose of 2-4 mg/kg PO q24h) is more effective than aspirin for in vitro platelet inhibition. At this dose, effective levels of clopidogrel are achieved within 3 days; alternatively, an oral loading dose (10 mg/kg) can provide antithrombotic effect in dogs within 90 minutes. However, unlike in cats, there is no convincing evidence of clinical superiority of clopidogrel over aspirin. In a subsequent prospective study of dogs with IMHA, there was no difference in outcome between dogs given clopidogrel, ultra–low-dose aspirin, or both, although sample size was low. Both drugs are well-tolerated in dogs, with minimal GI effects of aspirin at such low doses; aspirin is less expensive than clopidogrel. Thus although many clinicians prefer clopidogrel based on its superior platelet inhibition in vitro, low-dose aspirin remains a reasonable, inexpensive alternative in dogs.

Anticoagulants are recommended in addition to antiplatelet drugs in dogs with aortic thrombosis. In the acute setting, unfractionated heparin remains the mainstay of treatment. A common initial dose is 100 IU/kg IV bolus followed by 600 to 800 IU/kg/day (as a CRI or divided into q8h intermittent boluses), although the ideal dose has not been established. Monitoring recommendations are similar to those for cats, with the goal of prolonging aPTT to 1.5-2.5× baseline value. However, recent evidence suggests that monitoring anti-FXa activity might better assess anticoagulant effects of unfractionated heparin and may improve survival. After initial stabilization, or for dogs with more chronic clinical signs, dogs are transitioned to more long-term anticoagulation with LMWH, warfarin, or a factor Xa inhibitor (see later).

In general, the prognosis for aortic thrombosis in dogs is guarded to poor, with 50% to 60% of dogs surviving to discharge. Rear limb function improvement could be seen within several days of initiating therapy; however, 2 or more weeks are required in most cases. Prognosis for dogs that are ambulatory on presentation, and those with chronic clinical signs, is much better than for dogs with acute-onset signs or that are nonambulatory on presentation.

PROPHYLAXIS AGAINST AORTIC THROMBOSIS

Strategies to prevent recurrence of ATE in dogs are similar to those used in cats. Generally, a combination of an antiplatelet (clopidogrel or aspirin) and anticoagulant is used. Options for long-term anticoagulants include LMWH, warfarin, and factor Xa inhibitors. LMWHs (such as dalteparin and enoxaparin) require SC administration, and their expense makes them cost-prohibitive for medium- to large-breed dogs. Therefore although LMWH has essentially replaced warfarin as the anticoagulant of choice in cats with ATE, warfarin remains a reasonable treatment option for dogs with aortic thrombosis because of their larger body size.

Warfarin inhibits the enzyme (vitamin K epoxide reductase) responsible for activating the vitamin K–dependent clotting factors (II, VII, IX, and X), as well as proteins C and S. Initial warfarin treatment causes transient hypercoagulability

because the anticoagulant proteins have a shorter half-life than most procoagulant factors. Therefore unfractionated heparin or LMWH is given concurrently for 2 to 4 days after warfarin is initiated. There is wide variability in dose response to warfarin and potential for serious bleeding. Warfarin is highly protein bound; concurrent use of other protein-bound drugs or change in serum protein concentration can markedly alter the anticoagulant effect. Intensive monitoring is required and frequent dose adjustments might be necessary initially. Uneven distribution of drug within the tablets is reported, so compounding rather than administering tablet fragments is recommended.

The initial recommended dose of warfarin is 0.05 to 0.2 mg/kg PO q24h. After initiation of treatment, the dose is adjusted based on PT and international normalization ratio (INR). INR is a more precise method of serial coagulation monitoring recommended to prevent problems related to variation in commercial PT assays. The INR is calculated by dividing the animal's PT by the control PT and raising the quotient to the power of the international sensitivity index (ISI) of the thromboplastin used in the assay, or INR = (animal PT/control PT)^{ISI}. The ISI is provided with each batch of thromboplastin made. Extrapolation from human data suggests that an INR of 2 to 3 provides therapeutic anticoagulation with less chance for bleeding. Heparin overlap until the INR is greater than 2 is recommended. A coagulation panel, INR, and platelet count are evaluated at baseline before warfarin administration. INR is then rechecked 1 to 3 days after initiation of warfarin and then at progressively increasing time intervals, with INR values guiding dose adjustments and time interval until the next recheck (see Table 12.1). Dose adjustments are small (5%-20%) and are made based on the total *weekly* dose, which may require some variation in day-to-day doses. Drug administration and blood sampling times should be consistent. If the INR increases excessively, warfarin is discontinued and vitamin K_1 administered (1-2 mg/kg/day administered orally or subcutaneously) until the PT is normal and the packed cell volume (PCV) is stable. Transfusion with fresh-frozen plasma, packed red blood cells, or whole fresh blood sometimes is necessary.

Direct factor Xa inhibitors are emerging as attractive alternatives to warfarin for long-term management of thrombotic disease in dogs. In people, these oral medications have equal or superior efficacy to warfarin with reduced risk of bleeding. The favorable adverse effect profile also means less monitoring and increased convenience. Fondaparinux (Arixtra) is a synthetic pentasaccharide that binds to both AT and factor Xa with high affinity, thus selectively inhibiting factor Xa. Rivaroxaban (Xarelto) and apixaban (Eliquis) directly bind to and inhibit factor Xa without involvement of AT. Although there are published doses in cats for all three factor Xa inhibitors, rivaroxaban is the only drug with clinical dosing information described in dogs. A dose of rivaroxaban 0.5 to 1.0 mg/kg PO q24h appears to be well tolerated and was associated with decreased thrombus size in a small number of dogs. Although further research will be required to establish efficacy and ideal dosing protocols, these drugs provide an exciting alternative to warfarin in dogs with aortic thrombosis.

TABLE 12.1

Guidelines for Adjusting Total Weekly Warfarin Dose*

INR	TOTAL WEEKLY WARFARIN DOSE ADJUSTMENT	RECHECK INR IN
1.0-1.4	Increase TWD by 10%-20%	1 week
1.5-1.9	Increase TWD by 5%-10%	2 weeks
2.0-3.0	No change in TWD	4-6 weeks
3.1-4.0	Decrease TWD by 5%-10%	2 weeks
4.1-5.0	Stop warfarin for 1 day Decrease TWD 10%-20%	1 week
>5.0	Stop warfarin until INR < 3.0 Decrease TWD 20%-40%	1 week

INR = (animal PT/control PT)^{ISI}
Control PT, Laboratory reference mean prothrombin time; *INR,* international normalized ratio; *ISI,* international sensitivity index (of the thromboplastin reagent); *TWD,* total weekly warfarin dose.
*See text for additional information.
Modified from Winter RL et al.: Aortic thrombosis in dogs: presentation, therapy, and outcome in 26 cases, *J Vet Cardiol* 14:333, 2012.

VENOUS THROMBOSIS

Thrombosis in large veins is more likely to be clinically evident than thrombosis in small vessels. Cranial vena caval thrombosis in dogs has been associated with many disease processes causing hypercoagulability, including IMHA and/or immune-mediated thrombocytopenia, sepsis, neoplasia, protein-losing nephropathies, fungal disease, cardiac disease, and glucocorticoid therapy. Most cases have more than one predisposing factor. An indwelling jugular catheter or permanent pacemaker lead increases the risk for cranial caval thrombosis, probably by causing vascular endothelial damage or laminar flow disruption or by acting as a nidus for clot formation.

Portal vein thrombosis, along with DIC, has occurred in dogs with pancreatitis and pancreatic necrosis. Peritonitis, neoplasia, hepatitis, protein-losing nephropathy, IMHA, and vasculitis have also been diagnosed occasionally in dogs with portal thrombosis. A high proportion of dogs with incidental portal or splenic vein thrombosis were receiving corticosteroids.

Venous thrombosis produces signs related to increased venous pressure upstream from the obstruction. Portal vein thrombosis can result in ascites. Thrombosis of the cranial vena cava can lead to the cranial caval syndrome, characterized by bilaterally symmetric subcutaneous edema of the head, neck, and forelimbs. Another cause of this syndrome

is external compression of the cranial cava, usually by a mass. Pleural effusion occurs commonly; the effusion is often chylous because lymph flow from the thoracic duct into the cranial vena cava also is impaired. Thrombosis that extends into the jugular veins is palpable in some cases. Because vena caval obstruction reduces pulmonary blood flow and both left heart and right heart filling, signs of poor cardiac output are common.

Diagnosis of venous thrombosis is confirmed using ultrasound or contrast imaging (angiography or CT with contrast). Vena caval thrombosis might be visible on echocardiogram, especially when the clot extends into the RA. Thrombosis of the portal vein or caudal vena cava can be documented on abdominal ultrasound. Computer tomography with contrast can allow imaging of multiple body areas to demonstrate thrombosis (luminal masses within vessels with associated filling defects).

Clinicopathologic findings generally reflect underlying disease and tissue damage resulting from vascular obstruction. Cranial caval thrombosis has been associated with thrombocytopenia. Management is as discussed earlier for arterial thrombosis, with an emphasis on anticoagulants rather than antiplatelet drugs because of the low shear conditions in the venous system. Stenting of the affected vessel is another therapeutic option.

Suggested Readings

Alwood AJ, et al. Anticoagulant effects of low-molecular–weight heparins in healthy cats. *J Vet Intern Med*. 2007;21:378–387.

Bedard C, Lanevschi-Pietersma A, Dunn M. Evaluation of coagulation markers in the plasma of healthy cats and cats with asymptomatic hypertrophic cardiomyopathy. *Vet Clin Pathol*. 2007;36:167–172.

Borgeat K, et al. Arterial thromboembolism in 250 cats in general practice: 2004-2012. *J Vet Intern Med*. 2014;28:102–108.

Boswood A, Lamb CR, White RN. Aortic and iliac thrombosis in six dogs. *J Small Anim Pract*. 2000;41:109–114.

Bright JM, Dowers K, Powers BE. Effects of the glycoprotein IIb/IIIa antagonist abciximab on thrombus formation and platelet function in cats with arterial injury. *Vet Ther*. 2003;4:35–46.

Carr AP, Panciera DL, Kidd L. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. *J Vet Intern Med*. 2002;16:504–509.

De Laforcade AM, et al. Hemostatic changes in dogs with naturally occurring sepsis. *J Vet Intern Med*. 2003;17:674–679.

Goncalves R, et al. Clinical and neurological characteristics of aortic thromboembolism in dogs. *J Small Anim Pract*. 2008;49:178–184.

Good LI, Manning AM. Thromboembolic disease: physiology of hemostasis and pathophysiology of thrombosis. *Compend Contin Educ Pract Vet*. 2003;25:650–658.

Good LI, Manning AM. Thromboembolic disease: predispositions and clinical management. *Compend Contin Educ Pract Vet*. 2003;25:660–674.

Goodwin JC, Hogan DF, Green HW. The pharmacodynamics of clopidogrel in the dog. *J Vet Intern Med*. 2007;21:609.

Goodwin LV, et al. Hypercoagulability in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2011;25:273–277.

Heilmann RM, et al. Hyperhomocysteinemia in greyhounds and its association with hyperfolatemia and other clinicopathologic variables. *J Vet Intern Med*. 2017;31:109–116.

Hogan DF, et al. Antiplatelet effects and pharmacodynamics of clopidogrel in cats. *J Am Vet Med Assoc*. 2004;225:1406–1411.

Hogan DF, et al. Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT). *J Vet Cardiol*. 2015;17:S306–S317.

Kidd L, Stepien RL, Amrheiw DP. Clinical findings and coronary artery disease in dogs and cats with acute and subacute myocardial necrosis: 28 cases. *J Am Anim Hosp Assoc*. 2000;36:199–208.

Kidd L, Mackman N. Prothrombotic mechanisms and anticoagulant therapy in dogs with immune-mediated hemolytic anemia. *J Vet Emerg Crit Care (San Antonio)*. 2013;23:3013.

Lake-Bakaar GA, Johnson EG, Griffiths LG. Aortic thrombosis in dogs: 31 cases (2000-2010). *J Am Vet Med Assoc*. 2012;241:910–915.

Laurenson MP, et al. Concurrent diseases and conditions in dogs with splenic vein thrombosis. *J Vet Intern Med*. 2010;24:1298–1304.

Licari LG, Kovacic JP. Thrombin physiology and pathophysiology. *J Vet Emerg Crit Care (San Antonio)*. 2009;19:11–22.

Mellett AM, Nakamura RK, Bianco D. A prospective study of clopidogrel therapy in dogs with primary immune-mediated hemolytic anemia. *J Vet Intern Med*. 2011;25:71–75.

Moore KE, et al. Retrospective study of streptokinase administration in 46 cats with arterial thromboembolism. *J Vet Emerg Crit Care (San Antonio)*. 2000;10:245–257.

Morassi A, et al. Evaluation of the safety and tolerability of rivaroxaban in dogs with presumed primary immune-mediated hemolytic anemia. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:488–494.

Myers JA, et al. Pharmacokinetics and pharmacodynamics of the factor Xa inhibitor apixaban after oral and intravenous administration to cats. *Am J Vet Res*. 2015;76:732–738.

Nelson OL, Andreasen C. The utility of plasma D-dimer to identify thromboembolic disease in dogs. *J Vet Intern Med*. 2003;17:830–834.

Olsen LH, et al. Increased platelet aggregation response in Cavalier King Charles Spaniels with mitral valve prolapse. *J Vet Intern Med*. 2001;15:209–216.

Ralph AG, et al. Spontaneous echocardiographic contrast in three dogs. *J Vet Emerg Crit Care (San Antonio)*. 2011;21:158–165.

Respess M, et al. Portal vein thrombosis in 33 dogs: 1998-2011. *J Vet Intern Med*. 2012;26:230–237.

Schermerhorn TS, Pembleton-Corbett JR, Kornreich B. Pulmonary thromboembolism in cats. *J Vet Intern Med*. 2004;18:533–535.

Smith CE, et al. Use of low molecular weight heparin in cats: 57 cases (1999-2003). *J Am Vet Med Assoc*. 2004;225:1237–1241.

Smith SA. The cell-based model of coagulation. *J Vet Emerg Crit Care (San Antonio)*. 2009;19:3–10.

Smith SA, et al. Arterial thromboembolism in cats: acute crisis in 127 cases (1992-2001) and long-term management with low-dose aspirin in 24 cases. *J Vet Intern Med*. 2003;17:73–83.

Smith SA, Tobias AH. Feline arterial thromboembolism: an update. *Vet Clin North Am Small Anim Pract*. 2004;34:1245–1271.

Stokol T, et al. D-dimer concentrations in healthy dogs and dogs with disseminated intravascular coagulation. *Am J Vet Res*. 2000;61:393–398.

Stokol T, et al. Hypercoagulability in cats with cardiomyopathy. *J Vet Intern Med*. 2008;22:546–552.

Thompson MF, Scott-Moncrieff JC, Hogan DF. Thrombolytic therapy in dogs and cats. *J Vet Emerg Crit Care (San Antonio)*. 2001;11:111–121.

Van De Wiele CM, et al. Antithrombotic effect of enoxaparin in clinically healthy cats: a venous stasis model. *J Vet Intern Med*. 2010;24:185–191.

Van Winkle TJ, Hackner SG, Liu SM. Clinical and pathological features of aortic thromboembolism in 36 dogs. *J Vet Emerg Crit Care (San Antonio)*. 1993;3:13–21.

Weinkle TK, et al. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *J Am Vet Med Assoc*. 2005;226:1869–1880.

Welch KM, et al. Prospective evaluation of tissue plasminogen activator in 11 cats with arterial thromboembolism. *J Feline Med Surg*. 2010;12:122–128.

Williams TPE, et al. Aortic thrombosis in dogs. *J Vet Emerg Crit Care (San Antonio)*. 2017;27:9–22.

Winter RL, et al. Aortic thrombosis in dogs: presentation, therapy, and outcome in 26 cases. *J Vet Cardiol*. 2012;14:333–342.

Yang VK, et al. The use of rivaroxaban for the treatment of thrombotic complications in four dogs. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:729–736.



Drugs Used in Cardiovascular Disorders

GENERIC NAME	TRADE NAME	DOG	CAT
Diuretics			
Furosemide	Lasix Salix	Chronic therapy: 1-3 (or more) mg/kg q8-24h PO (use lowest effective dose; maximum daily dose ~10[-12] mg/kg/day, depending on renal function). Acute: 2(-4+) mg/kg initial bolus, then 1-4 mg/kg q1-4h until RR decreases, then 1-4 mg/kg q6-12h IV, IM, SC; or follow IV bolus with 0.6-1 mg/kg/h CRI until RR decreases (see Chapter 3)	Chronic therapy: 1-2 (or more) mg/kg q8-24h PO (use lowest effective dose; maximum daily dose ~8 mg/kg/day, depending on renal function). Acute: 1-2 mg/kg initial bolus, then 1-2 mg/kg q1-4h until RR decreases, then 1-2 mg/kg q6-12h IV, IM, SC; or follow IV bolus with 0.3-0.6 mg/kg/h CRI until RR decreases (see Chapter 3)
Torsemide	Demadex	1/10 (1/12-1/8) of total daily furosemide dose, divide q12h (in place of furosemide)	~1/10 of total daily furosemide dose, divide q12h (in place of furosemide)
Spironolactone	Aldactone	2 mg/kg PO q24h (or divided q12h); can start lower	1-2 mg/kg PO q24h (or divided q12h); can start lower
Chlorothiazide	Diuril	10-40 mg/kg PO q12-48h (start qod with low dose)	10-40 mg/kg PO q12-48h (start qod with low dose)
Hydrochlorothiazide	Hydrodiuril	0.5-4 mg/kg PO q12-48h (start qod with low dose)	0.5-2 mg/kg PO q12-48h (start qod with low dose)
Angiotensin-Converting Enzyme Inhibitors			
Enalapril	Enacard Vasotec	0.5 mg/kg PO q12(-24)h	0.25-0.5 mg/kg PO q24h
Benazepril	Lotensin	0.25-0.5 mg/kg PO q12(-24)h	0.25-0.5 mg/kg PO q24h
Captopril	Capoten	0.5-2 mg/kg PO q8-12h	0.5-1.25 mg/kg PO q(8-)24h
Lisinopril	Prinivil Zestril	0.25-0.5 mg/kg PO q(12-)24h	0.25-0.5 mg/kg PO q24h
Ramipril	Altace	0.125-0.25 mg/kg PO q24h	0.125 mg/kg PO q24h
Angiotensin-Receptor Blockers			
Telmisartan	Micardis Semintra	1 mg/kg PO q24h	(1-)2 mg/kg PO q24h
Irbesartan	Avapro	–	10 mg/kg PO q24h (experimental)

Continued



Drugs Used in Cardiovascular Disorders—cont'd

GENERIC NAME	TRADE NAME	DOG	CAT
Other Vasodilators			
Hydralazine	Apresoline	0.5-1 mg/kg initial (up to 2-3 mg/kg) PO q12h For acute decompensated CHF: 0.5-1 mg/kg PO, repeat in 2-3 hours if needed, then q12h, or low dose IV (see Chapter 3 and Box 3.1) For hypertensive crisis: (0.1-) 0.2 mg/kg, IV or IM, q2h as needed	2.5 (up to 10) mg/cat PO q12h
Amlodipine besylate	Norvasc	0.1-0.3 (-0.5) mg/kg PO q(12-)24h; as adjunct in CHF, initial dose 0.05 mg/kg	0.625 (-1.25) mg/cat (or 0.1-0.5 mg/kg) PO q(12)-24h
Nitroprusside	Nitropress	1-2.5 µg/kg/min CRI (initial), uptitrate as needed to 5-15 µg/kg/min CRI	0.5-1 µg/kg/min CRI (initial), uptitrate as needed to 5 µg/kg/min CRI
Nitroglycerin ointment 2%	Nitrobid Nitrol	¼-1½ inch q4-6h cutaneously for 24-48 hours	¼-½ inch q4-6h cutaneously for 24-48 hours
Sildenafil citrate	Viagra Revatio	1-3 (-4) mg/kg PO q8-12h	1-2 mg/kg PO q8-12h
Prazosin	Minipress	0.05-0.2 mg/kg PO q8-12h	0.25-0.5 mg/cat PO q12-24h
Phenoxybenzamine	Dibenzyline	0.25 mg/kg PO q8-12h or 0.5 mg/kg q24h	2.5 mg/cat PO q8-12h or 0.5 mg/kg q(12-)24h
Acepromazine		0.01-0.05 (-0.1) mg/kg (up to 3 mg total) IV (IM, SC)	0.01-0.05 mg/kg IV (IM, SC)
Positive Inotropic Drugs			
Pimobendan	Vetmedin	0.2-0.3 mg/kg PO q12h; can increase up to 0.5 mg/kg q8h	Same, or 1.25 mg/cat PO q12h; can increase up to 0.5 mg/kg q8h
Digoxin	Cardoxin Digitek Lanoxin	Oral: 0.003-0.005 mg/kg q12h; maximum 0.5 mg/day (less in some dogs; monitor serum concentration); decrease by 10% for elixir PO loading: give first 1-2 doses at twice calculated maintenance dose IV loading (note: not advised unless other therapy not effective or available): 0.0025 mg/kg slow IV bolus, repeat hourly over 4-hour period to effect (or total of 0.01 mg/kg)	Oral: 0.007 mg/kg (or ¼ of 0.125 mg tab/cat) q48h
Dobutamine	Dobutrex	1 µg/kg/min initial CRI; titrate upward to effect q15-30 min, as needed, up to 20 µg/kg/min CRI	1 µg/kg/min initial CRI; titrate upward to effect q15-30 min, as needed, up to 10 µg/kg/min CRI
Dopamine	Intropin	1-10 µg/kg/min CRI (start low, titrate upward to effect q15-30 min, as needed)	1-5 µg/kg/min CRI (start low, titrate upward to effect q15-30 min, as needed)
Amrinone	Inocor	1-3 mg/kg initial bolus, IV; 10-100 µg/kg/min CRI	Same?
Milrinone	Primacor	50 µg/kg IV over 10 min initially; 0.375-0.75 µg/kg/min CRI (humans)	Same?



Drugs Used in Cardiovascular Disorders—cont'd

GENERIC NAME	TRADE NAME	DOG	CAT
Antiarrhythmic Drugs			
Class I			
Lidocaine	Xylocaine	Initial boluses of 2 mg/kg slowly IV, up to 8 mg/kg (over ≥10 min); or initial rapid IV infusion at 0.8 mg/kg/min; if effective, 25-80 µg/kg/min CRI	Initial bolus of 0.25-0.5 mg/kg slowly IV; can repeat boluses of 0.15-0.25 mg/kg, up to total of 4 mg/kg; if effective, 10-40 µg/kg/min CRI (note: use with extreme caution; other agents preferred)
Mexiletine	Mexitil	4-6 (-8) mg/kg PO q8h	—
Procainamide	Pronestyl Pronestyl SR Procan SR	2 mg/kg IV over 2 minutes; repeat if necessary, up to cumulative dose of 20 mg/kg; 10-50 µg/kg/min CRI; 6-20 (up to 30) mg/kg IM q4-6h; (PO, if available, 10-20 mg/kg q8-12h [sustained-release prep.])	1-2 mg/kg IV over 2 minutes, repeat if necessary, up to cumulative dose of 10 mg/kg; 10-20 µg/kg/min CRI; 7.5-20 mg/kg IM q(6-)8h
Quinidine (note: other agents preferred)		6-20 mg/kg IM q6h (loading dose, 14-20 mg/kg); 6-16 mg/kg PO q6h; sustained action preparations, 8-20 mg/kg PO q8h	6-16 mg/kg, IM or PO, q8h
Flecainide	Tambocor	1-2 (up to 4?) mg/kg PO q(8-)12h, (start low; not advised if CHF or impaired LV function present)	—
Propafenone	Rythmol	2-4 (up to 6?) mg/kg PO q8h (start low)	—
Class II			
Atenolol	Tenormin	0.2-1 mg/kg PO q12(-24)h (start low)	Same, or 6.25(-12.5) mg/cat PO q12(-24)h
Esmolol	Brevibloc	50-100 µg/kg IV over 5 minutes (loading dose), followed by infusion of 25-50 µg/kg/min	Same
Metoprolol	Lopressor	0.1-0.2 mg/kg initial dose PO q24(-12)h; up to 1(-2) mg/kg q8(-12)h	2 up to 15 mg/cat PO q8(-12)h, start low
Propranolol	Inderal	0.02 mg/kg initial bolus slowly IV (up to maximum of 0.1 mg/kg); initial oral dose, 0.1-0.2 mg/kg PO q8h, up to 1 mg/kg q8h	IV: Same Oral: 2.5 (up to 10) mg/cat q8-12h
Class III			
Sotalol	Betapace	1-3 (up to 5?) mg/kg PO q12h	10-20 mg/cat (or 2-4 mg/kg) PO q12h
Amiodarone	Cordarone Pacerone Nexterone	PO loading: 10 (up to 15) mg/kg PO q12h for 4-7 days, then same dose q24h for 7 days, then reduce to maintenance dose PO maintenance: 5-7.5 mg/kg PO q24h. For IV administration use aqueous formulation (Nexterone, 1.5 mg/mL), not standard amiodarone, see p. 95): 3-5 mg/kg slow IV over 15 min; can continue 0.05 mg/kg/min CRI if needed	IV: aqueous formulation (1.5 mg/mL): 2.5 mg/kg slow bolus over 15 minutes (optimal dose uncertain)

Continued



Drugs Used in Cardiovascular Disorders—cont'd

GENERIC NAME	TRADE NAME	DOG	CAT
Class IV			
Diltiazem	Cardizem Cardizem-CD Dilacor XR Dilacor ER	Acute IV for rapid rate control of AF: 0.05-0.10 mg/kg IV over 2-5 minutes, can repeat if needed Acute IV for SVT: 0.1-(0.2) mg/kg over 2-5 minutes IV, can repeat to cumulative IV dose of 0.3-0.4 mg/kg; monitor blood pressure. CRI (if frequent SVT recurrence): 0.002-0.006 mg/kg/min (or 0.12-0.35 mg/kg/h) PO loading dose: 0.5 mg/kg PO followed by 0.25 mg/kg PO q1h to a total of 1.5(-2.0) mg/kg or conversion Oral maintenance (regular diltiazem): initial dose 0.5-1 mg/kg (up to 2-3 mg/kg) PO q8h Extended release (diltiazem ER): 1-4 (up to 6) mg/kg PO q12h	Cat: Same?; Or 1.5-2.5 mg/kg (or 7.5-10 mg/cat) PO q8h. Sustained-release preparations: diltiazem ER, 30 mg/cat/day (one half of a 60-mg controlled-release tablet within the 240-mg gelatin capsule), can increase to 60 mg/day in some cats if necessary Cardizem-CD, 10 mg/kg/day (45 mg/cat ~ 105 mg of Cardizem-CD ≅ amount that fits into small end of No. 4 gelatin capsule)
Antiarrhythmic Drugs			
Atropine		0.02-0.04 mg/kg IV, IM, SC. 0.04 mg/kg PO q6-8h. Atropine challenge test: 0.04 mg/kg IV (see Chapter 4, p. 97)	Same
Glycopyrrolate	Robinul	0.005-0.01 mg/kg IV, IM; 0.01-0.02 mg/kg SC	Same
Propantheline Br	Pro-Banthine	0.25-0.5 mg/kg or 3.73-7.5 (-15) mg/dog PO q8-12h	—
Hyoscyamine	Anaspaz, Levsin	0.003-0.006 mg/kg PO q8h	—
Sympathomimetics			
Isoproterenol	Isuprel	0.04-0.08 µg/kg/min CRI	Same
Terbutaline	Brethine Bricanyl	0.14 mg/kg, or 2.5-5 mg/dog, PO q8-12h	0.1 -0.2 mg/kg, or 0.625-1.25 mg/cat, PO q12h
Theophylline ER	Theolair	10 mg/kg PO q12h	10-15 mg/kg q24h
Drugs for Heartworm Disease ***Heartworm adulticide***			
Melarsomine	Immiticide	See Chapter 10 Follow manufacturer's injection instructions carefully; 2.5 mg/kg deep IM for 1 dose, then 1 month later give 2.5 mg/kg deep IM q24h for 2 doses	—
Heartworm prevention			
Ivermectin	Heartgard Iverhart Tri-Heart	0.006-0.012 mg/kg PO once a month	0.024 mg/kg PO once a month
Milbemycin oxime	Interceptor Sentinel Trifexis	0.5-1.0 mg/kg PO once a month	2 mg/kg PO once a month



Drugs Used in Cardiovascular Disorders—cont'd

GENERIC NAME	TRADE NAME	DOG	CAT
Selamectin	Revolution	6-12 mg/kg topically once a month	Same
Moxidectin/ imidacloprid	Advantage Multi	2.5 mg/kg moxidectin and 10 mg/kg imidacloprid topically once a month	1 mg/kg moxidectin and 10 mg/kg imidacloprid topically once a month
Antithrombotic Agents			
Aspirin		0.5-1.0 mg/kg PO q24h	(20-)81 mg/cat PO q72h
Clopidogrel	Plavix	2-4 mg/kg PO q24h; (oral loading dose, 10 mg/kg)	18.75 mg/cat (or 2-4 mg/kg) PO q24h; oral loading dose, 75 mg/cat
Heparin Na (unfractionated heparin)		100-300 IU/kg IV, followed by 100-300 IU/kg SC q8h (or CRI 600-800 IU/kg/day) for 2-4 days or as needed	100 IU/kg IV, followed by 200 IU/kg SC q8h (or CRI 600 IU/kg/day) for 2-4 days or as needed
Dalteparin	Fragmin	50-100 U/kg SC q12-24h	100 U/kg SC q12-24h
Enoxaparin	Lovenox	1.5 mg/kg SC q12-24h	1.5 mg/kg SC q12-24h
Warfarin	Coumadin	0.1 mg/kg PO q24h initially; titrate based on PT/INR (see p. 233)	0.25 mg/cat PO q24h initially; titrate based on PT/INR (see p. 233)
Fondaparinux	Arixtra	—	0.06 mg/kg SC q12h for thromboprophylaxis 0.2 mg/kg SC q12h for thrombosis treatment
Rivaroxaban	Xarelto	0.5-1.0 mg/kg PO q24h	2.5 mg/cat PO q24h
Apixaban	Eliquis	—	0.625 mg/cat PO q12h

CHF, Congestive heart failure; *CRI,* constant-rate infusion; *IM,* intramuscular; INR, international normalization ratio; *IV,* intravenous; *PO,* by mouth; PT, prothrombin time; *RR,* respiratory rate; *SC,* subcutaneous.

CHAPTER 13

Clinical Manifestations of Nasal Disease



GENERAL CONSIDERATIONS

The nasal cavity and paranasal sinuses have a complex anatomy and are lined by mucosa. Their rostral portion is inhabited by bacteria in health. Nasal disorders are frequently associated with mucosal edema, inflammation, and secondary bacterial infection. They are often focal or multifocal in distribution. These factors combine to make the accurate diagnosis of nasal disease a challenge that can be met only through a thorough, systematic approach.

Diseases of the nasal cavity and paranasal sinuses typically cause nasal discharge, congestion, sneezing, or stertor (i.e., snoring or snorting sounds). Less common signs include facial deformity, systemic signs of illness (e.g., lethargy, inappetence, weight loss), or, rarely, central nervous system signs. The general diagnostic approach to animals with nasal disease is included in the discussion of nasal discharge. Specific considerations related to sneezing, stertor, and facial deformity follow. Stenotic nares are discussed in the section on brachycephalic airway syndrome (see Chapter 18).

Nasal foreign bodies are mentioned throughout the discussion of nasal disease. Nasal foreign bodies most often enter the nasal cavity through the external nares, although nasal or pharyngeal signs can also be the result of foreign material taken into the mouth and subsequently coughed into the caudal nasopharynx. Plant material is most often the culprit. Blades of grass, grass seeds arranged in heads with stiff bristles (grass awns; Fig. 13.1), and thin, stiff leaves (such as those of juniper bushes and cedar trees) have a physical design that facilitates movement in one direction. Consider running a blade of grass between your fingertips. Usually the grass moves smoothly in one direction but resists movement in the other. Because of this property, attempts to expel the foreign material by coughing or sneezing often cause the material to travel more deeply into the body instead. Nasal foreign bodies are particularly common in the western United States, where "foxtail" grasses (those with awns) are widespread. Awns can enter the body through any orifice, even through intact skin; the external nares are one common route.

NASAL DISCHARGE

Classification and Etiology

Nasal discharge is most commonly associated with disease localized solely within the nasal cavity and paranasal sinuses, although it may also develop with disorders of the lower respiratory tract, such as bacterial pneumonia and infectious tracheobronchitis, or with systemic disorders, such as coagulopathies and systemic hypertension. Nasal discharge is characterized as serous, mucopurulent with or without hemorrhage, or purely hemorrhagic (epistaxis). Serous nasal discharge has a clear, watery consistency. Depending on the quantity and duration of the discharge, a serous discharge may be normal, may be indicative of viral upper respiratory infection, or may precede the development of a mucopurulent discharge. As such, many of the causes of mucopurulent discharge can initially cause serous discharge (Box 13.1).

Mucopurulent nasal discharge typically is characterized by a thick, ropey consistency and has a white, yellow, or green tint. A mucopurulent nasal discharge implies inflammation. Most intranasal diseases result in inflammation and secondary bacterial infection, making this nonspecific sign a common presentation for most nasal diseases. Potential etiologies include infectious agents, foreign bodies, neoplasia, polyps, and extension of disease from the oral cavity (see Box 13.1). If mucopurulent discharge is present in conjunction with signs of lower respiratory tract disease, such as cough, respiratory distress, or auscultable crackles, the diagnostic emphasis is initially on evaluation of the lower airways and pulmonary parenchyma. Hemorrhage may be associated with mucopurulent exudate from any etiology, but significant and prolonged bleeding in association with



FIG 13.1
Typical grass awn. Seed heads from "foxtail" grasses have stiff bristles that facilitate movement of the awns in one direction and make it difficult for the awns to be expelled from the body. (Courtesy Lynelle R. Johnson.)

mucopurulent discharge is usually associated with neoplasia or mycotic infections.

Persistent pure hemorrhage (epistaxis) can result from trauma, local aggressive disease processes (e.g., neoplasia, mycotic infections), systemic bleeding disorders, or systemic hypertension. Systemic hemostatic disorders that can cause epistaxis include thrombocytopenia, thrombocytopathies, von Willebrand disease, rodenticide toxicity, and vasculitides. Ehrlichiosis, Rocky Mountain spotted fever and, potentially, bartonellosis can cause epistaxis through several of these mechanisms. Nasal foreign bodies may cause hemorrhage after entry into the nasal cavity, but the bleeding tends to subside quickly. Bleeding can also occur after aggressive sneezing from any cause.

Diagnostic Approach

A complete history and physical examination can be used to prioritize the differential diagnoses for each type of nasal discharge (see Box 13.1). Acute and chronic diseases are defined by obtaining historical information regarding the onset of signs and by evaluating the overall condition of the animal. Acute processes, such as foreign bodies or acute feline viral infections, often result in a sudden onset of signs, including sneezing, although the animal's body condition is excellent. In chronic processes, such as mycotic infections or neoplasia, signs are present over a long period, and the overall body condition may be deleteriously affected. A history of gagging, retching, or reverse sneezing may indicate masses, foreign bodies, or exudate in the caudal nasopharynx.

Nasal discharge is characterized as unilateral or bilateral on the basis of both historical and physical examination findings. When nasal discharge is apparently unilateral, a cold microscope slide may be held close to the external nares to determine the patency of the side of the nasal cavity without discharge. Condensation will not be visible in front

BOX 13.1

Differential Diagnoses for Nasal Discharge in Dogs and Cats

Serous Discharge

Normal
Viral infection
Early sign of etiology of mucopurulent discharge

Mucopurulent Discharge with or without Hemorrhage

Viral infection
  Feline herpesvirus (rhinotracheitis virus)
  Feline calicivirus
  Canine influenza virus
Bacterial infection (usually secondary)
  Mycoplasma felis (possibly primary)
Fungal infection
  Aspergillus
  Cryptococcus
  Penicillium
  Rhinosporidium
Nasal parasites
  Pneumonyssoides
  Capillaria (Eucoleus)
Foreign body
Neoplasia
  Carcinoma
  Sarcoma
  Malignant lymphoma
Nasopharyngeal polyp
Extension of oral disease
  Tooth root abscess
  Oronasal fistula
  Deformed palate
Allergic rhinitis
Feline chronic rhinosinusitis
Canine chronic/lymphoplasmacytic rhinitis

Pure Hemorrhagic Discharge (Epistaxis)

Nasal disease
  Acute trauma
  Acute foreign body
  Neoplasia
  Fungal infection
  Less commonly, other etiologies as listed for mucopurulent discharge
Systemic disease
  Clotting disorders
  • Thrombocytopenia
  • Thrombocytopathy
  • Coagulation defect
  Vasculitis
  Hyperviscosity syndrome
  Polycythemia
  Systemic hypertension

of the naris if airflow is obstructed, which suggests that the disease is actually bilateral. Although any bilateral process can cause signs from one side only and unilateral disease can progress to involve the opposite side, some generalizations can be made. Systemic disorders and infectious diseases tend to involve both sides of the nasal cavity, whereas foreign bodies, polyps, and tooth root abscessation tend to cause unilateral discharge. Neoplasia initially may cause unilateral discharge that later becomes bilateral after destruction of the nasal septum.

Ulceration of the nasal plane is highly suggestive of a diagnosis of nasal aspergillosis (Fig. 13.2). Polypoid masses protruding from the external nares in the dog are typical of rhinosporidiosis, and in the cat they are typical of cryptococcosis.

A thorough assessment of the head, including facial symmetry, teeth, gingiva, hard and soft palate, mandibular lymph nodes, and eyes, should be performed. Mass lesions invading beyond the nasal cavity can cause deformity of facial bones or the hard palate, exophthalmos, or inability to retropulse the eye. Pain on palpation of the nasal bones is suggestive of aspergillosis. Gingivitis, dental calculi, loose teeth, or pus in the gingival sulcus should raise an index of suspicion for oronasal fistulae or tooth root abscess, especially if unilateral nasal discharge is present. Foci of inflammation and folds of hyperplastic gingiva in the dorsum of the mouth should be probed for oronasal fistulae. **A normal examination of the oral cavity does not rule out oronasal fistulae or tooth root abscess.** The hard and soft palates are examined for deformation, erosions, or congenital defects such as clefts or hypoplasia. Mandibular lymph node enlargement suggests active inflammation or neoplasia, and fine-needle aspirates of enlarged or firm nodes are evaluated for organisms, such as *Cryptococcus,* and neoplastic cells (Fig. 13.3). A fundic examination should always be performed because active chorioretinitis can occur with cryptococcosis, ehrlichiosis, and malignant lymphoma (Fig. 13.4). Retinal detachment can occur with systemic hypertension or mass lesions extending into the bony orbit. With epistaxis, identification of petechiae or hemorrhage in other mucous membranes, skin, ocular fundus, feces, or urine supports a systemic bleeding disorder. Note that melena may be present as a result of swallowing blood from the nasal cavity.



FIG 13.2
Depigmentation and ulceration of the planum nasale are suggestive of nasal aspergillosis. The visible lesions usually extend from one or both nares and are most severe ventrally. This dog has unilateral depigmentation and mild ulceration.

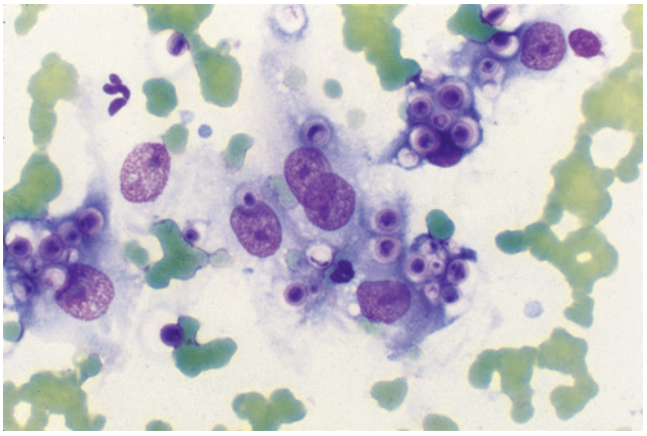


FIG 13.3
Photomicrograph of fine-needle aspirate of a cat with facial deformity. Identification of cryptococcal organisms provides a definitive diagnosis for cats with nasal discharge or facial deformity. Organisms can often be found in swabs of nasal discharge, fine-needle aspirates of facial masses, or fine-needle aspirates of enlarged mandibular lymph nodes. The organisms are variably sized, ranging from about 3 to 30 μm in diameter, with a wide capsule and narrow-based budding. They may be found intracellularly or extracellularly.

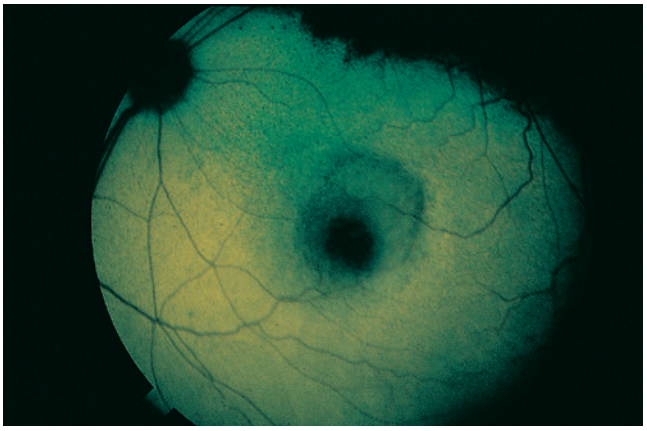


FIG 13.4
Fundic examination can provide useful information in animals with signs of respiratory tract disease. This fundus from a cat with chorioretinitis caused by cryptococcosis has a large, focal, hyporeflective lesion in the area centralis. Smaller regions of hyporeflectivity are also seen. The optic disk can be seen in the upper left-hand corner of the photograph. (Courtesy M. Davidson, North Carolina State University, Raleigh, NC.)

Diagnostic tests that should be considered for a dog or cat with nasal discharge are presented in Box 13.2. The signalment, history, and physical examination findings dictate in part which diagnostic tests are ultimately required to establish the diagnosis. As a general rule, less invasive diagnostic tests are performed initially. A complete blood count with platelet count, a coagulation panel (i.e., activated clotting time or prothrombin and partial thromboplastin times), buccal mucosal bleeding time, and arterial blood pressure should be evaluated in dogs and cats with epistaxis. Von Willebrand factor assays are performed in purebred dogs with epistaxis and in dogs with prolonged mucosal bleeding times. Determination of *Ehrlichia* spp. and Rocky Mountain spotted fever titers are indicated for dogs with epistaxis in regions of the country where potential exposure to these rickettsial agents exists. Testing for *Bartonella* spp. is also considered. Testing for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) should be performed in cats with chronic nasal discharge and potential exposure. Cats infected with FeLV may be predisposed to chronic infection with herpesvirus or calicivirus, whereas those with FIV may have chronic nasal discharge without concurrent infection with these upper respiratory viruses.

Most animals with intranasal disease have normal thoracic radiographs. However, thoracic radiographs may be useful in identifying primary bronchopulmonary disease, pulmonary involvement with cryptococcosis, and rare metastases from neoplastic disease. They may also serve as a useful preanesthetic screening test for animals that will require nasal imaging, rhinoscopy, and nasal biopsy.

Cytologic evaluation of superficial nasal swabs may identify cryptococcal organisms in cats (see Fig. 13.3). Nonspecific findings include proteinaceous background, moderate to severe inflammation, and bacteria. Mandibular lymph node aspirates may provide a diagnosis of cryptococcosis in cats or neoplasia in dogs or cats.

Tests to identify herpesvirus, calicivirus, and *Mycoplasma felis* infections may be performed in cats with acute and chronic rhinitis. These tests are most useful in evaluating cattery problems or cats with persistent clinical signs (see Chapter 15, Feline Upper Respiratory Infection).

Fungal titer determinations are available for aspergillosis in dogs and cryptococcosis in dogs and cats. The test for aspergillosis detects antibodies in the blood. A single positive test result strongly suggests active infection by the organism; however, a negative titer does not rule out the disease. In either case, the result of the test must be

BOX 13.2

General Diagnostic Approach to Dogs and Cats with Chronic Nasal Discharge

Phase I (Noninvasive Testing)

All Patients	Dogs	Cats	Dogs and Cats with Hemorrhage
History	*Aspergillus* titer	Nasal swab cytologic evaluation (cryptococcosis)	Complete blood count
Physical examination	Fecal flotation	Cryptococcal antigen titer	Platelet count
Funduscopic examination	*Capillaria/Eucoleus)*	Viral testing	Coagulation times
Thoracic radiographs		Feline leukemia virus	Buccal mucosal bleeding time
Mandibular lymph node cytology		Feline immunodeficiency virus	Tests for tick-borne diseases (dogs)
		Herpesvirus (PCR, virus isolation)	Arterial blood pressure
		±Calicivirus (PCR, virus isolation)	von Willebrand factor assay (dogs)
		Mycoplasma felis PCR or culture	

Phase II—All Patients (General Anesthesia Required)

Computed tomography (CT) or nasal radiography
Oral examination
Rhinoscopy: external nares and nasopharynx
Dental radiographs (if CT and rhinoscopy are not diagnostic)
Nasal biopsy/histologic examination
Deep nasal culture
- Fungal
- Bacterial (significance of growth is uncertain)

Phase III—All Patients (Referral Usually Required)

CT (if not previously performed) or magnetic resonance imaging (MRI)
Frontal sinus exploration (if involvement identified by CT, MRI, or radiography)

Phase IV—All Patients (Consider Referral)

Phase II repeated in several months using CT or MRI
Exploratory rhinotomy with turbinectomy

interpreted in conjunction with results of nasal imaging, rhinoscopy, and nasal histology and culture.

The blood test of choice for cryptococcosis is the latex agglutination capsular antigen test (LCAT). Because organism identification is usually possible in specimens from infected organs, organism identification is the method of choice for a definitive diagnosis. The LCAT is performed if cryptococcosis is suspected but an extensive search for the organism has failed. The LCAT is also performed in animals with a confirmed diagnosis as a means of monitoring therapeutic response (see Chapter 97).

Most often, computed tomography (CT) or nasal radiography, rhinoscopy, and biopsy are required to establish a diagnosis of intranasal disease in dogs and cats in which acute viral infection is not suspected. Dental radiographs should also be obtained if a diagnosis is not obvious from CT or rhinoscopy, as they can be more sensitive for detecting tooth root disease than CT. These diagnostic tests are performed with the dog or cat under general anesthesia. CT scans or nasal radiographs are obtained first, followed by oral examination and rhinoscopy, and then specimen collection. This order is recommended because results of CT or radiography and rhinoscopy are often useful in the selection of biopsy sites. In addition, hemorrhage from biopsy sites could obscure or alter radiographic and rhinoscopic detail if the specimen were collected first. However, in dogs and cats highly suspected of having acute foreign body inhalation, rhinoscopy is performed first in the hopes of identifying and removing the foreign material. (See Chapter 14 for more detail on nasal radiography, CT, and rhinoscopy.)

The combination of radiography, rhinoscopy, and nasal biopsy has been reported to have a diagnostic success rate of approximately 80% in dogs; however, a diagnosis of idiopathic disease was considered a diagnostic success in dogs without progressive signs. The success rate was closer to 50% if the diagnosis of idiopathic disease was excluded. It is more difficult to evaluate the success rate for cats. High proportions of cats with chronic nasal discharge suffer from feline chronic rhinosinusitis (idiopathic rhinitis) and are diagnosed only through exclusion. Dogs with persistent signs in which a diagnosis cannot be obtained after the assessment described earlier require further evaluation. Cats are evaluated further only if signs suggestive of another disease are found during any part of the evaluation, or if the clinical signs are progressive or intolerable to the owners.

Nasal CT is considered if not performed previously and if a diagnosis has not been made. CT provides excellent visualization of all of the nasal sinuses and may allow identification of small masses that are not visible on nasal radiography or rhinoscopy. CT is also more accurate than nasal radiography in determining the extent of nasal tumors. Magnetic resonance imaging (MRI) may be more accurate than CT in the assessment of soft tissues, such as nasal neoplasia. Dental radiographs should also be obtained if not previously performed. In the absence of a diagnosis, nasal imaging (preferably CT or MRI), dental radiographs, rhinoscopy, and biopsy can be repeated after a 1- to 2-month period.

Frontal sinus exploration should be considered in dogs with fluid or tissue opacity in the frontal sinus in the absence of a diagnosis. Aspergillosis, in particular, may be localized within the frontal sinus and may elude diagnosis through rhinoscopy.

Exploratory rhinotomy with turbinectomy is the most aggressive diagnostic test. Surgical exploration of the nose allows direct visualization of the nasal cavity for detecting the presence of foreign bodies, mass lesions, or fungal mats and for obtaining biopsy and culture specimens. The potential benefits of surgery, however, should be weighed against the potential complications associated with rhinotomy and turbinectomy. The Suggested Readings section offers surgical references.

SNEEZING

Etiology and Diagnostic Approach

A sneeze is an explosive release of air from the lungs through the nasal cavity and mouth. It is a protective reflex that expels irritants from the nasal cavity. Intermittent, occasional sneezing is considered normal. Persistent, paroxysmal sneezing should be considered abnormal. Disorders commonly associated with acute-onset, persistent sneezing include nasal foreign body and feline upper respiratory infection. The canine nasal mite, *Pneumonyssoides caninum,* and exposure to irritating aerosols are less common causes of sneezing. All nasal diseases considered as differential diagnoses for nasal discharge are also potential causes for sneezing; however, animals with these diseases more often present with nasal discharge as the primary complaint.

The owners should be questioned carefully concerning possible recent exposure of the pet to foreign bodies (e.g., rooting in the ground, running through grassy fields) or irritants (powders and aerosols) or, in cats, exposure to respiratory viruses through new cats or kittens. Sneezing is an acute phenomenon that often subsides with time. A foreign body should not be excluded from the differential diagnoses just because sneezing subsides. In the dog a history of acute sneezing followed by the development of a nasal discharge is suggestive of a foreign body or progressive disease.

Other findings may help narrow the list of differential diagnoses. Dogs with foreign bodies or nasal mites may paw at their nose. Foreign bodies are typically associated with unilateral, mucopurulent nasal discharge, although serous or serosanguineous discharge may be present initially. Foreign bodies in the caudal nasopharynx may cause gagging, retching, or reverse sneezing. The nasal discharge associated with reactions to aerosols, powders, or other inhaled irritants is usually bilateral and serous in nature. In cats other clinical signs supportive of a diagnosis of upper respiratory infection, such as conjunctivitis and fever, may be present as well as a history of exposure to other cats or kittens.

Dogs in which acute, paroxysmal sneezing develops should undergo prompt rhinoscopic examination (see Chapter 14). With time, foreign material may become covered with mucus

or may migrate more deeply into the nasal passages, and any delay in performing rhinoscopy may interfere with identification and removal of foreign bodies. Nasal mites are also identified rhinoscopically. In contrast, cats sneeze more often as a result of acute viral infection rather than a foreign body. Immediate rhinoscopic examination is not indicated unless there has been known exposure to a foreign body and the history and physical examination findings do not support a diagnosis of viral upper respiratory infection.

REVERSE SNEEZING

Reverse sneezing is a paroxysm of noisy, labored inspiration that can be initiated by nasopharyngeal irritation. Such irritation can be the result of a foreign body located dorsal to the soft palate, or it may be associated with nasopharyngeal inflammation. Foreign bodies usually originate from grass or plant material that is prehended into the oral cavity and that, presumably, is coughed up or migrates into the nasopharyx. Most cases are idiopathic. Small-breed dogs are usually affected, and signs may be associated with excitement or drinking. The paroxysms last only seconds and do not significantly interfere with oxygenation. Although these animals usually display this sign throughout their lifetime, the problem rarely progresses.

Clients may present a dog with reverse sneeze for respiratory distress if they are not familiar with this sign. Their ability to describe the events may be limited, and dogs will rarely exhibit reverse sneeze during an examination. A key historic feature of reverse sneezing is that the dog instantly returns to normal breathing and attitude as soon as the event is over. This immediate return to normal is not characteristic of more serious problems, such as upper airway obstructions. Confirmation that described events indicate reverse sneezing can be obtained by showing the client a video recording of a dog reverse sneezing (Video 13.1). This approach is usually more efficient than having the client try to capture the reverse sneeze by video, although the latter is ideal.

A thorough history and physical examination is indicated to identify signs of potential underlying nasal or pharyngeal disorders. Further evaluation is needed if syncope, exercise intolerance, stertor, or other signs of respiratory disease are reported, or if reverse sneezing is severe or progressive.

In the absence of an underlying disease, treatment is rarely needed for reverse sneezing itself, because episodes are nearly always self-limiting. Some owners report that massaging the neck shortens an ongoing episode, or that administration of antihistamines decreases the frequency and severity of episodes, but controlled studies are lacking.

STERTOR

Stertor refers to coarse, audible snoring or snorting sounds associated with breathing. It indicates upper airway obstruction. Stertor is most often the result of pharyngeal disease (see Chapter 16). Intranasal causes of stertor include obstruction caused by congenital deformities, masses, exudate, or blood clots. Evaluation for nasal disease proceeds as described for nasal discharge.

FACIAL DEFORMITY

Carnassial tooth root abscess in dogs can result in swelling, often with drainage, adjacent to the nasal cavity and beneath the eye. Excluding dental disease, the most common causes of facial deformity adjacent to the nasal cavity are neoplasia and, in cats, cryptococcosis (Fig. 13.5). Visible swellings can

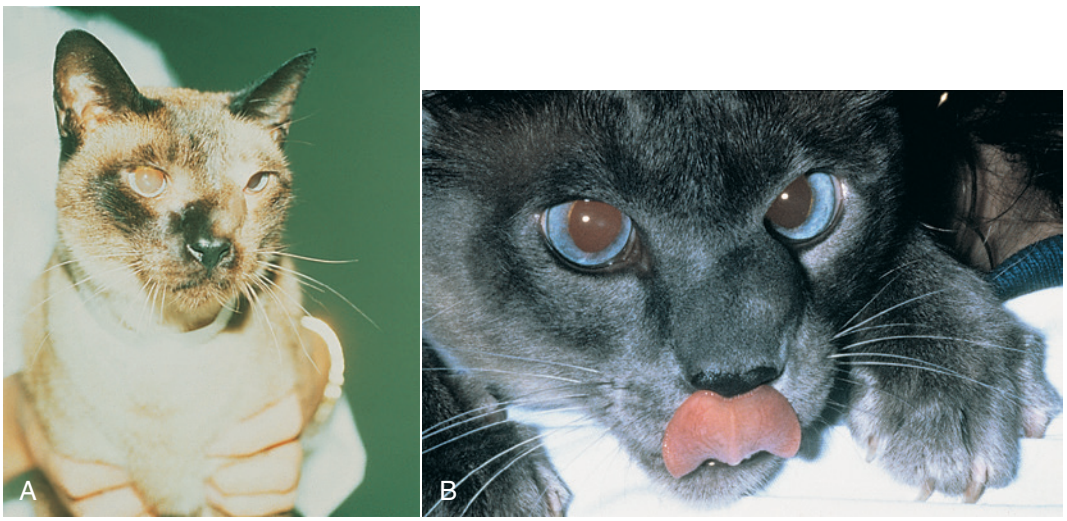


FIG 13.5
Facial deformity characterized by firm swelling over the maxilla in two cats. **(A)** Deformity in this cat was the result of carcinoma. Notice the ipsilateral blepharospasm. **(B)** Deformity in this cat was the result of cryptococcosis. A photomicrograph of the fine-needle aspirate of this swelling is provided in Fig. 13.3.

often be evaluated directly through fine-needle aspiration or punch biopsy (see Fig. 13.3). Further evaluation proceeds as for nasal discharge if such an approach is not possible or is unsuccessful.

Suggested Readings

Bissett SA, et al. Prevalence, clinical features, and causes of epistaxis in dogs: 176 cases (1996-2001). *J Am Vet Med Assoc*. 1843;231:2007.

Demko JL, et al. Chronic nasal discharge in cats. *J Am Vet Med Assoc*. 2007;230:1032.

Fossum TW. *Small animal surgery*. 5th ed. St Louis: Elsevier Mosby; 2019.

Greene LM, et al. Severity of nasal inflammatory disease questionnaire for canine idiopathic rhinitis control: instrument development and initial validity evidence. *J Vet Intern Med*. 2017;31:124.

Henderson SM. Investigation of nasal disease in the cat: a retrospective study of 77 cases. *J Feline Med Surg*. 2004;6:245.

Pomrantz JS, et al. Comparison of serologic evaluation via agar gel immunodiffusion and fungal culture of tissue for diagnosis of nasal aspergillosis in dogs. *J Am Vet Med Assoc*. 2007;203:1319.

CHAPTER 14

Diagnostic Tests for the Nasal Cavity and Paranasal Sinuses



NASAL IMAGING

Nasal imaging is a key component of the diagnostic assessment of animals with signs of intranasal disease, allowing assessment of bone and soft tissue structures that are not visible by physical examination or rhinoscopy. Nasal radiography, the type of imaging most readily available in general practice, is described in some detail. However, computed tomography (CT) provides images that are superior to radiographs in most cases and has widespread availability. The role of magnetic resonance imaging (MRI) in the evaluation of canine and feline nasal disease has not been well established, but it likely provides more accurate images of soft tissue than are provided by CT. MRI is not used routinely on account of its limited availability and relatively high expense. High-quality dental imaging is indicated for patients in which CT and rhinoscopy do not provide an obvious diagnosis. Dental radiographs can be more sensitive than CT for the diagnosis of tooth root disease.

Because nasal imaging rarely provides a definitive diagnosis, it is usually followed by rhinoscopy and nasal biopsy. All of these procedures require general anesthesia. Nasal imaging should be performed before, rather than after, these procedures for two reasons: (1) The results of nasal imaging help the clinician direct biopsy instruments to the most abnormal regions, and (2) rhinoscopy and biopsy cause hemorrhage, which obscures soft tissue detail.

RADIOGRAPHY

Nasal radiographs are useful for identifying the extent and severity of disease, localizing sites for biopsy within the nasal cavity, and prioritizing the differential diagnoses. The dog or cat must be anesthetized to prevent motion and facilitate positioning. Radiographic abnormalities are often subtle. At least four views should be taken: lateral, ventrodorsal, intraoral, and frontal sinus or skyline. The intraoral view is particularly helpful for detecting subtle asymmetry between the left and right nasal cavities. Radiographs of the tympanic bullae are obtained in cats to determinate extension of disease into the middle ear, particularly with nasopharyngeal polyps. High quality dental films are indicated in dogs and cats with possible tooth root abscess. Because nasal signs may be the only indication of tooth root disease, imaging is indicated for patients without an obvious diagnosis from CT and rhinoscopy.

The intraoral view is taken with the animal in sternal recumbency. The corner of a nonscreen film is placed above the tongue as far into the oral cavity as possible, and the radiographic beam is positioned directly above the nasal cavity (Figs. 14.1 and 14.2). The frontal sinus view is obtained with the animal in dorsal recumbency. Adhesive tape can be used to support the body and draw the forelimbs caudally, out of the field. The head is positioned perpendicular to the spine and the table by drawing the muzzle toward the sternum with adhesive tape. Endotracheal tube and anesthetic tubes are displaced lateral to the head to remove them from the field. A radiographic beam is positioned directly above the nasal cavity and frontal sinuses (Figs. 14.3 and 14.4). The frontal sinus view identifies disease involving the frontal sinuses, which in diseases such as aspergillosis or neoplasia may be the only area of disease involvement. The tympanic bullae are best seen with an open-mouth projection in which the beam is aimed at the base of the skull (Figs. 14.5 and 14.6). The bullae are also evaluated individually by lateral-oblique films, offsetting each bulla from the surrounding skull.

Nasal radiographs are evaluated for increased fluid density, loss of turbinates, lysis of facial bones, radiolucency at the tips of the tooth roots, and the presence of radiodense foreign bodies (Box 14.1). Increased fluid density can be caused by mucus, exudate, blood, or soft tissue masses such as polyps, tumors, or granulomas. Soft tissue masses may appear localized, but the surrounding fluid often obscures their borders. A thin rim of lysis surrounding a focal density may represent a foreign body. Fluid density within the frontal sinuses may represent normal mucus accumulation caused by obstruction of drainage into the nasal cavity, extension of disease into the frontal sinuses from the nasal cavity, or primary disease involving the frontal sinuses.

Loss of the normal fine turbinate pattern in combination with increased fluid density within the nasal cavity can occur



FIG 14.1
Positioning of a dog for intraoral radiographs.

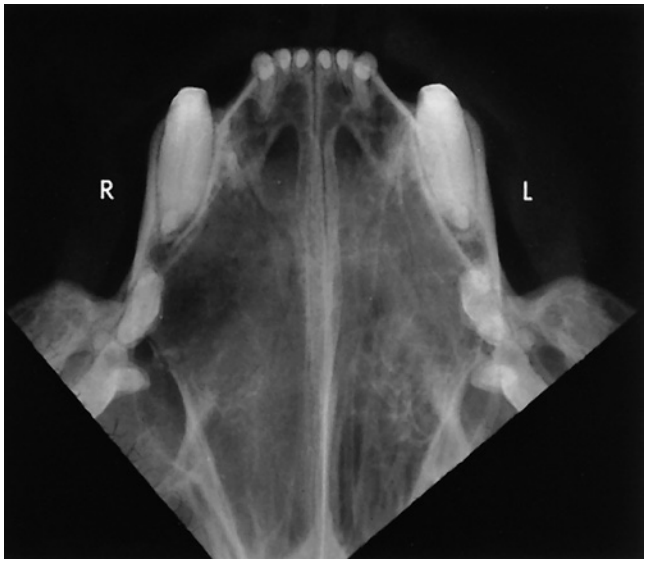


FIG 14.2
Intraoral radiograph of a cat with carcinoma. Normal fine turbinate pattern is visible on the left side *(L)* of the nasal cavity and provides a basis for comparison with the right side *(R)*. The turbinate pattern is less apparent on the right side, and an area of turbinate lysis can be seen adjacent to the first premolar.

with chronic inflammatory conditions of any etiology. Early neoplastic changes can also be associated with an increase in soft tissue density and destruction of the turbinates (see Figs. 14.2 and 14.4). More aggressive neoplastic changes may include marked lysis or deformation of the vomer and/or facial bones. Multiple, well-defined lytic zones within the nasal cavity and increased radiolucency in the rostral portion of the nasal cavity suggest aspergillosis (Fig. 14.7). The vomer bone may be roughened but is rarely destroyed. Previous traumatic fracture of the nasal bones and secondary osteomyelitis can also be detected radiographically.



FIG 14.3
Positioning of a dog for frontal sinus radiographs. The endotracheal and anesthetic tubes are displaced laterally in this instance by taping them to an upright metal cylinder.

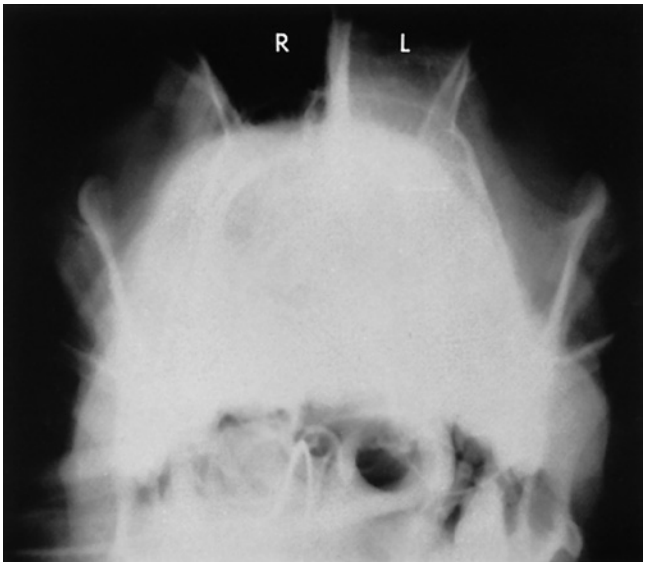


FIG 14.4
Frontal sinus view of a dog with a nasal tumor. The left frontal sinus *(L)* has increased soft tissue density compared with the air-filled sinus on the right side *(R)*.



FIG 14.5
Positioning of a cat for open-mouth projection of the tympanic bullae. The beam *(arrow)* is aimed through the mouth toward the base of the skull. Adhesive tape *(t)* is holding the head and mandible in position.



FIG 14.6
Radiograph obtained from a cat with nasopharyngeal polyp using the open-mouth projection demonstrated in Fig. 14.5. The left bulla has thickening of bone and increased fluid density, indicating bulla osteitis and probable extension of the polyp.

BOX 14.1

Radiographic Signs of Common Nasal Diseases*

Feline Chronic Rhinosinusitis

Soft tissue opacity within nasal cavity, possibly asymmetric
Mild turbinate lysis
Soft tissue opacity in frontal sinus(es)

Nasopharyngeal Polyp

Soft tissue opacity above soft palate
Soft tissue opacity within nasal cavity, usually unilateral
Mild turbinate lysis possible
Bulla osteitis: soft tissue opacity within bulla, thickening of bone

Nasal Neoplasia

Soft tissue opacity, possibly asymmetric
Turbinate destruction
Vomer bone and/or facial bone destruction
Soft tissue mass external to facial bones

Nasal Aspergillosis

Well-defined lucent areas within the nasal cavity
Increased radiolucency rostrally
Increased soft tissue opacity possibly also present
No destruction of vomer or facial bones, although signs often bilateral
Vomer bone sometimes roughened
Fluid density within the frontal sinus; frontal bones sometimes thickened or moth-eaten

Cryptococcosis

Soft tissue opacity, possibly asymmetric
Turbinate lysis
Facial bone destruction
Soft tissue mass external to facial bones

Canine Chronic/Lymphoplasmacytic Rhinitis

Soft tissue opacity
Lysis of nasal turbinates, especially rostrally

Allergic Rhinitis

Increased soft tissue opacity
Mild turbinate lysis possible

Tooth Root Abscesses

Radiolucency adjacent to tooth roots, commonly apically

Foreign Bodies

Mineral and metallic dense foreign bodies readily identified
Plant foreign bodies: focal, ill-defined, increased soft tissue opacity
Lucent rim around abnormal tissue (rare)

*Note that these descriptions represent typical cases and are not specific findings.

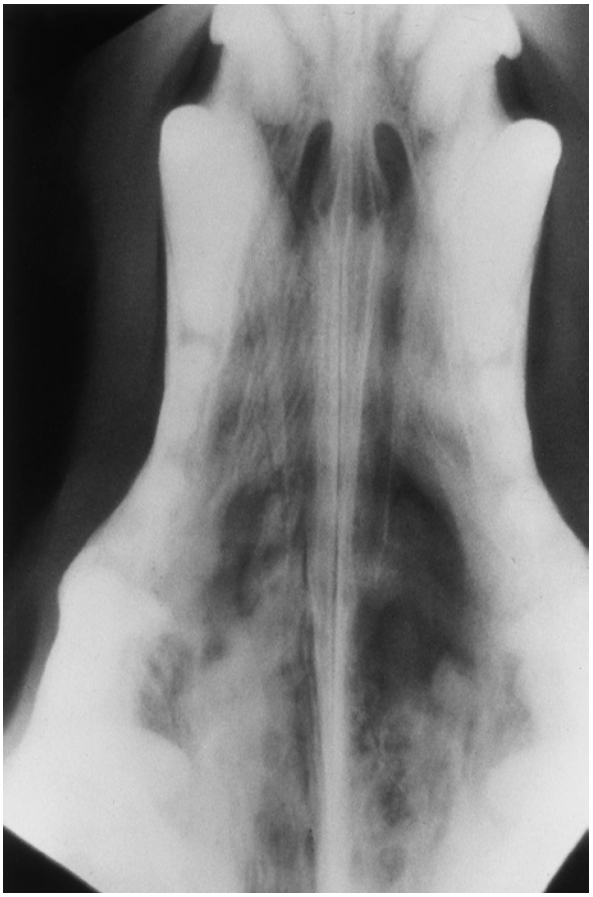


FIG 14.7
Intraoral radiograph of a dog with nasal aspergillosis. Focal areas of marked turbinate lysis are present on both sides of the nasal cavity. The vomer bone remains intact.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

CT provides excellent visualization of the nasal turbinates, nasal septum, hard palate, and cribriform plate (Fig. 14.8). In cats CT is also useful for determining middle ear involvement with nasopharyngeal polyps or other nasal disease. CT is more accurate than conventional radiography in assessing the extent of neoplastic disease insofar as it allows more accurate localization of mass lesions for subsequent biopsy than nasal radiography, and it is instrumental for radiotherapy treatment planning. Determination of the integrity of the cribriform plate is important in treatment planning for nasal aspergillosis. CT may also identify the presence of lesions in animals with undiagnosed nasal disease when other techniques have failed. Typical lesions are as described in Box 14.1. MRI may be more accurate than CT in the assessment of soft tissues, such as nasal neoplasia.

RHINOSCOPY

Rhinoscopy allows visual assessment of the nasal cavity through the use of a rigid or flexible endoscope or an otoscopic cone. Rhinoscopy is used to visualize and remove foreign bodies; to grossly assess the nasal mucosa for the presence of inflammation, turbinate erosion, mass lesions, fungal plaques, and parasites; and to aid in the collection of nasal specimens for histopathologic examination and culture. Complete rhinoscopy always includes a thorough examination of the oral cavity and caudal nasopharynx,

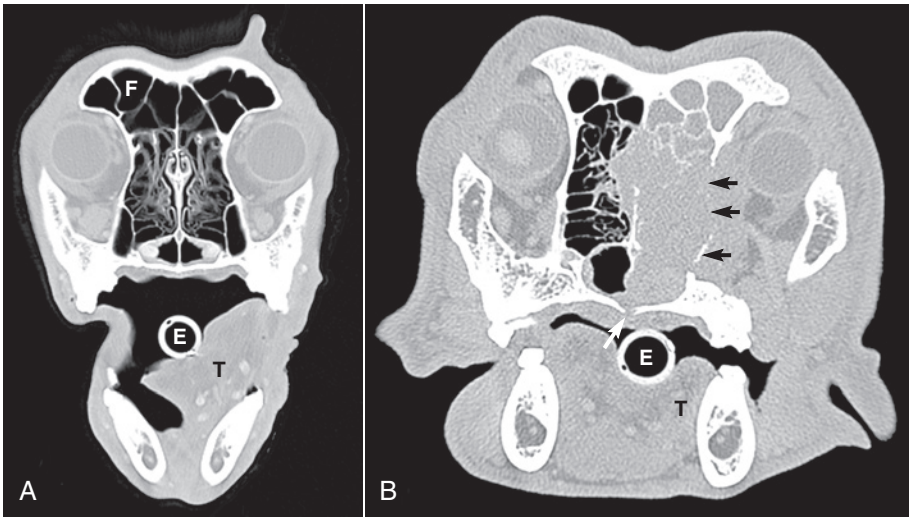


FIG 14.8
Computed tomography scans of the nasal cavity of two different dogs at the level of the eyes. **(A)** Normal nasal turbinates and intact nasal septum are present. **(B)** Neoplastic mass is present within the right cavity; it is eroding through the hard palate *(white arrow)*, the frontal bone into the retrobulbar space *(small black arrows)*, and the nasal septum. The tumor also extends into the right frontal sinus. *E,* Endotracheal tube; *F,* frontal sinus; *T,* tongue.

in addition to visualization of the nasal cavity through the external nares.

The extent of visualization depends on the quality of the equipment and the outside diameter of the rhinoscope. A narrow (2- to 3-mm diameter), rigid fiberoptic endoscope provides good visualization through the external nares in most patients. Endoscopes without biopsy or suction channels are preferable because of their small outside diameter. Some of these systems are relatively inexpensive. Scopes designed for arthroscopy, cystoscopy, and sexing of birds also work well. In medium-sized to large dogs, a flexible pediatric bronchoscope (e.g., 4-mm outer diameter) can be used. Flexible endoscopes are now available in smaller sizes, similar to small rigid scopes, although they are relatively more expensive and fragile. If an endoscope is not available, the rostral region of the nasal cavity can be examined with an otoscope. Human pediatric otoscopic cones (2- to 3-mm diameter) can be purchased for examining cats and small dogs.

General anesthesia is required for rhinoscopy. Rhinoscopy is usually performed immediately after nasal imaging unless a foreign body is strongly suspected. The oral cavity and caudal nasopharynx should be assessed first. During the oral examination, the hard and soft palates are visually examined and palpated for deformation, erosions, or defects, and the gingival sulci are probed for fistulae.

The caudal nasopharynx is evaluated for the presence of nasopharyngeal polyps, neoplasia, foreign bodies, and strictures (stenosis). Foreign bodies, particularly grass or plant material, are commonly found in this location in cats and occasionally in dogs. The caudal nasopharynx is best visualized with a flexible endoscope passed into the oral cavity and retroflexed around the soft palate (Figs. 14.9 through 14.11).

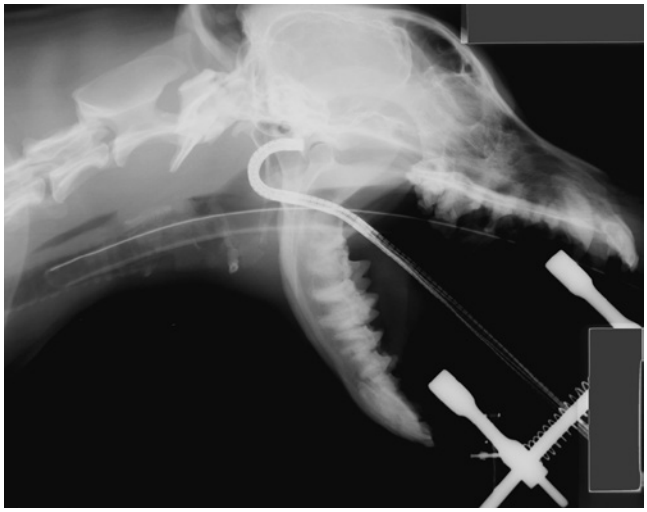


FIG 14.9
The caudal nasopharynx is best examined with a flexible endoscope that is passed into the oral cavity and retroflexed 180 degrees around the edge of the soft palate, as shown in this radiograph.

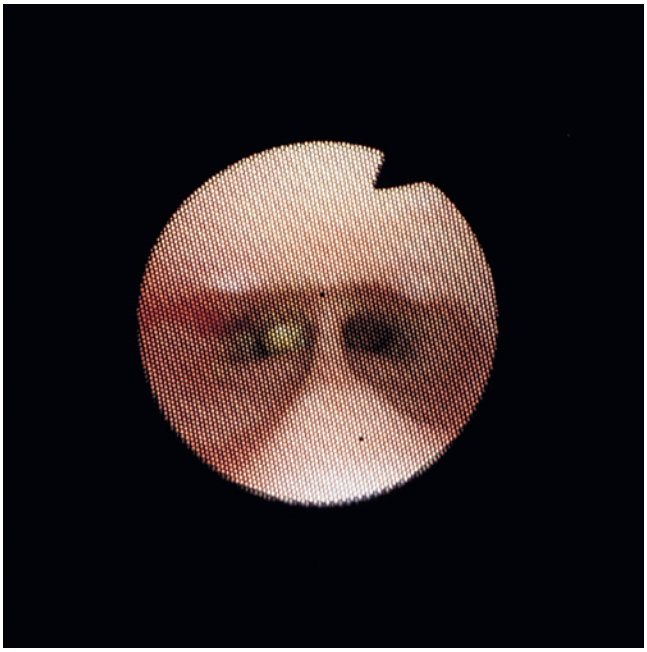


FIG 14.10
View of the internal nares obtained by passing a flexible bronchoscope around the edge of the soft palate in a dog with sneezing. A small white object is seen within the left nasal cavity adjacent to the septum. Note that the septum is narrow and the right internal naris is oval in shape and is not obstructed. On removal, the object was found to be a popcorn kernel. The dog had an abnormally short soft palate, and the kernel presumably entered the caudal nasal cavity from the oropharynx.

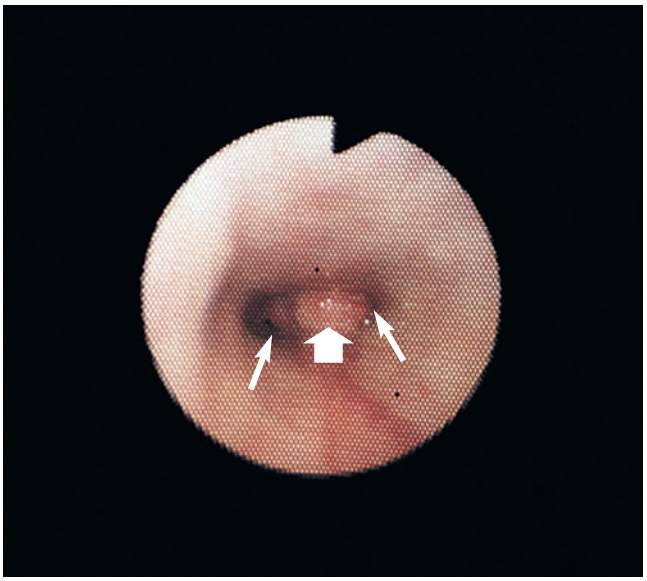


FIG 14.11
View of the internal nares *(thin arrows)* obtained by passing a flexible bronchoscope around the edge of the soft palate in a dog with nasal discharge. A soft tissue mass *(broad arrow)* is blocking the normally thin septum and is partially obstructing the airway lumens. Compare this view with the appearance of the normal septum and the right internal naris in Fig. 14.10.

Alternatively, the caudal nasopharynx can be evaluated with the aid of a dental mirror, penlight, and spay hook, which is attached to the caudal edge of the soft palate and pulled forward to improve visualization of the area. It may be possible to visualize nasal mites of infected dogs by observing the caudal nasopharynx while flushing anesthetic gases (e.g., isoflurane and oxygen) through the nares.

Rhinoscopy must be performed patiently, gently, and thoroughly to maximize the likelihood of identifying gross abnormalities and to minimize the risk of hemorrhage. The more normal side of the nasal cavity is examined first. The tip of the scope is passed through the naris with the tip pointed medially. Each nasal meatus is evaluated, beginning ventrally and working dorsally. Each nasal meatus should be examined as far caudally as the scope can be passed without trauma.

Although the rhinoscope can be used to evaluate the large chambers of the nose, many of the small recesses cannot be examined, even with the smallest endoscopes. Thus disease or a foreign body may be missed if only these small recesses are involved. Swollen and inflamed nasal mucosa, hemorrhage caused by the procedure, and the accumulation of exudate and mucus can also interfere with visualization of the nasal cavity. Foreign bodies and masses are frequently coated and effectively hidden by seemingly insignificant amounts of mucus, exudate, or blood. The tenacious material must be removed using a rubber catheter with the tip cut off attached to a suction unit. No catheter should ever be passed blindly into the nasal cavity beyond the level of the medial canthus of the eye to avoid entering the cranial vault through the cribriform plate.

If necessary, saline flushes can also be used, although resulting fluid bubbles may further interfere with visualization. Some clinicians prefer to maintain continuous saline infusion of the nasal cavity using a standard intravenous administration set attached to a catheter or, if available, the biopsy channel of the rhinoscope. The entire examination is done "underwater."

Particular care must be exercised to avoid aspiration of blood or saline into the lungs, particularly if saline is infused. The clinician must be sure the endotracheal tube cuff is fully inflated and the back of the pharynx is packed with gauze. The gauze should be checked frequently and replaced if saturated. The clinician must be careful not to overinflate the endotracheal tube cuff, which could result in a tracheal tear.

The nasal mucosa is normally smooth and pink, with a small amount of serous to mucoid fluid present along the mucosal surface. Potential abnormalities visualized with the rhinoscope include inflammation of the nasal mucosa; mass lesions; erosion of the turbinates (Fig. 14.12, *A*); mats of fungal hyphae (see Fig. 14.12, *B*); foreign bodies; and, rarely, nasal mites or *Capillaria* worms (Fig. 14.13). Differential diagnoses for gross rhinoscopic abnormalities are provided in Box 14.2.

The location of any abnormality should be noted, including the meatus involved (common, ventral, middle, dorsal), the medial-to-lateral orientation within the meatus, and the distance caudal from the naris. Exact localization is critical for directing instruments for the retrieval of foreign bodies or nasal biopsy specimens should visual guidance become impeded by hemorrhage or size of the cavity.

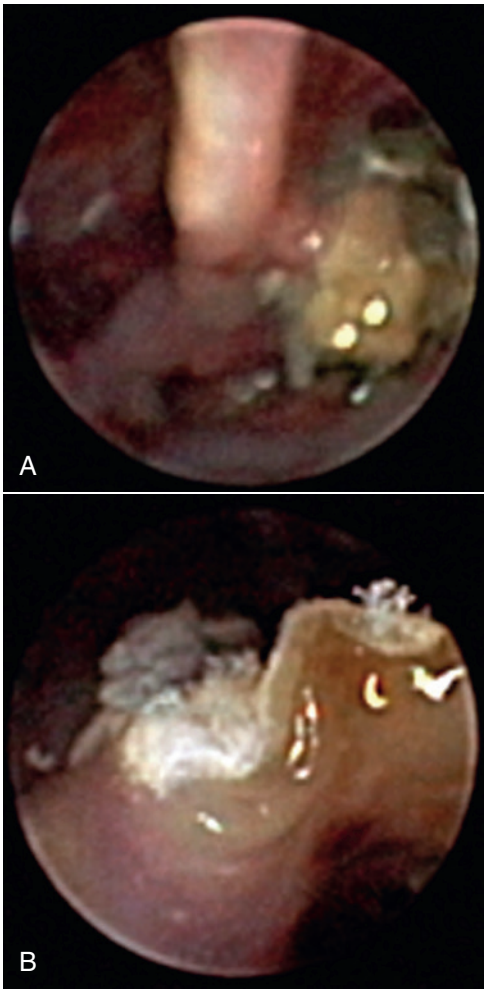


FIG 14.12
(A) Rhinoscopic view through the external naris of a dog with aspergillosis showing erosion of turbinates and a green-brown granulomatous mass. **(B)** A closer view of the fungal mat shows white, filamentous structures (hyphae).

FRONTAL SINUS EXPLORATION

Occasionally the primary site of disease is the frontal sinuses, most often in dogs with aspergillosis. Boney destruction may be sufficient to allow visualization and sampling by rhinoscopy through the external naris. However, in cases with evidence of frontal sinus involvement on imaging studies and the absence of a diagnosis through rhinoscopy and biopsy, surgical exploration of the frontal sinus may be necessary.

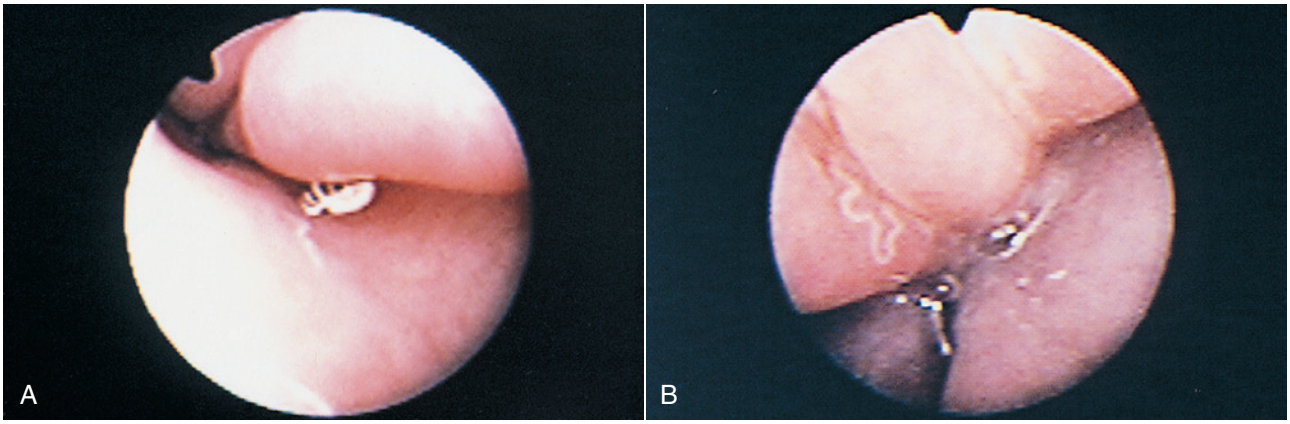


FIG 14.13
Rhinoscopic view through the external naris. **(A)** A single nasal mite is seen in this dog with *Pneumonyssoides caninum*. **(B)** A thin white worm is seen in this dog with *Capillaria (Eucoleus) boehmi*.

BOX 14.2

Differential Diagnoses for Gross Rhinoscopic Abnormalities in Dogs and Cats

- Inflammation (Mucosal Swelling, Hyperemia, Increased Mucus, Exudate)
  - Nonspecific finding; consider all differential diagnoses for mucopurulent nasal discharge (infectious, inflammatory, neoplastic)
- Mass
  - Neoplasia
  - Nasopharyngeal polyp
  - Cryptococcosis
  - Mat of fungal hyphae or fungal granuloma (aspergillosis, penicilliosis, rhinosporidiosis)
- Turbinate Erosion
  - Mild
    - Feline herpesvirus
    - Chronic inflammatory process
  - Marked
    - Aspergillosis
    - Neoplasia
    - Cryptococcosis
    - Penicilliosis
- Fungal Plaques
  - Aspergillosis
  - Penicilliosis
- Parasites
  - Mites: *Pneumonyssoides caninum*
  - Worms: *Capillaria (Eucoleus) boehmi*
- Foreign Bodies

NASAL BIOPSY: INDICATIONS AND TECHNIQUES

Visualization of a foreign body or nasal parasites during rhinoscopy establishes a diagnosis. For many dogs and cats, however, the diagnosis must be based on cytologic, histologic, and microbiologic evaluation of nasal biopsy specimens. Nasal biopsy specimens should be obtained immediately after nasal imaging and rhinoscopy while the animal is still anesthetized. These earlier procedures can help localize the lesion, maximizing the likelihood of obtaining material representative of the primary disease process.

Nasal biopsy techniques include nasal swab, nasal flush, pinch biopsy, and turbinectomy. Fine-needle aspirates can be obtained from mass lesions as described in Chapter 74. Pinch biopsy is the preferred nonsurgical method of specimen collection. It is more likely than nasal swabs or flushes to provide pieces of nasal tissue that extend beneath the superficial inflammation, which is common to many nasal disorders. In addition, the pieces of tissue obtained with this more aggressive method can be evaluated histologically, whereas the material obtained with the less traumatic techniques may be suitable only for cytologic analysis. Histopathologic examination is preferred over cytologic examination in most cases because the marked inflammation that accompanies many nasal diseases makes it difficult to cytologically differentiate primary from secondary inflammation and reactive from neoplastic epithelial cells. Carcinomas can also appear cytologically as lymphoma and vice versa.

Regardless of the technique used (except for nasal swab), the cuff of the endotracheal tube should be inflated (avoiding overinflation) and the caudal pharynx packed with gauze sponges to prevent the aspiration of fluid. Intravenous crystalloid fluids (10-20 mL/kg/h plus replacement of estimated blood loss) are recommended during the procedure to counter the hypotensive effects of prolonged anesthesia and blood loss from hemorrhage after biopsy. Blood-clotting capabilities should be assessed before the more aggressive biopsy techniques are performed if there is any history of hemorrhagic exudate or epistaxis or any other indication of coagulopathy.

NASAL SWAB

The least traumatic techniques are the nasal swab and nasal flush. Unlike the other collection techniques, nasal swabs can be collected from an awake animal. Nasal swabs are useful for identifying cryptococcal organisms cytologically and should be collected early in the evaluation of cats with chronic rhinitis. Other findings are generally nonspecific. Exudate immediately within the external nares or draining from the nares is collected using a cotton-tipped swab. Relatively small swabs are available that can facilitate specimen collection from cats with minimal discharge. The swab is then rolled on a microscope slide. Routine cytologic stains are generally used, although India ink can be applied to reveal cryptococcal organisms (see Chapter 97).

NASAL FLUSH

Nasal flush is a minimally invasive technique. A soft catheter is positioned in the caudal region of the nasal cavity via the oral cavity and internal nares, with the tip of the catheter pointing rostrally. With the animal in sternal recumbency and the nose pointed toward the floor, approximately 100 mL of sterile saline solution is forcibly injected in pulses by syringe. The fluid exiting the external nares is collected in a bowl and can be examined cytologically. Occasionally nasal mites can be identified in nasal flushings. Magnification or placement of dark paper behind the specimen for contrast may be needed to visualize the mites. A portion of fluid can also be filtered through a gauze sponge. Large particles trapped in the sponge can be retrieved and submitted for histopathologic analysis. These specimens are often insufficient for providing a definitive diagnosis.

PINCH BIOPSY

Pinch biopsy is the author's preferred method of nasal biopsy. In the pinch biopsy technique, alligator cup biopsy forceps (minimum size, 2 × 3 mm) are used to obtain pieces of nasal mucosa for histologic evaluation (Fig. 14.14). Full-thickness tissue specimens can be obtained, and guided specimen collection is more easily performed with this technique than with previously described methods. When possible, the biopsy forceps are passed adjacent to a rigid endoscope and directed to any gross lesions. If a flexible scope is used, biopsy instruments can be passed through the biopsy channel of the endoscope. The resulting specimens are extremely small and may not be of sufficient quality for diagnostic purposes. Larger alligator forceps are preferred. If lesions are not present grossly but are present radiographically or by CT, the biopsy instrument can be guided using the relationship of the lesion to the upper teeth.

After the first piece is taken, bleeding will prevent further visual guidance; therefore the forceps are passed blindly to the position identified during rhinoscopic examination (e.g., meatus involved and depth from external naris). If a mass is present, the forceps are passed in a closed position until just before the mass is reached. The forceps are then opened and passed a short distance farther until resistance is felt. Larger forceps, such as a mare uterine biopsy instrument, are useful for collecting large volumes of tissue from medium-sized to large dogs with nasal masses. *No forceps should ever be passed into the nasal cavity deeper than the level of the medial canthus of the eye without visual guidance to keep from penetrating the cribriform plate.*

A minimum of six tissue specimens (using 2 × 3-mm forceps or larger) should be obtained from any lesion. If no

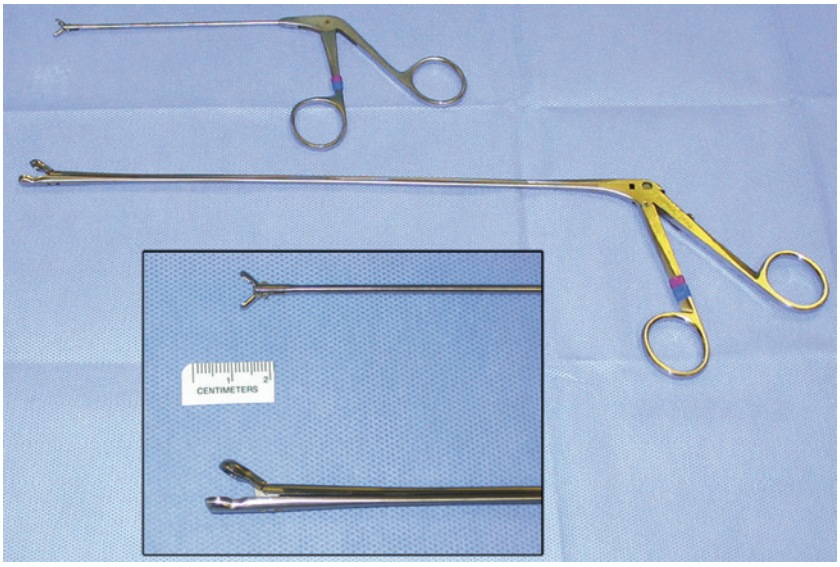


FIG 14.14
Cup biopsy forceps are available in different sizes. To obtain sufficient tissue, a minimum size of 2 × 3 mm is recommended. The larger forceps are particularly useful for obtaining biopsy specimens from nasal masses in dogs.

localizable lesion is identified radiographically or rhinoscopically, multiple biopsy specimens (usually 6-10) are obtained randomly from both sides of the nasal cavity.

TURBINECTOMY

Turbinectomy provides the best tissue specimens for histologic examination and allows the clinician to remove abnormal or poorly vascularized tissues, debulk fungal granulomas, and place drains for subsequent topical nasal therapy. Turbinectomy is performed through a rhinotomy incision and is a more invasive technique than those previously described. Turbinectomy is a reasonably difficult surgical procedure that should be considered only when other less invasive techniques have failed to establish the diagnosis. Potential operative and postoperative complications include pain, excessive hemorrhage, inadvertent entry into the cranial vault, and recurrent nasal infections. Cats may be anorectic postoperatively. Placement of an esophagostomy or gastrostomy tube (see Chapter 28) should be considered if necessary to provide a means for meeting nutritional requirements during the recovery period. (See Suggested Readings in Chapter 13 for information on the surgical procedure.)

Complications

The major complication associated with nasal biopsy is hemorrhage. The severity of hemorrhage depends on the method used to obtain the biopsy, but even with aggressive techniques the hemorrhage is rarely life-threatening. When any technique is used, the floor of the nasal cavity is avoided to prevent damage to major blood vessels. For minor hemorrhage, the rate of administration of intravenous fluids should be increased and manipulations within the nasal cavity should be stopped until the bleeding subsides. Cold saline solution with or without diluted epinephrine (1:100,000) can be gently infused into the nasal cavity. Persistent severe hemorrhage can be controlled by packing the nasal cavity with umbilical. The tape must be packed through the nasopharynx as well as through the external nares, or the blood will only be redirected. Similarly, placing swabs or gauze in the external nares serves only to redirect blood caudally. In the rare event of uncontrolled hemorrhage, the carotid artery on the involved side can be ligated without subsequent adverse effects. Rhinotomy should not be attempted. In the vast majority of animals, only time or cold saline infusions are required to control hemorrhage. The fear of severe hemorrhage should not prevent the collection of good-quality tissue specimens.

Trauma to the brain is prevented by never passing any object into the nasal cavity beyond the level of the medial canthus of the eye without visual guidance. The distance from the external nares to the medial canthus is noted by holding the instrument or catheter against the face, with the tip at the medial canthus. The level of the nares is marked on the instrument or catheter with a piece of tape or marking pen. The object should never be inserted beyond that mark.

Aspiration of blood, saline solution, or exudate into the lungs must be avoided. A cuffed endotracheal tube should be in place during the procedure, and the caudal pharynx should be packed with gauze after visual assessment of the oral cavity and nasopharynx. The cuff should be sufficiently inflated to prevent audible leakage of air during gentle compression of the reservoir bag of the anesthesia machine. Overinflation of the cuff may lead to tracheal trauma or tear. The nose is pointed toward the floor over the end of the examination table, allowing blood and fluid to drip out from the external nares after rhinoscopy and biopsy. Finally, the caudal pharynx is examined during gauze removal and before extubation for visualization of continued accumulation of fluid. Gauze sponges are counted during placement and then re-counted during removal so that none are inadvertently left behind.

NASAL CULTURES: SAMPLE COLLECTION AND INTERPRETATION

Microbiologic cultures of nasal specimens are often performed but can be difficult to interpret. Aerobic and anaerobic bacterial cultures, mycoplasmal cultures, and fungal cultures can be performed on material obtained by swab, nasal flush, or tissue biopsy. However, a wide range of organisms that may be pathogenic in some settings can be present in the proximal nasal cavity in healthy dogs and cats, including *Pseudomonas, Mycoplasma,* and *Aspergillus* organisms, along with a variety of other aerobic and anaerobic bacteria and fungi. Thus bacterial or fungal growth from nasal specimens does not necessarily confirm the presence of infection.

Cultures should be performed on specimens collected within the caudal nasal cavity of anesthetized patients. Bacterial growth from superficial specimens, such as nasal discharge or swabs inserted into the external nares of unanesthetized patients, is unlikely to be clinically significant. It is difficult for a culture swab to be passed into the caudal nasal cavity without its being contaminated with superficial (insignificant) organisms. Guarded specimen swabs can prevent contamination but are relatively expensive and may be too long to safely extrude into the nasal cavity of cats and small dogs. Alternatively, mucosal biopsies from the caudal nasal cavity can be obtained for culture using sterilized biopsy forceps; the results may be more indicative of true infection than those from swabs because, in theory, the organisms have invaded the tissues. Superficial contamination may still occur.

Regardless of the method used, the growth of many colonies of one or two types of bacteria rather than the growth of many different organisms more likely reflects infection. The microbiology laboratory should be asked to report all growth. Otherwise, the laboratory may report only one or two organisms that more often are pathogenic and provide misleading information about the relative purity of the culture. The presence of septic inflammation based on histologic examination of nasal specimens and a positive response to antibiotic therapy support a diagnosis of bacterial infection contributing to clinical signs. Although bacterial rhinitis is rarely a

primary disease entity, improvement in nasal discharge may be seen if the bacterial component of the problem is treated; however, the improvement is generally transient unless the underlying disease process can be corrected. Some animals in which a primary disease process is never identified or cannot be corrected (e.g., cats with chronic rhinosinusitis) respond well to long-term antibiotic therapy. Sensitivity data from bacterial cultures considered to represent significant infection may help in antibiotic selection. (See Chapter 15 for further therapeutic recommendations.)

The role of *Mycoplasma* spp. in respiratory tract infections of dogs and cats is still being elucidated, although a recent systematic review found a significant association between the isolation of *Mycoplasma felis* and upper respiratory tract signs in cats (LeBoedec, 2017). Cultures or polymerized chain reaction (PCR) for *Mycoplasma* spp. and treatment with appropriate antibiotics are a consideration for cats with chronic rhinosinusitis.

A diagnosis of nasal aspergillosis or penicilliosis requires the presence of several supportive signs, and fungal cultures are indicated whenever fungal disease is one of the differential diagnoses. The growth of *Aspergillus* or *Penicillium* organisms is considered along with other clinical data, such as radiographic and rhinoscopic findings, and serologic titers. Fungal growth supports a diagnosis of mycotic rhinitis only when other data also support the diagnosis. The fact that fungal infection occasionally occurs secondary to nasal tumors should not be overlooked during initial evaluation and monitoring of therapeutic response. The sensitivity of fungal culture can be greatly enhanced by collecting a swab or biopsy for culture directly from a fungal plaque or granuloma with rhinoscopic guidance.

Suggested Readings

Harcourt-Brown N. Rhinoscopy in the dog, part I: anatomy and techniques. *In Pract*. 2006;18:170.

LeBoedec K. A systematic review and meta-analysis of the association between Mycoplasma spp and upper and lower respiratory tract disease in cats. *J Am Vet Med Assoc*. 2017;250:397.

McCarthy TC. Rhinoscopy: the diagnostic approach to chronic nasal disease. In: McCarthy TR, ed. *Veterinary endoscopy for the small animal practitioner*. St Louis: Saunders; 2005:137.

Saylor DK, Williams JE. Rhinoscopy. In: Tams TR, Rawlins CA, eds. *Small animal endoscopy*. 3rd ed. Elsevier Mosby; 2011:563.

Wilson M, et al. Small animal skull and nasofacial radiography, including the nasal cavity and frontal sinuses. *Today's Veterinary Practice*. 2014;4:47.

CHAPTER 15

Disorders of the Nasal Cavity



FELINE UPPER RESPIRATORY INFECTION

Etiology

Upper respiratory infections (URIs) are common in cats. Feline herpesvirus (FHV), also known as *feline rhinotracheitis virus* and *feline calicivirus (FCV),* cause nearly 90% of these infections. *Bordetella bronchiseptica* and *Chlamydophila felis* (previously known as *Chlamydia psittaci*) are less commonly involved. Other viruses and *Mycoplasmas* (particularly *M. felis*) may play a primary or secondary role, whereas other bacteria are considered secondary pathogens.

Cats become infected through contact with actively infected cats, carrier cats, and fomites. Cats that are young, stressed, or immunosuppressed are most likely to develop clinical signs. Infected cats often become carriers of FHV or FCV after resolution of the clinical signs. The duration of the carrier state is not known, but it may last from weeks to years. *Bordetella* and *M. felis* can be isolated from asymptomatic cats, although the effectiveness of transmission of disease from such cats is not known.

Clinical Features

Clinical manifestations of feline URI can be acute, chronic and intermittent, or chronic and persistent. Acute disease is most common. The clinical signs of acute URI include fever, sneezing, serous or mucopurulent nasal discharge, conjunctivitis and ocular discharge, hypersalivation, anorexia, and dehydration. FHV can also cause corneal ulceration, abortion, and neonatal death, whereas FCV can cause oral ulcerations, interstitial pneumonia, or polyarthritis. Rare, short-lived outbreaks of highly virulent strains of calicivirus have been associated with severe upper respiratory disease, signs of systemic vasculitis (facial and limb edema progressing to focal necrosis), and high rates of mortality. *Bordetella* can cause cough and, in young kittens, pneumonia. *Chlamydophila* infections are commonly associated with conjunctivitis.

Some cats that recover from the acute disease have periodic recurrence of acute signs, usually in association with stressful or immunosuppressive events. Other cats may have chronic, persistent signs, most notably serous to mucopurulent nasal discharge with or without sneezing. Chronic nasal discharge can presumably result from persistence of an active viral infection or from irreversible damage to turbinates and mucosa by FHV; the latter predisposes the cat to an exaggerated response to irritants and secondary bacterial rhinitis. Unfortunately, correlation between tests to confirm exposure to or the presence of viruses and clinical signs is poor (Johnson et al., 2005). Because the role of viral infection in cats with chronic rhinosinusitis is not well understood, cats with chronic signs of nasal disease are discussed in the later section on feline chronic rhinosinusitis.

Diagnosis

Acute URI is usually diagnosed on the basis of history and physical examination findings. Specific tests that are available to identify FHV, FCV, *Bordetella, Mycoplasma,* and *Chlamydophila* organisms include polymerase chain reaction (PCR), and virus isolation procedures or bacterial cultures. PCR testing and virus isolation can be performed on pharyngeal, conjunctival, or nasal swabs (using sterile polyester swabs) or on tissue specimens such as tonsillar biopsy specimens or mucosal scrapings. Tissue specimens are usually preferred. Specimens are placed in appropriate transport media. Routine cytologic preparations of conjunctival smears can be examined for intracytoplasmic inclusion bodies suggestive of *Chlamydophila* infection, but these findings are nonspecific. Although routine bacterial cultures of the oropharynx can be used to identify *Bordetella,* the organism can be found in both healthy and infected cats. Regardless of the method used, close coordination with the diagnostic laboratory on specimen collection and handling is recommended for optimal results.

Tests to identify specific agents are particularly useful in cattery outbreaks in which the clinician is asked to recommend specific preventive measures. Multiple cats, both with and without clinical signs, should be tested when cattery surveys are performed. Test panels are commercially available to probe specimens for multiple respiratory pathogens by PCR. Specific diagnostic tests are less useful for testing

individual cats with acute disease because most cats recover uneventfully. It may be of value to test individual cats with severe or persistent signs because specific antimicrobial treatment for FHV, *Chlamydia,* or *Mycoplasma* can be prescribed. False-negative results may occur if signs are the result of permanent nasal damage or if the specimen does not contain the agent, and positive results may merely reflect a carrier cat that has a concurrent disease process causing the clinical signs.

Treatment

In most cats URI is a self-limiting disease, and treatment of cats with acute signs includes appropriate supportive care. Fluid therapy and nutritional supplementation should be provided when necessary. Dried mucus and exudate should be cleaned from the face and nares. The cat can be placed in a steamy bathroom or a small room with a vaporizer for 15 to 20 minutes two or three times daily to help clear excess secretions. Severe nasal congestion is treated with pediatric topical decongestants such as 0.25% phenylephrine or 0.025% oxymetazoline. A drop is gently placed in each nostril daily for a maximum of 3 days. If longer therapy is necessary, the decongestant is withheld for 3 days before another 3-day course is begun to prevent possible rebound congestion after withdrawal of the drug (based on problems with rebound congestion that occurs in people).

The Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases recommends that antibiotic treatment be considered during the first 10 days of clinical signs only if fever, lethargy, or anorexia is present concurrently with mucopurulent nasal discharge (Lappin et al., 2017). This group recommends doxycycline (5 mg/kg, PO, q12h; or 10 mg/kg, PO, q24h; always followed by a bolus of water or food) as the first-line option because of its efficacy against *Chlamydia* and *Mycoplasma*. Amoxicillin (22 mg/kg, PO, q8-12h given orally) is considered an acceptable alternative when those organisms are not highly suspected. Doxycycline should be administered for 42 days in cats infected with *Chlamydophila felis* or *Mycoplasma* spp. to eliminate detectable organisms (Hartmann et al., 2008). Azithromycin (5-10 mg/kg q12h for 1 day, then every 3 days, orally) can be prescribed for cats that are difficult to medicate.

Cats with FHV infection may benefit from treatment with famcylovir. Several clinical trials have shown therapeutic benefit. In a placebo-controlled trial, 26 cats receiving a dosage of 90 mg/kg three times daily had significantly reduced clinical signs (Thomasy et al., 2016). In these cats, the time to clinical improvement was 3 to 28 days (median, 7 days). Side effects occurred in 15% of cats receiving this dosage and were primarily gastrointestinal, including diarrhea, vomiting, anorexia, and weight loss. Experience with a larger number of cats and chronic administration of drug is needed to fully understand the potential risks of treatment with this drug. Thomasy and Maggs (2016) recommend that cats should be closely monitored, and that CBC, serum biochemistry panel, and urinalysis be considered for those cats with known concurrent disease and for cats expected to receive famcyclovir for long periods. They also state that twice-daily dosing at 90 mg/kg is likely to be sufficient, based on pharmacokinetic studies.

It has been postulated that excessive concentrations of L-lysine may antagonize arginine, a promoter of herpesvirus replication. Lysine (500 mg/cat q12h), obtained from health food stores, is often added to food for the treatment or prevention of FHV. Its effectiveness is not certain (Thomasy and Maggs, 2016).

Chlamydophila infection should be suspected in cats with conjunctivitis as the primary problem and in cats from catteries in which the disease is endemic. Oral antibiotics are administered for a minimum of 42 days. In addition, chloramphenicol or tetracycline ophthalmic ointment should be applied at least three times daily and continued for a minimum of 14 days after signs have resolved.

Corneal ulcers resulting from FHV are treated with topical antiviral drugs, such as trifluridine, idoxuridine, or adenine arabinoside. One drop should be applied to each affected eye five to six times daily for no longer than 2 to 3 weeks. Routine ulcer management is also indicated. Tetracycline or chloramphenicol ophthalmic ointment is administered two to four times daily. Topical atropine is used for mydriasis as needed to control pain. Treatment is continued for 1 to 2 weeks after epithelialization has occurred.

Topical and systemic corticosteroids are contraindicated in cats with acute URI or ocular manifestations of FHV infection. They can prolong clinical signs and increase viral shedding.

Treatment of cats with chronic signs is discussed later with feline chronic rhinosinusitis.

Prevention in the Individual Pet Cat

Prevention of URI in all cats is based on avoiding exposure to the infectious agents (e.g., FHV, FCV, *Bordetella, Mycoplasma,* and *Chlamydophila* organisms) and strengthening immunity against infection. Most household cats are relatively resistant to prolonged problems associated with URIs, and routine health care with regular vaccination using a subcutaneous product is adequate. Vaccination decreases the severity of clinical signs resulting from URIs but does not prevent infection. Owners should be discouraged from allowing their cats to roam freely outdoors.

Subcutaneous modified-live virus vaccines for FHV and FCV are used for most cats and are available in combination with panleukopenia vaccine. These vaccines are convenient to administer, do not result in clinical signs when used correctly, and provide adequate protection for cats that are not heavily exposed to these viruses. These vaccines are not effective in kittens while maternal immunity persists. Kittens are usually vaccinated beginning at 6 to 10 weeks of age and again in 3 to 4 weeks. At least two vaccines must be given initially, with the final vaccine administered after the kitten is 16 weeks old. A booster vaccination is recommended 1 year after the final vaccine in the initial series. Subsequent booster vaccinations are recommended every 3 years, unless

the cat has increased risk of exposure to infection. Detection of FHV and FCV antibodies in the serum of cats is predictive of susceptibility to disease and therefore may be useful in determining the need for revaccination (Lappin et al., 2002). Queens should be vaccinated before breeding.

Subcutaneous modified-live vaccines for FHV and FCV are safe but can cause disease if introduced into the cat by the normal oronasal route of infection. The vaccine should not be aerosolized in front of the cat. Vaccine inadvertently left on the skin after injection should be washed off immediately before the cat licks the area.

Modified-live vaccines should not be used in pregnant queens. Killed products are available for FHV and FCV that can be used in pregnant queens. Killed vaccines have also been recommended for cats with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection.

Modified-live vaccines for FHV and FCV are also available for intranasal administration. Signs of acute URI occasionally occur after vaccination. Attention should be paid to ensure that panleukopenia is included in the intranasal product or that a panleukopenia vaccine is administered subcutaneously.

Vaccines against *Bordetella* or *Chlamydophila* are recommended for use only in catteries or shelters where these infections are endemic. Infections with *Bordetella* or *Chlamydophila* are less common than FHV and FCV infection, and disease resulting from *Bordetella* infections occurs primarily in cats housed in crowded conditions. Furthermore, these diseases can be effectively treated with antibiotics.

Prognosis

The prognosis for cats with acute URI is good. Chronic disease does not develop in most pet cats.

BACTERIAL RHINITIS

Acute bacterial rhinitis caused by *Bordetella bronchiseptica* occurs occasionally in cats (see the section on feline URI) and rarely in dogs (see the section on canine infectious respiratory disease complex in Chapter 21). *Mycoplasma* spp. and *Streptococcus equi,* subsp. *zooepidemicus,* also may act as primary nasal pathogens. In the vast majority of cases, bacterial rhinitis is a *secondary* complication and not a primary disease process. Bacterial rhinitis occurs secondarily to almost all diseases of the nasal cavity. The bacteria that inhabit the nasal cavity in health are quick to overgrow when disease disrupts normal mucosal defenses. Antibiotic therapy often leads to clinical improvement, but the response is usually temporary. Therefore management of dogs and cats with suspected bacterial rhinitis should include a thorough diagnostic evaluation for an underlying disease process, particularly when signs are chronic.

Diagnosis

Most dogs and cats with bacterial rhinitis have mucopurulent nasal discharge. No clinical signs are pathognomonic for bacterial rhinitis, and it is difficult to make a definitive diagnosis because of the diverse flora in the normal nasal cavity. Microscopic evidence of neutrophilic inflammation and bacteria is a nonspecific finding and is found in the majority of animals with nasal signs (Fig. 15.1). Bacterial cultures of swabs or nasal mucosal biopsy specimens collected deep within the nasal cavity can be performed. The growth of many colonies of only one or two organisms may represent significant infection. Growth of many different organisms or small numbers of colonies probably represents normal flora. The microbiology laboratory should be requested to report all growth. Specimens for *Mycoplasma* cultures should be placed in appropriate transport media for culture using specific isolation methods. Beneficial response to antibiotic therapy is often used to support a diagnosis of bacterial involvement.

Treatment

The bacterial component of nasal disease is treated with antibiotic therapy. If growth obtained by bacterial culture is believed to be significant, sensitivity information can be used in selecting antibiotics. Anaerobic organisms may be involved. Broad-spectrum oral antibiotics that may be effective include amoxicillin (22 mg/kg q8-12h) or clindamycin (10 mg/kg q12h). Doxycycline (5 mg/kg q12h or 10 mg/kg q24h; always followed by a bolus of water) is often effective against *Bordetella* and *Mycoplasma* organisms.

For acute infection or in cases in which the primary etiology (e.g., foreign body, diseased tooth root) has been eliminated, antibiotics are administered for 7 to 10 days. Chronic infections require prolonged treatment. Antibiotics are

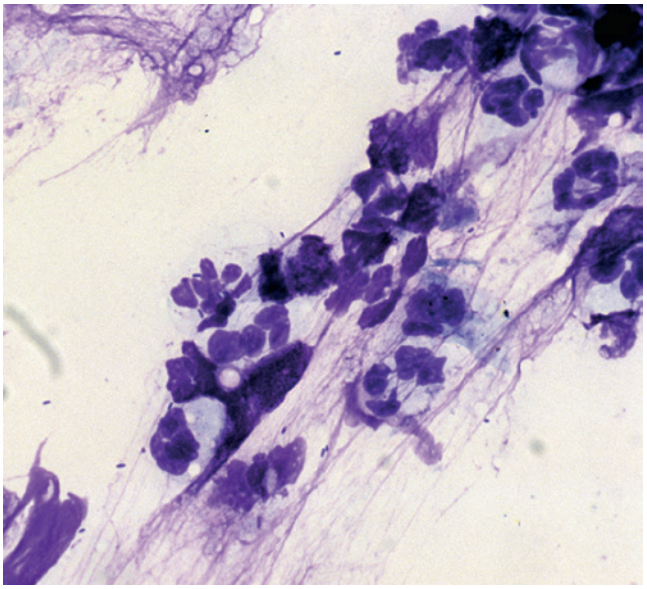


FIG 15.1
A photomicrograph of a slide prepared from a nasal swab of a patient with chronic mucopurulent discharge shows the typical findings of mucus, neutrophilic inflammation, and intracellular and extracellular bacteria. These findings are not specific and generally reflect secondary processes.

administered initially for 1 week. If a beneficial response is seen, the drug is continued for a minimum of 4 to 6 weeks. If signs recur after discontinuation of drug after 4 to 6 weeks, the same antibiotic is reinstituted for even longer periods.

If no response is seen after the initial week of treatment, the drug should be discontinued. Another antibiotic can be tried, although further evaluation for another, as yet unidentified, primary disorder should be pursued. Further diagnostic evaluation is particularly warranted in dogs because, compared with cats, they less frequently have idiopathic disease. Frequent stopping and starting of different antibiotics every 7 to 14 days is not recommended and may predispose the animal to the growth of resistant gram-negative infections.

Prognosis

Bacterial rhinitis is usually responsive to antibiotic therapy. However, long-term resolution of signs depends on the identification and correction of any underlying disease process.

NASAL MYCOSES

CRYPTOCOCCOSIS

Cryptococcus neoformans is a fungal agent that infects cats and, less commonly, dogs. It most likely enters the body through the respiratory tract and, in some animals, may disseminate to other organs. In cats clinical signs usually reflect infection of the nasal cavity, central nervous system (CNS), eyes, or skin and subcutaneous tissues. In dogs signs of CNS involvement are most common. The lungs are commonly infected in both species, but clinical signs of lung involvement (e.g., cough, dyspnea) are rare. Clinical features, diagnosis, and treatment of cryptococcosis are discussed in Chapter 97.

ASPERGILLOSIS

Aspergillus fumigatus is a normal inhabitant of the nasal cavity in many animals. In some dogs and, rarely, cats, it becomes a pathogen. The mold form of the organism can develop into visible fungal plaques that invade the nasal mucosa ("fungal mats") and fungal granulomas. An animal that develops aspergillosis will rarely have another nasal condition such as neoplasia, foreign body, prior trauma, or immune deficiency that predisposes the animal to secondary fungal infection. Most often no underlying disease is identified. Excessive exposure to *Aspergillus* organisms may explain the frequent occurrence of disease in otherwise healthy animals. Another type of fungus, *Penicillium,* can cause signs similar to those of aspergillosis.

Clinical Features

Aspergillosis can cause chronic nasal disease in dogs of any age or breed but is most common in young male dogs. Nasal infection is rare in cats. The discharge can be mucoid, mucopurulent with or without hemorrhage, or purely hemorrhagic. The discharge can be unilateral or bilateral. Sneezing may be reported. Features that are not common, but are highly suggestive of aspergillosis are sensitivity to palpation of the face or depigmentation and ulceration of the external nares (see Fig. 13.2). Lung involvement is not expected.

Systemic aspergillosis in dogs is generally caused by *Aspergillus terreus* and other *Aspergillus* spp. rather than *A. fumigatus*. It is an unusual, generally fatal disease that occurs primarily in German Shepherd Dogs. Nasal signs are not reported.

Diagnosis

No single test result is diagnostic for infection with aspergillosis. The diagnosis is based on the cumulative findings of a comprehensive evaluation of a dog with appropriate clinical signs. As aspergillosis can be an opportunistic infection, underlying nasal disease must also be considered.

Radiographic signs of aspergillosis include well-defined lucent areas within the nasal cavity and increased radiolucency rostrally (see Fig. 14.7). Typically no destruction of the vomer or facial bones occurs, although the bones may appear roughened. However, destruction of these bones or the cribriform plate may occur in dogs with advanced disease. Increased fluid opacity may be present. Fluid opacity within the frontal sinus can represent a site of infection or mucus accumulation from obstructed drainage. The bones surrounding the frontal sinus may be thickened or appear moth-eaten. In some patients the frontal sinus is the only site of infection.

Imaging by computed tomography (CT) is preferred over nasal radiography. The enhanced imaging allows for more accurate assessment of extent of disease. The presence or absence of plaques in the frontal sinuses (Fig. 15.2), integrity



FIG 15.2
Computed tomography scan of a dog with nasal aspergillosis. The right side is unaffected, providing comparison for the abnormalities on the left *(L)*. There is lysis of the nasal turbinates with increased soft-tissue density. Irregularly shaped soft tissue is apparent in the left frontal sinus *(*)*, which was confirmed to be a fungal plaque during frontal sinusotomy performed for debridement and infusion of clotrimazole cream. There is also mild osteitis of the bone surrounding the left frontal sinus.

of the cribriform plate, and extension of disease beyond the nasal cavity impact treatment decisions, as discussed later.

Rhinoscopic abnormalities include erosion of nasal turbinates and fungal plaques, which appear as white-to-green plaques of mold on the nasal mucosa (see Fig. 14.12). Failure to visualize these lesions does not rule out aspergillosis. Confirmation that presumed plaques are indeed fungal hyphae can be achieved by cytology (Fig. 15.3) and culture of material collected by biopsy or swab under visual guidance. During rhinoscopy, plaques are mechanically debulked by scraping or vigorous flushing to increase the efficacy of topical treatment. The frontal sinuses are included in examination and debriding whenever turbinate erosion allows.

Multiple biopsy specimens should be obtained because the mucosa is affected focally or multifocally rather than diffusely. Best results are obtained when mucosa with visible fungus is sampled. Invading *Aspergillus* organisms can generally be seen with routine staining techniques, although special staining can be performed to improve sensitivity. Neutrophilic, lymphoplasmacytic, or mixed inflammation is usually also present.

Results of fungal cultures are difficult to interpret, unless the specimen is obtained from a visualized plaque. The organism can be found in the nasal cavity of normal animals, and false-negative culture results can also occur. A positive culture, in conjunction with other appropriate clinical and diagnostic findings, supports the diagnosis.

Positive serum antibody titers also support a diagnosis of infection. Although titers provide indirect evidence of infection, animals with *Aspergillus* organisms as a normal nasal inhabitant do not usually develop measurable antibodies against the organism. Pomerantz et al. (2007) found that serum antibodies had a sensitivity of 67%, a specificity of 98%, a positive predictive value of 98%, and a negative predictive value of 84% for the diagnosis of nasal aspergillosis.

Treatment

Topical treatment is currently recommended for nasal aspergillosis, after aggressive debridement of fungal plaques. Oral itraconazole is recommended for patients with extension of disease beyond the nasal cavity and frontal sinuses. Oral therapy is simpler to administer than topical therapy but appears to be somewhat less successful, has potential systemic side effects, and requires prolonged treatment. Itraconazole is administered orally at a dose of 5 mg/kg q12h and must be continued for 60 to 90 days or longer. Some clinicians give terbinafine concurrently. In a recent study, dogs with nasal aspergillosis that had failed topical and oral treatment had resolution or significant improvement in clinical signs with oral posaconazole (5 mg/kg q12h), terbinafine (30 mg/kg q12h), and doxycycline (5 mg/kg q12h) (Stewart and Bianco, 2017). Prolonged treatment was necessary with an average duration of 9 months (range 6-18 months). (See Chapter 97 for a complete discussion of these drugs.)

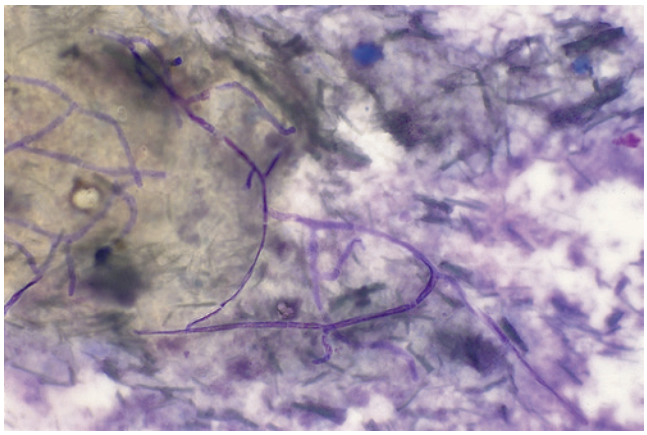


FIG 15.3
Branching hyphae of *Aspergillus fumigatus* from a swab of a visualized fungal plaque.

Successful topical treatment of aspergillosis was originally documented with enilconazole administered through tubes placed surgically into both frontal sinuses and both sides of the nasal cavity. The drug was administered through the tubes twice daily for 7 to 10 days. Subsequently, it was discovered that the over-the-counter drug clotrimazole was equally efficacious when infused through surgically placed tubes over a 1-hour period (70% success with a single treatment; Mathews et al., 1996). During 1-hour infusion, the dogs were kept under anesthesia and the caudal nasopharynx and external nares were packed to allow filling of the nasal cavity. It has since been demonstrated that good distribution of the drug can be achieved in some cases using a noninvasive technique (discussed in the next paragraphs).

Unfortunately, after a full review of the literature, success rate following a single topical treatment with enilconazole or clotrimazole was only 46% (Sharman et al., 2010). As a result, the following adjunctive treatments are currently recommended in addition to noninvasive clotrimazole soaks. Visible fungal plaques are aggressively debrided during rhinoscopy immediately before topical therapy. In dogs with frontal sinus involvement, surgical or endoscopic debridement is performed and clotrimazole cream is packed into the sinuses. All dogs are reevaluated 2 to 3 weeks after treatment. Rhinoscopy, debridement, and topical treatment are repeated if signs persist. In the previously mentioned report (Sharman et al., 2010), 70% of dogs recovered after receiving multiple treatments.

For noninvasive clotrimazole soaks (without the placement of tubes through the frontal sinuses), the animal is anesthetized and oxygenated through a cuffed endotracheal tube. The dog is positioned in dorsal recumbency with the nose pulled down parallel with the table (Figs. 15.4 and 15.5). For a large-breed dog, a 24F Foley catheter with a 5-mL balloon is passed through the oral cavity, around the soft palate, and into the caudal nasopharynx such that the bulb is at the junction of the hard and soft palates. The bulb is inflated with approximately 10 mL of air to ensure a snug fit. A laparotomy sponge is inserted within the oropharynx, caudal to the balloon and ventral to the soft palate, to help hold the balloon in position and to further obstruct the nasal pharynx. Additional laparotomy sponges are packed

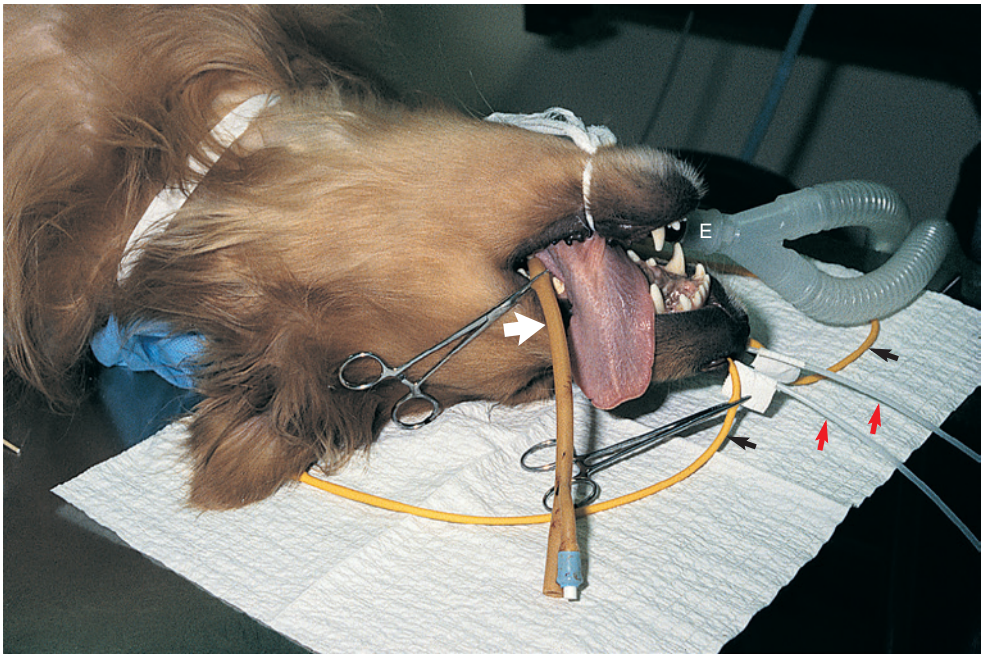


FIG 15.4
Dog with nasal mycotic infection prepared for a 1-hour soak with clotrimazole. A cuffed endotracheal tube is in place *(E)*. A 24F Foley catheter *(broad arrow)* is in the caudal nasopharynx. A 12F Foley catheter *(black arrowheads)* is obstructing each nostril. A 10F polypropylene catheter *(red arrowheads)* is placed midway into each dorsal meatus for infusion of the drug. Laparotomy sponges are used to further pack the caudal nasopharynx around the tracheal tube and the caudal oral cavity.

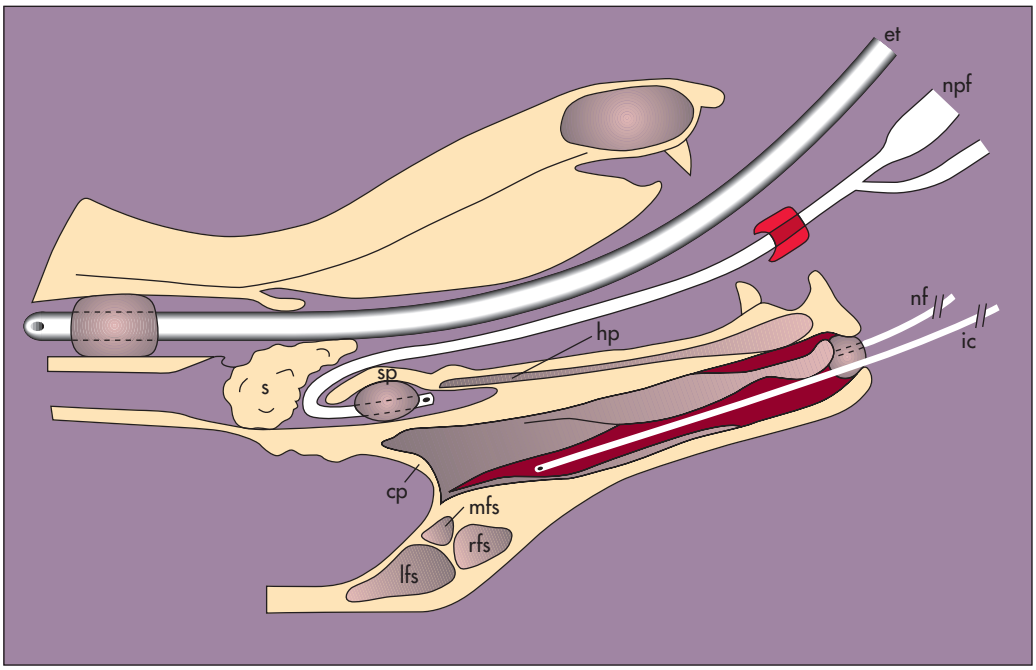


FIG 15.5
Schematic diagram of a cross section of the head of a dog prepared for a 1-hour soak with clotrimazole. *cp,* Cribriform plate; *et,* endotracheal tube; *hp,* hard palate; *ic,* polypropylene infusion catheter; *lfs,* lateral frontal sinus; *mfs,* medial frontal sinus; *nf,* rostral Foley catheter obstructing nostril; *npf,* Foley catheter placed in caudal nasopharynx; *rfs,* rostral frontal sinus; *s,* pharyngeal sponges; *sp,* soft palate. (Reprinted with permission from Mathews KG et al.: Computed tomographic assessment of noninvasive intranasal infusions in dogs with fungal rhinitis, *Vet Surg* 25:309, 1996.)

carefully into the back of the mouth around the tracheal tube to prevent any drug that might leak past the nasopharyngeal packing from reaching the lower airways.

A 10F polypropylene urinary catheter is passed into the dorsal meatus of each nasal cavity to a distance approximately midway between the external naris and the medial canthus of the eye. The correct distance is marked on the catheters with tape to prevent accidental insertion of the catheters too far during the procedure. A 12F Foley catheter with a 5-mL balloon is passed adjacent to the polypropylene catheter into each nasal cavity. The cuff is inflated and pulled snugly against the inside of the naris. A small suture is placed across each naris lateral to the catheter to prevent balloon migration. A gauze sponge is placed between the endotracheal tube and the incisive ducts behind the upper incisors to minimize leakage.

A solution of 1% clotrimazole is administered through the polypropylene catheters. Approximately 30 mL is used for each side in a typical retriever-size dog. Each Foley catheter is checked for filling during the initial infusion and is then clamped when clotrimazole begins to drip from the catheter. The solution is viscous, but excessive pressure is not required for infusion. Additional clotrimazole is administered during the next hour at a rate that results in approximately 1 drop every few seconds from each external naris. In dogs of the size described, a total of approximately 100 to 120 mL will be used.

After the initial 15 minutes, the head is tilted slightly to one side and then the other for 15 minutes each and then back into dorsal recumbency for 15 minutes. After this hour of contact time, the dog is rolled into sternal recumbency with the head hanging over the end of the table and the nose pointing toward the floor. The catheters are removed from the external nares, and the clotrimazole and resulting mucus are allowed to drain. Drainage will usually subside in 10 to 15 minutes. A flexible suction tip may be used to expedite this process. The laparotomy pads are then carefully removed from the nasopharynx and oral cavity and are counted to ensure that all are retrieved. The catheter in the nasopharynx is removed. Any drug within the oral cavity is swabbed or suctioned.

Two potential complications of clotrimazole treatment are aspiration pneumonia and meningoencephalitis. Meningoencephalitis is a risk when clotrimazole, polyethylene glycol carrier, and/or organisms and debris from the nasal cavity make contact with the brain through a compromised cribriform plate. It is difficult to determine the integrity of the cribriform plate before treatment without the aid of CT or magnetic resonance imaging (MRI), although marked radiographic changes in the caudal nasal cavity should increase concern. Fortunately, these complications are not common.

Some dogs have a persistent nasal discharge after treatment for aspergillosis. Most often the discharge indicates incomplete elimination of the fungal infection. However, some dogs may have secondary bacterial rhinitis or sensitivity to inhaled irritants because of the damaged nasal anatomy and mucosa. If recurrence of fungal infection cannot be found and signs persist despite repeated treatments, dogs are managed as described in the section on canine chronic/lymphoplasmacytic rhinitis in this chapter.

Prognosis

The prognosis for dogs with nasal aspergillosis has improved with debridement and repeated topical treatments. For most animals a fair to good prognosis is warranted. Reported success rates were provided in the treatment section.

NASAL PARASITES

NASAL MITES

Pneumonyssoides caninum is a small white mite approximately 1 mm in size (see Fig. 14.13, *A*). Most infestations are clinically silent, but some dogs may have moderate to severe clinical signs.

Clinical Features and Diagnosis

A common clinical feature of nasal mites is sneezing, which is often violent. Head shaking, pawing at the nose, reverse sneezing, chronic nasal discharge, and epistaxis can also occur. These signs are similar to those caused by nasal foreign bodies. The diagnosis is made by visualizing the mites during rhinoscopy or by retrograde nasal flushing, as described in Chapter 14. The mites can be easily overlooked in the retrieved saline solution; they should be specifically searched for with slight magnification or by placing dark material behind the specimen for contrast. Further, the mites are often located in the frontal sinuses and the caudal nasal cavity. Flushing the nasal cavities from the nares with an anesthetic gas in oxygen may cause the mites to migrate to the caudal nasopharynx. The mites can be visualized in the nasopharynx by endoscopy during the flushing procedure.

Treatment

Milbemycin oxime (0.5-1 mg/kg, orally, every 7-10 days for three treatments) and selemectin (6-24 mg/kg, topically over the shoulders, every 2 weeks for three treatments) have been used successfully for treating nasal mites. Ivermectin is also effective (0.2 mg/kg, administered subcutaneously and repeated in 3 weeks), but it is not safe for certain breeds. Any dogs in direct contact with the affected animal should also be treated.

Prognosis

The prognosis for dogs with nasal mites is excellent.

NASAL CAPILLARIASIS

Nasal capillariasis is caused by a nematode, *Capillaria (Eucoleus) boehmi,* originally identified as a worm of the frontal sinuses in foxes. The adult worm is small, thin, and white and lives on the mucosa of the nasal cavity and frontal sinuses of dogs (see Fig. 14.13, *B*). The adults shed eggs that

are swallowed and pass in the feces. Clinical signs include sneezing and mucopurulent nasal discharge, with or without hemorrhage. The diagnosis is made by identifying double operculated *Capillaria (Eucoleus)* eggs on routine fecal flotation (similar to the eggs of *Capillaria [Eucoleus] aerophila;* see Fig. 20.12, *C*) or by visualizing adult worms during rhinoscopy. Treatments include ivermectin (0.2 mg/kg, orally, once) or fenbendazole (25-50 mg/kg, orally, q12h for 10-14 days). Ivermectin is not safe for certain breeds. Success of treatment should be confirmed with repeated fecal examinations, in addition to resolution of clinical signs. Repeated treatments may be necessary, and reinfection is possible if exposure to contaminated soil continues.

FELINE NASOPHARYNGEAL POLYPS

Nasopharyngeal polyps are benign growths that occur most often in kittens and young adult cats, although they are occasionally found in older animals. Their origin is unknown, but they are often attached to the base of the eustachian tube. They can extend into the external ear canal, middle ear, pharynx, and nasal cavity. Grossly, they are pink, polypoid growths, often arising from a stalk (Fig. 15.6). Because of their gross appearance, they are sometimes mistaken for neoplasia.

Clinical Features

Respiratory signs caused by nasopharyngeal polyps include stertorous breathing, upper airway obstruction, and serous to mucopurulent nasal discharge. Signs of otitis externa or otitis media/interna, such as head tilt, nystagmus, or Horner syndrome, can also occur.



FIG 15.6
A nasopharyngeal polyp was visualized during rhinoscopy through the exterior naris of a cat with chronic nasal discharge. The polyp was excised by traction and has an obvious stalk.

Diagnosis

Identification of a soft tissue opacity above the soft palate radiographically and gross visualization of a mass in the nasopharynx, nasal cavity, or external ear canal support a tentative diagnosis of nasopharyngeal polyp. Complete evaluation of cats with polyps also includes a deep otoscopic examination and radiographs or CT scans of the osseous bullae to determine the extent of involvement. Most cats with polyps have otitis media, detectable radiographically as thickened bone or increased soft tissue opacity of the bulla (see Fig. 14.6). The definitive diagnosis is made by histopathologic analysis of tissue that is usually obtained during surgical excision. Nasopharyngeal polyps are composed of inflammatory tissue, fibrous connective tissue, and epithelium.

Treatment

The primary treatment of nasopharyngeal polyps is surgical excision by way of traction via the oral cavity. Recurrence is possible as a result of tissue being left behind. Cats with radiographic or CT evidence of involvement of the osseous bullae are at increased risk of recurrence, and bulla osteotomy for complete removal has been recommended for such cats. However, Anderson et al. (2000) reported successful treatment with traction alone, particularly when followed by a course of prednisolone. Prednisolone was administered orally at 1 to 2 mg/kg q24h for 2 weeks, then at half the original dose for 1 week, then every other day for 7 to 10 more days. A course of antibiotics (e.g., amoxicillin) was also administered. Therefore removal of the polyp by traction followed by a course of corticosteroids and antibiotics is generally recommended before exploration of the middle ear via bulla osteotomy. Rarely, rhinotomy is required for complete removal of a nasal polyp.

Prognosis

The prognosis is excellent, but treatment of recurrent disease may be necessary. Regrowth of a polyp can occur at the original site if abnormal tissue remains, with signs of recurrence typically appearing within 1 year. Bulla osteotomy, if not performed with initial treatment, should be considered in cats with recurrence and signs of otitis media.

CANINE NASAL POLYPS

Dogs rarely develop nasal polyps. These masses can result in chronic nasal discharge, with or without hemorrhage. They are often locally destructive to turbinates and bone, and as a result can be misdiagnosed as neoplasia. The diagnosis is made by histologic evaluation of biopsy specimens. Aggressive surgical removal is recommended. Complete excision may be impossible and signs may recur.

NASAL TUMORS

Most nasal tumors in the dog and cat are malignant. Adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma are common nasal tumors in dogs. Lymphoma and adenocarcinoma are common in cats. Fibrosarcomas and other sarcomas also occur in both species. Benign tumors include adenomas, fibromas, papillomas, and transmissible venereal tumors (the latter only in dogs).

Clinical Features

Nasal tumors usually occur in older animals but cannot be excluded from the differential diagnosis of young dogs and cats. No breed predisposition has been consistently identified.

The clinical features of nasal tumors are usually chronic and reflect the locally invasive nature of these tumors. Nasal discharge is the most common complaint. The discharge can be serous, mucoid, mucopurulent, or hemorrhagic. One or both nostrils can be involved. With bilateral involvement, the discharge is often worse from one nostril than from the other. For many animals, the discharge is initially unilateral and progresses to bilateral. Sneezing may be reported and may be the only clinical sign early in the disease process. Obstruction of the nasal cavity by the tumor may cause decreased or absent air flow through one or both of the nares.

Deformation of the facial bones, hard palate, or maxillary dental arcade may be visible (see Fig. 13.5). Tumor growth extending into the cranial vault can result in neurologic signs. Growth into the orbit may cause exophthalmos or inability to retropulse the eye. Animals only rarely experience neurologic signs (e.g., seizures, behavior changes, abnormal mental status) or ocular abnormalities as the primary complaints (i.e., no signs of nasal discharge). Weight loss and anorexia are other rare complaints.

Diagnosis

A diagnosis of neoplasia is supported by typical abnormalities detected by imaging of the nasal cavity and frontal sinuses or rhinoscopy. Abnormalities can reflect soft tissue mass lesions; turbinate, vomer bone, or facial bone destruction; or diffuse infiltration of the mucosa with neoplastic and inflammatory cells (see Figs. 14.2, 14.4, and 14.8, *B*). Identification of neoplastic cells in fine-needle aspirates of nasal masses or affected mandibular lymph nodes may further support the diagnosis. Be aware that a cytologic diagnosis of neoplasia from a mass aspirate must be accepted cautiously, with consideration of concurrent inflammation and potentially marked hyperplastic and metaplastic change. Furthermore, in some cases the cytologic characteristics of lymphoma and carcinoma will mimic each other, which may lead to an erroneous classification of the neoplasia.

A definitive diagnosis requires histopathologic examination of a biopsy specimen. Biopsy specimens should always include tissue from deep within the lesion. Nasal neoplasms frequently cause a marked inflammatory response of the nasal mucosa and, in some patients, secondary infection. Superficial specimens are more likely to lead to a misdiagnosis.

Not all cases of neoplasia will be diagnosed on initial evaluation of the dog or cat. Imaging, rhinoscopy, and biopsy may need to be repeated in 1 to 3 months in animals with persistent signs in which a definitive diagnosis has not been made. CT and MRI are more sensitive techniques than routine radiography for imaging nasal tumors, and one of these should be performed when available (see Fig. 14.8, *B*). Surgical exploration is occasionally necessary to obtain a definitive diagnosis.

Once a definitive diagnosis has been made, determining the extent of disease can help in assessing the feasibility of surgical or radiation therapy versus chemotherapy. Some information can be obtained from high-quality nasal radiographs, but CT and MRI are more sensitive methods for evaluating the extent of abnormal tissue. Aspirates of mandibular lymph nodes should be examined cytologically for evidence of local spread. Thoracic radiographs are evaluated, although pulmonary metastases are uncommon at the time of initial diagnosis. Cytologic evaluation of bone marrow aspirates, as well as abdominal radiography or ultrasound, is indicated for patients with lymphoma. Cats with lymphoma are also tested for FeLV and FIV.

Treatment

Benign tumors, though rare, may be treatable with surgical excision. Radiation therapy is generally recommended for malignant tumors. Chemotherapy is considered for adjunctive therapy for patients with metastatic disease, or as a sole treatment for patients with lymphoma (Chapter 79). Chemotherapy can also be the sole treatment when radiation is not readily available. Carcinomas may be responsive to cisplatin, carboplatin, or multiagent chemotherapy. (See Chapter 76 for a discussion of general principles for the selection of chemotherapy.) Surgical excision alone is not successful for managing malignant nasal tumors, although some oncologists have recommended surgical excision following radiation therapy.

Palliation of clinical signs can often be achieved with radiation treatment at a reduced dose and frequency, avoiding many of the side effects of full dose radiation. Similarly, palliation can sometimes be achieved with piroxicam (DOSE) or corticosteroids at antiinflammatory dosages (prednisone or prednisolone, 0.5-1 mg/kg/day orally, gradually tapered to lowest effective dose). Note that these two drugs should not be given in combination.

Prognosis

The prognosis for dogs and cats with malignant nasal tumors is poor without treatment. Survival after diagnosis is usually only a few months. Euthanasia is often requested because of persistent epistaxis or discharge, and eventually, labored respirations, anorexia and weight loss, or neurologic signs. Epistaxis is a poor prognostic indicator. In a study of 132 dogs with untreated nasal carcinoma by Rassnick et al. (2006), the median survival time of dogs with epistaxis was

88 days (95% confidence interval [CI], 65-106 days) and of dogs without epistaxis was 224 days (95% CI, 54-467 days). The overall median survival time was 95 days (range, 7-1114 days).

Radiation therapy can prolong survival and improve quality of life in some animals and consultation with a radiation oncologist is recommended. The therapy is well tolerated by most animals, and in those that achieve remission the quality of life is usually excellent. The prognosis for a given patient is dependent upon a number of variables, including histopathologic classification, extent of the tumor, and the presence and location of metastatic disease. Early studies of dogs treated with megavoltage radiation, with or without prior surgical treatment, found median survival times of approximately 1 year. Less information is available concerning prognosis in cats. A study by Theon et al. (1994) of 16 cats with nonlymphoid neoplasia receiving radiation therapy showed a 1-year survival rate of 44% and a 2-year survival rate of 17%. Cats with nasal lymphoma treated with radiation and chemotherapy had a median survival time of 511 days, according to preliminary data from Arteaga et al. (2007).

ALLERGIC RHINITIS

Etiology

Allergic rhinitis has not been well characterized in dogs or cats. However, dermatologists provide anecdotal reports of atopic dogs rubbing the face (possibly indicating nasal pruritus) and experiencing serous nasal discharge, in addition to dermatologic signs. Allergic rhinitis is generally considered to be a hypersensitivity response within the nasal cavity and sinuses to airborne antigens. It is possible that food allergens play a role in some patients. Other antigens are capable of inducing a hypersensitivity response as well, and thus the differential diagnoses must include parasites, other infectious diseases, and neoplasia.

Clinical Features

Dogs or cats with allergic rhinitis experience sneezing and/or serous or mucopurulent nasal discharge. Signs may be acute or chronic. Careful questioning of the owner may reveal a relationship between signs and potential allergens. For instance, signs may be worse during certain seasons, or after the introduction of a new brand of kitty litter or new perfumes, cleaning agents, furniture, or fabric in the house. Note that worsening of signs may simply be a result of exposure to irritants, such as cigarette smoke, rather than an actual allergic response. Debilitation of the animal is not expected.

Diagnosis

Identifying a historical relationship between signs and a particular allergen and then achieving resolution of signs after removal of the suspected agent from the animal's environment support the diagnosis of allergic rhinitis. When this approach is not possible or successful, a thorough diagnostic evaluation of the nasal cavity is indicated (see Chapters 13 and 14). Nasal radiographs reveal increased soft tissue opacity with minimal or no turbinate destruction. Classically, nasal biopsy reveals eosinophilic inflammation. It is possible that with chronic disease, a mixed inflammatory response occurs, obscuring the diagnosis. There should be no indication in any of the diagnostic tests of an aggressive disease process, parasites or other active infection, or neoplasia.

Treatment

Removing the offending allergen from the animal's environment or diet is the ideal treatment for allergic rhinitis. When this is not possible, a beneficial response may be achieved with antihistamines. Chlorpheniramine can be administered orally at a dose of 4 to 8 mg/dog q12h or 2 mg/cat q12h. The second-generation antihistamine cetirizine may be more successful in cats. A pharmacokinetic study of this drug in healthy cats found a dosage of 1 mg/kg, administered orally every 24 hours, to maintain plasma concentrations similar to those reported in people (Papich et al., 2006). Glucocorticoids may be used if antihistamines are unsuccessful. Prednisone is initiated at a dose of 0.25 mg/kg, orally, q12h until signs resolve. The dose is then tapered to the lowest effective amount. If treatment is effective, signs will generally resolve within a few days. Drugs are continued only as long as needed to control signs. Administration of steroids via face mask using a metered dose inhaler, as described for the treatment of feline bronchitis (see Chapter 21), can also be tried. Although the inhalers are designed to deliver drug to the lower airways, some drug will also be deposited within the nasal cavity.

Prognosis

The prognosis for dogs and cats with allergic rhinitis is excellent if the allergen can be eliminated. Otherwise, the prognosis for control is good, but a cure is unlikely.

IDIOPATHIC RHINITIS

Idiopathic rhinitis is a more common diagnosis in cats compared with dogs. The diagnosis cannot be made without a thorough diagnostic evaluation to rule out specific diseases (see Chapters 13 and 14).

FELINE CHRONIC RHINOSINUSITIS

Etiology

Feline chronic rhinosinusitis has long been presumed to be a result of viral infection with FHV or FCV (see the earlier section on feline URI). Persistent viral infection has been implicated, but studies have failed to show an association between tests indicating exposure to or infection with these viruses and clinical signs. It is possible that infection with these viruses results in damaged mucosa that is more susceptible to bacterial infection or that mounts an excessive

inflammatory response to irritants or normal nasal flora. Preliminary studies have failed to show an association with feline chronic rhinosinusitis and *Bartonella* infection, based on serum antibody titers or PCR of nasal tissue (Berryessa et al., 2008). In the absence of a known cause, this disease will be denoted by the term *idiopathic feline chronic rhinosinusitis*.

Clinical Features and Diagnosis

Chronic mucoid or mucopurulent nasal discharge is the most common clinical sign of idiopathic feline chronic rhinosinusitis. The discharge is typically bilateral. Fresh blood may be seen in the discharge of some cats but is not usually a primary complaint. Sneezing may occur. Given that this is an idiopathic disease, the lack of specific findings is important. Cats should have no funduscopic lesions, no lymphadenopathy, no facial or palate deformities, and healthy teeth and gums. Anorexia and weight loss are rarely reported. Thorough diagnostic testing is indicated, as described in Chapters 13 and 14. Results of such testing do not support the diagnosis of a specific disease. Usual nonspecific findings include turbinate erosion, mucosal inflammation, and increased mucus accumulation as assessed by nasal imaging and rhinoscopy; neutrophilic or mixed inflammation with bacteria on cytology of nasal discharge; and neutrophilic and/or lymphoplasmacytic inflammation on nasal biopsy. Nonspecific abnormalities attributable to chronic inflammation, such as epithelial hyperplasia and fibrosis, may also be seen. Secondary bacterial rhinitis or *Mycoplasma* infection may be identified.

Treatment

Cats with idiopathic chronic rhinosinusitis often require management for years. Fortunately, most of these cats are healthy in all other respects. Treatment strategies include facilitating drainage of discharge; decreasing irritants in the environment; controlling secondary bacterial infections; treating possible *Mycoplasma* or FHV infection; reducing inflammation; and, as a last resort, performing a turbinectomy and frontal sinus ablation (Box 15.1).

Keeping secretions moist, performing intermittent nasal flushes, and judiciously using topical decongestants facilitate drainage. Keeping the cat in a room with a vaporizer, for instance, during the night can provide symptomatic relief by keeping secretions moist. Alternatively, drops of sterile saline can be placed into the nares. Some cats experience a marked improvement in clinical signs for weeks after flushing of the nasal cavity with copious amounts of saline. General anesthesia is required, and the lower airways must be protected with an endotracheal tube, gauze sponges, and positioning of the head to facilitate drainage from the external nares. Topical decongestants, as described for feline URI, may provide symptomatic relief during episodes of severe congestion.

Irritants in the environment can further exacerbate mucosal inflammation. Irritants such as smoke (from tobacco or fireplace) and perfumed products should be avoided. Motivated clients can take steps to improve the air quality in their homes, such as by cleaning carpet, furniture, drapery, and furnace; regularly replacing air filters; and using an air cleaner. The American Lung Association has a useful Web site with nonproprietary recommendations for improving indoor air quality (www.lung.org).

Long-term antibiotic therapy may be required to manage secondary bacterial infections. Broad-spectrum oral antibiotics such as amoxicillin (22 mg/kg q8-12h) are often successful. Doxycycline (5 mg/kg q12h or 10 mg/kg q24h, followed by a bolus of water) has activity against some bacteria and *Chlamydophila* and *Mycoplasma* organisms and can be effective in some cats when other drugs have failed. Azithromycin (5-10 mg/kg q12h for 1 day, then every 3 days) can be prescribed for cats that are difficult to medicate. This author reserves fluoroquinolones for cats with documented resistant gram-negative infections that have failed other treatment attempts. If a beneficial response to antibiotic therapy is seen within 1 week of its initiation, the antibiotic should be continued for at least 4 to 6 weeks. If a beneficial



BOX 15.1

Management Considerations for Cats With Idiopathic Chronic Rhinosinusitis

Facilitate Drainage of Discharge

Vaporizer treatments
Topical saline administration
Nasal cavity flushes under anesthesia
Topical decongestants

Decrease Irritants in the Environment

Improvement of indoor air quality

Control Secondary Bacterial Infections

Long-term antibiotic treatment

Treat Possible Mycoplasma Infection

Antibiotic treatment

Treat Possible Herpesvirus Infection

Lysine treatment

Reduce inflammation

Second-generation antihistamine treatment
Oral prednisolone treatment
Other unproven treatments with possible antiinflammatory effects
- Azithromycin
- Piroxicam
- Leukotriene inhibitors
- Omega-3 fatty acids

Provide Surgical Intervention

Turbinectomy
Frontal sinus ablation

response is not seen, the antibiotic is discontinued. Note that frequent stopping and starting of different antibiotics every 7 to 14 days is not recommended and may predispose the cat to resistant gram-negative infections. Cats that respond well during the prolonged course of antibiotics but that relapse shortly after discontinuation of the drug despite 4 to 6 weeks of relief are candidates for continuous long-term antibiotic therapy. Treatment with the previously used antibiotic often can be successfully reinstituted. Amoxicillin administered twice daily is often sufficient.

Treatment with famcyclovir may be effective in cats with active herpesvirus infection, as discussed in the section on feline URIs earlier in this chapter. Anecdotal success in occasional cats has been reported with treatment with the second-generation antihistamine cetirizine, as described previously for allergic rhinitis.

Cats with severe signs that persist despite the previously described methods of supportive care may benefit from glucocorticoids to reduce inflammation. However, certain risks are involved. Glucocorticoids may further predispose the cat to secondary infection, increase viral shedding, and mask signs of a more serious disease. Glucocorticoids should be prescribed only after a complete diagnostic evaluation has been performed to rule out other diseases. Prednisolone is administered orally at a dose of 0.5 mg/kg q12h If a beneficial response is seen within 1 week, the dose is gradually decreased to the lowest effective dose. A dose as low as 0.25 mg/kg every 2 to 3 days may be sufficient to control clinical signs. If a clinical response is not seen within 1 week, the drug should be discontinued. As discussed with allergic rhinitis, administration of glucocorticoids via metered dose inhaler may be effective in cats responsive to oral glucocorticoids.

Other drugs with potential antiinflammatory effects that may provide relief include azithromycin (described with antibiotics), piroxicam, and leukotriene inhibitors. Omega-3 fatty acid supplementation may also serve to dampen the inflammatory response. Effectiveness of these treatments in cats with chronic signs is based on anecdotal reports of success in individual cats. Remember that piroxicam should not be given concurrently with corticosteroids.

Cats with severe or deteriorating signs that persist despite conscientious care are candidates for turbinectomy and frontal sinus ablation, if a complete diagnostic evaluation to eliminate other causes of chronic nasal discharge has been performed (see Chapters 13 and 14). Turbinectomy and frontal sinus ablation are difficult surgical procedures. Major blood vessels and the cranial vault must be avoided, and tissue remnants must not be left behind. Anorexia can be a postoperative problem; placement of an esophagostomy or gastrostomy tube serves as an excellent means of meeting nutritional requirements if necessary after surgery. Complete elimination of respiratory signs is unlikely, but signs may be more easily managed. The reader is referred to surgical texts for a description of surgical techniques (e.g., see Fossum in Suggested Readings).

IDIOPATHIC CANINE CHRONIC (LYMPHOPLASMACYTIC) RHINITIS

Etiology

Idiopathic chronic rhinitis in dogs is sometimes characterized by the inflammatory infiltrates seen in nasal mucosal biopsy specimens; thus the disease *lymphoplasmacytic rhinitis* has been described. It was originally reported to be a steroid-responsive disorder, but a subsequent report by Windsor et al. (2004) and clinical experience suggest that corticosteroids are not always effective in the treatment of lymphoplasmacytic rhinitis. It is not uncommon for neutrophilic inflammation to be found, predominantly or along with lymphoplasmacytic infiltrates. For these reasons, the less specific term *idiopathic canine chronic rhinitis* will be used.

Many specific causes of nasal disease result in a concurrent inflammatory response because of the disease itself or as a response to the secondary effects of infection or as an enhanced response to irritants; this makes a thorough diagnostic evaluation of these cases imperative. Windsor et al. (2004) performed multiple PCR assays on paraffin-embedded nasal tissue from dogs with idiopathic chronic rhinitis and failed to find evidence for a role of bacteria (based on DNA load), canine adenovirus-2, parainfluenza virus, *Chlamydophila* spp., or *Bartonella* spp. in affected dogs. Large amounts of fungal DNA were found in affected dogs, suggesting a possible contribution to clinical signs. Alternatively, the result may simply reflect decreased clearance of fungal organisms from the diseased nasal cavity.

Although not supported in the previously quoted study, a potential role for *Bartonella* infection has been suggested on the basis of a study that found an association between seropositivity for *Bartonella* spp. and nasal discharge or epistaxis (Henn et al., 2005) and a report of three dogs with epistaxis and evidence of infection with *Bartonella* spp. (Breitschwerdt et al., 2005). A study conducted in our laboratory (Hawkins et al., 2008) failed to find an obvious association between bartonellosis and idiopathic rhinitis, in agreement with findings by Windsor et al. (2004).

Clinical Features and Diagnosis

The clinical features and diagnosis of idiopathic canine chronic rhinitis are similar to those described for idiopathic feline chronic rhinosinusitis. Chronic mucoid or mucopurulent nasal discharge is the most common clinical sign and is typically bilateral. Fresh blood may be seen in the discharge of some dogs, but it is not usually a primary complaint. Given that it is an idiopathic disease, the lack of specific findings is important. Dogs should have no funduscopic lesions, no lymphadenopathy, no facial or palate deformities, and healthy teeth and gums. Anorexia and weight loss are rarely reported. Thorough diagnostic testing is indicated, as described in Chapters 13 and 14.

Results of such testing do not support the diagnosis of a specific disease. Usual nonspecific findings include turbinate erosion, mucosal inflammation, and increased mucus accumulation as assessed by nasal imaging and rhinoscopy; neutrophilic or mixed inflammation with bacteria on cytology of nasal discharge; and lymphoplasmacytic and/or neutrophilic inflammation on nasal biopsy. Nonspecific abnormalities attributable to chronic inflammation, such as epithelial hyperplasia and fibrosis, can also be seen. Secondary bacterial rhinitis or *Mycoplasma* infection may be identified.

Treatment

Treatment of idiopathic canine chronic rhinitis is also similar to that described for idiopathic feline rhinosinusitis (see previous section and Box 15.1). Dogs are treated for secondary bacterial rhinitis (as described the earlier in this chapter), and efforts are made to decrease irritants in the environment (see feline chronic rhinosinusitis). As with cats, some dogs will benefit from efforts to facilitate the draining of nasal discharge by humidification of air or instillation of sterile saline into the nasal cavity.

Although antiinflammatory treatment as described previously for cats may be beneficial in some dogs, successful treatment was originally reported in dogs with lymphoplasmacytic rhinitis using immunosuppressive doses of prednisone (1 mg/kg, orally, q12h). A positive response is expected within 2 weeks, at which time the dose of prednisone is decreased gradually to the lowest effective amount. If no response to initial therapy occurs, other immunosuppressive drugs such as azathioprine can be added to the treatment regimen (see Chapter 72). Unfortunately, immunosuppressive treatment is not always effective. If clinical signs worsen during treatment with corticosteroids, the clinician should discontinue therapy and carefully reevaluate the dog for other diseases.

Dogs with severe or nonresponsive signs are candidates for rhinotomy and turbinectomy, as described for feline chronic rhinosinusitis.

Prognosis

The prognosis for idiopathic chronic rhinitis in dogs is generally good with respect to improvement of signs and quality of life. However, some degree of clinical signs persists in many dogs.

Suggested Readings

Anderson DM, et al. Management of inflammatory polyps in 37 cats. *Vet Record*. 2000;147:684.

Arteaga T, et al. A retrospective analysis of nasal lymphoma in 71 cats (1999-2006), Abstract. *J Vet Intern Med*. 2007;21:573.

Berryessa NA, et al. Microbial culture of blood samples and serologic testing for bartonellosis in cats with chronic rhinitis. *J Am Vet Med Assoc*. 2008;233:1084.

Binns SH, et al. Prevalence and risk factors for feline *Bordetella bronchiseptica* infection. *Vet Rec*. 1999;144:575.

Breitschwerdt EB, et al. *Bartonella* species as a potential cause of epistaxis in dogs. *J Clin Microbiol*. 2005;43:2529.

Buchholz J, et al. 3D conformational radiation therapy for palliative treatment of canine nasal tumors. *Vet Radiol Ultrasound*. 2009;50:679.

Fossum TW. *Small Animal Surgery*. 5th ed. St Louis: Elsevier Mosby; 2018.

Greci V, Mortellaro CM. Management of otic and nasopharyngeal polyps in cats and dogs. *Vet Clin North Am Small Anim Pract*. 2016;46:643.

Gunnarsson L, et al. Efficacy of selemectin in the treatment of nasal mite *(Pneumonyssoides caninum)* infection in dogs. *J Am Anim Hosp Assoc*. 2004;40:400.

Hartmann AD, et al. Efficacy of pradofloxacin in cats with feline upper respiratory tract disease due to *Chlamydophila felis* or *Mycoplasma* infections. *J Vet Intern Med*. 2008;22:44.

Hawkins EC, et al. Failure to identify an association between serologic or molecular evidence of *Bartonella* spp infection and idiopathic rhinitis in dogs. *J Am Vet Med Assoc*. 2008;233:597.

Henn JB, et al. Seroprevalence of antibodies against *Bartonella* species and evaluation of risk factors and clinical signs associated with seropositivity in dogs. *Am J Vet Res*. 2005;66:688.

Holt DE, Goldschmidt MH. Nasal polyps in dogs: five cases (2005-2011). *J Small Anim Pract*. 2011;52:660.

Johnson LR, et al. Assessment of infectious organisms associated with chronic rhinosinusitis in cats. *J Am Vet Med Assoc*. 2005;227:579.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Lappin MR, et al. Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats. *J Am Vet Med Assoc*. 2002;220:38.

Mathews KG, et al. Computed tomographic assessment of noninvasive intranasal infusions in dogs with fungal rhinitis. *Vet Surg*. 1996;25:309.

Papich MG, et al. Cetirizine (Zyrtec) pharmacokinetics in healthy cats, Abstract. *J Vet Intern Med*. 2006;20:754.

Piva S, et al. Chronic rhinitis due to *Streptococcus equi* subspecies *zooepidemicus* in a dog. *Vet Rec*. 2010;167:177.

Pomerantz JS, et al. Comparison of serologic evaluation via agar gel immunodiffusion and fungal culture of tissue for diagnosis of nasal aspergillosis in dogs. *J Am Vet Med Assoc*. 2007;230:1319.

Rassnick KM, et al. Evaluation of factors associated with survival in dogs with untreated nasal carcinomas: 139 cases (1993-2003). *J Am Vet Med Assoc*. 2006;229:401.

Richards JR, et al. The 2006 American Association of Feline Practitioners Feline Vaccine Advisory Panel Report. *J Am Vet Med Assoc*. 2006;229:1405.

Schmidt BR, et al. Evaluation of piroxicam for the treatment of oral squamous cell carcinoma in dogs. *J Am Vet Med Assoc*. 2001;218:1783.

Sharman M, et al. Muti-centre assessment of mycotic rhinosinusitis in dogs: a retrospective study of initial treatment success. *J Small Anim Pract*. 2010;51:423.

Stewart J, Bianco D. Treatment of refractory sino-nasal aspergillosis with posaconazole and terbinafine in 10 dogs. *J Small Anim Pract*. 2017;58:504.

Thomasy SM, et al. Oral administration of famcyclovir for treatment of spontaneous ocular, respiratory, or dermatologic disease attributed to feline herpesvirus type 1: 59 cases (2006-2013). *J Am Vet Med Assoc*. 2016;249:526.

Thomasy SM, Maggs DJ. A review of antiviral drugs and other compounds with activity against feline herpesvirus-1. *Vet Ophthalmol*. 2016;19:119.

Theon AP, et al. Irradiation of nonlymphoproliferative neoplasms of the nasal cavity and paranasal sinuses in 16 cats. *J Am Vet Med Assoc*. 1994;204:78.

Windsor RC, et al. Idiopathic lymphoplasmacytic rhinitis in dogs: 37 cases (1997-2002). *J Am Vet Med Assoc*. 2004;224:1952.

CHAPTER 16

Clinical Manifestations of Laryngeal and Pharyngeal Disease



CLINICAL SIGNS

LARYNX

Regardless of the cause, diseases of the larynx result in similar clinical signs, most notably respiratory distress and stridor. Gagging or coughing may also be reported. Voice change is specific for laryngeal disease, though not always present. Clients may volunteer that they have noticed a change in the dog's bark or the cat's meow, but specific questioning may be necessary to obtain this important information. Localization of disease to the larynx can generally be achieved with a good history and physical examination. A definitive diagnosis is made through a combination of laryngeal radiography, laryngoscopy, and laryngeal biopsy. Fluoroscopy and computed tomography (CT) can be useful for dynamic disease and improved imaging of mass lesions or anatomic abnormalities, respectively.

Respiratory distress resulting from laryngeal disease is due to airway obstruction. Although most laryngeal diseases are progressive over several weeks to months, animals frequently present in acute distress. Dogs and cats seem to be able to compensate for their disease initially through self-imposed exercise restriction. Often an exacerbating event occurs, such as exercise, excitement, or high ambient temperature, resulting in markedly increased respiratory efforts. These increased efforts lead to excess negative pressures on the diseased larynx, sucking the surrounding soft tissues into the lumen and causing laryngeal inflammation and edema. Obstruction to airflow becomes more severe, leading to even greater respiratory efforts (Fig. 16.1). The airway obstruction can ultimately be fatal.

A characteristic breathing pattern can often be identified on physical examination of patients in distress from extrathoracic (upper) airway obstruction, such as that resulting from laryngeal disease (see Chapter 25). The respiratory rate is normal to only slightly elevated (often 30-40 breaths/min), which is particularly remarkable in the presence of overt distress. Inspiratory efforts are prolonged and labored, relative to expiratory efforts. The larynx tends to be sucked into the airway lumen as a result of negative pressure within the extrathoracic airways that occurs during inspiration, making inhalation of air more difficult. During expiration, pressures are positive in the extrathoracic airways, "pushing" the soft tissues open. Nevertheless, expiration may not be effortless. Some obstruction to airflow may occur during expiration with fixed obstructions, such as laryngeal masses. Even with the dynamic obstruction that results from laryngeal paralysis, in which expiration should be possible without any blockage of flow, resultant laryngeal edema and inflammation can interfere with normal expiration. On auscultation, referred upper airway sounds are heard and lung sounds are normal to increased.

Stridor, a high-pitched wheezing sound, is typically heard predominantly during inspiration. It is audible without a stethoscope, although auscultation of the neck may aid in identifying mild disease. Stridor is produced by air turbulence through the narrowed laryngeal opening. Narrowing of the extrathoracic trachea less commonly produces stridor, more often producing a coarse stertorous sound.

When patients are not presented for respiratory distress (e.g., patients with exercise intolerance or voice change), it may be necessary to exercise the patient to identify the characteristic breathing pattern and stridor associated with laryngeal disease (Video 16.1).

Some patients with laryngeal disease, particularly those whose laryngeal paralysis is an early manifestation of more diffuse neuromuscular disease or those presenting with distortion of normal laryngeal anatomy, have subclinical aspiration or overt aspiration pneumonia resulting from the loss of normal protective mechanisms. Patients may show clinical signs reflecting aspiration, such as cough, lethargy, anorexia, fever, tachypnea, and abnormal lung sounds. (See Chapter 22 for a discussion of aspiration pneumonia.)

PHARYNX

Space-occupying lesions of the pharynx can cause signs of upper airway obstruction as described for the larynx, but overt respiratory distress occurs only with advanced disease. More typical presenting signs of pharyngeal disease include stertor, reverse sneezing, gagging, retching, and dysphagia. Stertor is a loud, coarse sound such as that produced by snoring or snorting. Stertor results when excessive soft tissue

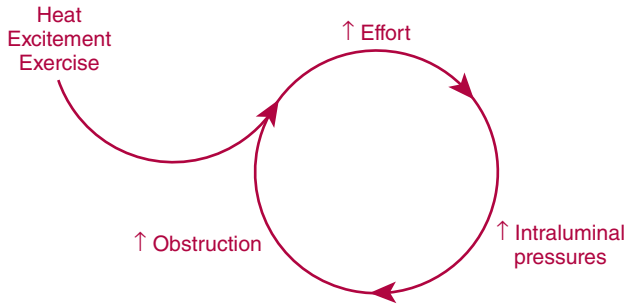


FIG 16.1
Patients with extrathoracic (upper) airway obstruction often present in respiratory distress as a result of progressive worsening of airway obstruction after an exacerbating event.

in the pharynx, such as an elongated soft palate or mass, causes turbulent airflow. Reverse sneezing (see Chapter 13), gagging, or retching may result from local stimulation from the tissue itself or from secondary secretions. Dysphagia results from physical obstruction, usually caused by a mass. As with laryngeal disorders, a definitive diagnosis is made through a combination of visual examination, radiography, and biopsy of abnormal tissue. Visual examination includes a thorough evaluation of the oral cavity, larynx, and caudal nasopharynx. In some cases, fluoroscopy or CT scan may be necessary to assess abnormalities visible only during the stress of labored breathing or to assess mass lesions resulting in external compression of the airway, respectively.

DIFFERENTIAL DIAGNOSES FOR LARYNGEAL SIGNS IN DOGS AND CATS

Differential considerations for dogs and cats with respiratory distress are discussed in Chapter 25.

Dogs are more commonly presented for laryngeal disease than cats and usually have laryngeal paralysis (Box 16.1). Laryngeal neoplasia can occur in dogs or cats. Obstructive laryngitis is a poorly characterized inflammatory disorder. Other possible diseases of the larynx include laryngeal collapse (see Laryngoscopy, Chapter 17), web formation (i.e., adhesions or fibrotic tissue across the laryngeal opening, usually as a complication of surgery), trauma, foreign body, and compression caused by an extraluminal mass. Acute laryngitis is not a well-characterized disease in dogs or cats but presumably could result from viral or other infectious agents, foreign bodies, or excessive barking. Gastroesophageal reflux, a cause of laryngitis in people, has recently been documented to cause laryngeal dysfunction in a dog (Lux, 2012).

DIFFERENTIAL DIAGNOSES FOR PHARYNGEAL SIGNS IN DOGS AND CATS

The most common pharyngeal disorders in dogs are brachycephalic airway syndrome and elongated soft palate (Box 16.2). Elongated soft palate is a component of brachycephalic airway syndrome, which is discussed in Chapter 18, but it can also occur in nonbrachycephalic dogs. Nasophparyngeal polyps are the most common pharyngeal disease in cats, followed by neoplasia. Nasopharyngeal polyps, nasal tumors, and foreign bodies are discussed in the chapters on nasal diseases (see Chapters 13 to 15). Other differential diagnoses are abscess or granuloma and compression caused by an extraluminal mass. Nasopharyngeal stenosis can occur as a complication of chronic inflammation (rhinitis or pharyngitis), vomiting, or gastroesophageal reflux in dogs or cats. Dogs with tracheobronchomalacia (see Chapter 21) who are presented for signs of upper airway obstruction resulting from extrathoracic tracheal collapse can have loud, stertorous breathing similar to that heard in dogs with brachycephalic airway syndrome. The difference in breed predisposition for these two conditions assists in prioritizing the differential diagnoses.

BOX 16.1

Differential Diagnoses for Laryngeal Disease in Dogs and Cats

Laryngeal paralysis
Laryngeal neoplasia
Obstuctive laryngitis
Laryngeal collapse
Web formation
Trauma
Foreign body
Extraluminal mass
Acute laryngitis

BOX 16.2

Differential Diagnoses for Pharyngeal Disease in Dogs and Cats*

Brachycephalic airway syndrome
Elongated soft palate
Nasopharyngeal polyp
Foreign body
Neoplasia
Abscess
Granuloma
Extraluminal mass
Nasopharyngeal stenosis

*Upper airway obstruction resulting from extra-thoracic tracheal collapse can mimic obstruction resulting from pharyngeal disease.

Suggested Readings

Hunt GB, et al. Nasopharyngeal disorders of dogs and cats: a review and retrospective study. *Compendium*. 2002;24:184.

Lux CN. Gastroesophageal reflux and laryngeal dysfunction in a dog. *J Am Vet Med Assoc*. 2012;240:1100.

CHAPTER 17

Diagnostic Tests for the Larynx and Pharynx



RADIOGRAPHY

Radiographs of the pharynx and larynx should be evaluated in animals with suspected upper airway disease (Figs. 17.1 and 17.2). Radiographs are particularly useful in identifying radiodense foreign bodies such as needles, which can be embedded in tissues, external compression of the airways, and adjacent bony changes. It may not be possible to identify or characterize these types of lesions with laryngoscopy alone. Intraluminal soft tissue masses and soft palate abnormalities may also be seen.

A lateral view of the larynx, caudal nasopharynx, and cranial cervical trachea is usually obtained. The vertebral column interferes with airway evaluation on dorsoventral or ventrodorsal projections. Care must be taken to assure excellent positioning of the head. Normal structures can appear to be abnormal (e.g., masses, palate abnormalities) if there is any rotation of the head and neck. The head should be held with the neck slightly extended. Padding under the neck and around the head may be needed to avoid rotation, but it should not distort the anatomic structures. Good positioning of radiographs can be assessed by the superimposition of the left and right osseous bullae, mandibles, and frontal sinuses. Regardless, abnormal soft tissue opacities or narrowing of the airway lumen identified radiographically must be confirmed with laryngoscopy, endoscopy and/or computed tomography, and biopsy. Laryngeal paralysis cannot be detected radiographically.

ULTRASONOGRAPHY

Ultrasonography provides another noninvasive imaging modality for evaluating the pharynx and larynx. Reportedly laryngeal motion can be assessed (Rudorf et al., 2001). Because air interferes with sound waves, accurate assessment of this area can be difficult. Experience is necessary to avoid misdiagnosis, particularly with respect to laryngeal motion as it can be the result of passive, paradoxical movement rather than active muscle contraction (see Laryngoscopy and Pharyngoscopy later in this chapter). Localization of mass lesions and guidance of needle aspiration of abnormal tissue or enlarged regional lymph nodes can provide a diagnosis in some cases.

FLUOROSCOPY

In some patients, signs of upper airway obstruction occur only during labored breathing. A diagnosis may be missed if adequate breathing efforts do not occur during routine radiography or during visual examination under anesthesia. In these cases, fluoroscopic evaluation during signs of airway obstruction, or audible sounds (stertor or stridor), can be invaluable. Unusual diagnoses, such as epiglottic retroversion and collapse of the dorsal pharyngeal wall, may not be possible by other means. Extrathoracic tracheal collapse, a differential diagnosis for upper airway obstruction due to pharyngeal or laryngeal disease, can often be diagnosed as well.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Computed tomography and magnetic resonance imaging are sensitive modalities for identifying masses that result in external compression of the larynx or pharynx. Extent of involvement and size of local lymph nodes can be assessed for patients with mass lesions external to or within the airway.

LARYNGOSCOPY AND PHARYNGOSCOPY

Laryngoscopy and pharyngoscopy allow visualization of the larynx and pharynx for assessment of structural



FIG 17.1
Lateral radiograph of the neck, larynx, and pharynx showing normal anatomy. Note that the patient's head and neck are not rotated. The left and right osseous bullae, mandibles, and frontal sinuses are all superimposed. Excellent visualization of the soft palate and epiglottis is possible. Images obtained from poorly positioned patients often result in the appearance of "lesions" such as masses or abnormal soft palate because normal structures are captured at an oblique angle or are superimposed on one another.

abnormalities and laryngeal function. These procedures are indicated in any dog or cat with clinical signs that suggest upper airway obstruction or laryngeal or pharyngeal disease. It should be noted that patients with increased respiratory efforts resulting from upper airway obstruction might have difficulty during recovery from anesthesia. For a period between removal of the endotracheal tube and full recovery of neuromuscular function, the patient may be unable to maintain an open airway. *Therefore laryngoscopy should not be undertaken in these patients unless the clinician is prepared to perform whatever surgical treatments may be indicated during the same anesthetic period.*

The animal is placed in sternal recumbency. Anesthesia is induced and maintained with a short-acting injectable agent without prior sedation. Propofol is commonly used. Depth of anesthesia is carefully titrated, with just enough drug administered to allow visualization of the laryngeal cartilages; some jaw tone is maintained, and spontaneous deep respirations occur. Gauze is passed under the maxilla behind the canine teeth, and the head is elevated by hand (preferred) or by tying the gauze to a stand (Fig. 17.3). This positioning avoids external compression of the neck.

Gentle retraction of the tongue with a gauze sponge should allow visualization of the caudal pharynx and larynx. Avoid distorting the normal anatomy with excessive retraction. A laryngoscope is used for proper illumination of this



FIG 17.2
Lateral radiograph of a dog with a neck mass showing marked displacement of the larynx.



FIG 17.3
Dog positioned with the head held off the table by gauze passed around the maxilla and hung from an intravenous pole. The tongue is pulled out, and a laryngoscope is used to visualize the pharyngeal anatomy and laryngeal motion.

region. A tongue depressor for elevating the soft palate and a head lamp or well-positioned surgical lamp facilitate the examination.

The motion of the arytenoid cartilages is evaluated while the patient takes several deep breaths. An assistant is needed to verbally report the onset of each inspiration by observing chest wall movements. Normally the arytenoid cartilages abduct symmetrically and widely with each inspiration and close on expiration (Fig. 17.4). Laryngeal paralysis resulting in signs of upper airway obstruction is usually bilateral. The cartilages are not abducted during inspiration. In fact, they may be passively forced outward during expiration and/or sucked inward during inspiration, resulting in paradoxical motion.

If the patient fails to take deep breaths, doxapram hydrochloride (1.1-2.2 mg/kg, administered intravenously) can be given to stimulate breathing. In a study by Tobias et al. (2004), none of the potential systemic side effects of the drug were noted following the 1.1 mg/kg dosage, but some dogs required intubation when increased breathing efforts resulted in significant obstruction to airflow at the larynx.

If no laryngeal motion is observed, examination of the arytenoid cartilages should be continued as long as possible while the animal recovers from anesthesia. Effects of anesthesia and shallow breathing are the most common causes of an erroneous diagnosis of laryngeal paralysis.

After evaluation of laryngeal function, the plane of anesthesia is deepened and the caudal pharynx and larynx are

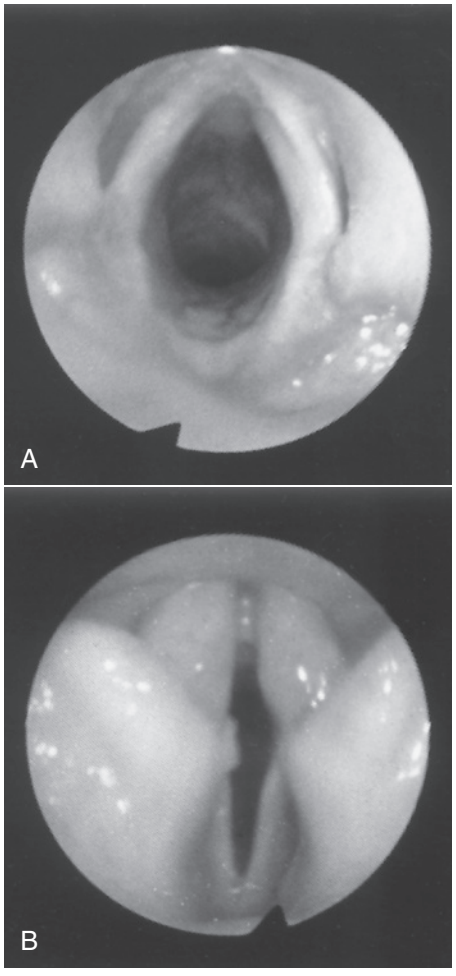


FIG 17.4
Canine larynx. **(A)** During inspiration, arytenoid cartilages and vocal folds are abducted, resulting in wide symmetric opening to the trachea. **(B)** During expiration, cartilages and vocal folds nearly close the glottis.

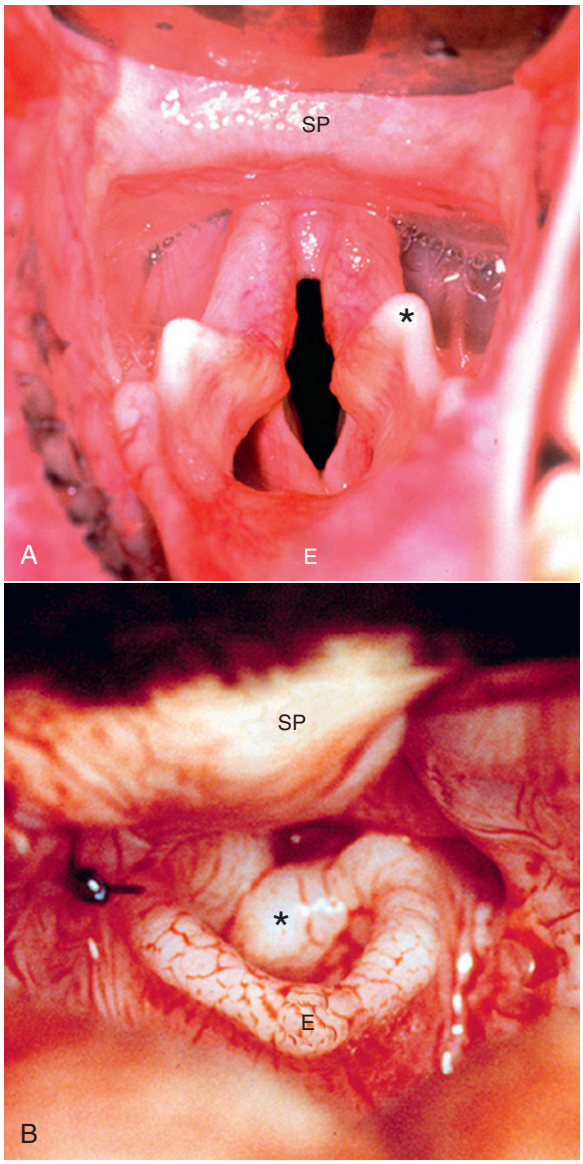


FIG 17.5
The laryngeal anatomy from a healthy dog **(A)** is contrasted with that of a dog with laryngeal collapse **(B).** In the collapsed larynx, the cuneiform process *(*)* of the arytenoid process has folded medially and obstructs most of the airway. Also labeled are the soft palate *(SP)* and the epiglottis *(E)*. In the photograph from the healthy dog, the soft palate is being held dorsally by a retractor (reflective, silver), and the tip of the epiglottis is not in view. (Courtesy Elizabeth M. Hardie.)

thoroughly evaluated for structural abnormalities, foreign bodies, or mass lesions. The length of the soft palate should be assessed. The soft palate normally extends to the tip of the epiglottis during inhalation. An elongated soft palate can contribute to signs of upper airway obstruction.

As described in Chapter 14, the caudal nasopharynx should be evaluated for nasopharyngeal polyps, mass lesions, foreign bodies, and nasopharyngeal stenosis. Needles or other sharp objects may be buried in tissue, and careful visual examination and palpation are required for detection. Brachycephalic patients are evaluated for obstruction of the internal nares by abnormal turbinate anatomy.

The trachea should be examined with a rigid or flexible endoscope if abnormalities are not identified on laryngoscopy in the dog or cat with signs of upper airway obstruction. If no endoscope is available, the laryngeal cartilages can be held open with an endotracheal tube for a cursory examination of the proximal trachea.

Neoplasia, granulomas, abscesses, or other masses can occur within or external to the larynx or pharynx, causing compression or deviation of normal structures or both. Severe, diffuse thickening of the laryngeal mucosa can be caused by infiltrative neoplasia or obstructive laryngitis. Biopsy specimens for histologic examination should be obtained from any lesions to establish an accurate diagnosis because the prognoses for these diseases are quite different. The normal diverse flora of the pharynx makes culture results difficult or impossible to interpret. Bacterial growth from abscess fluid or tissue obtained from granulomatous lesions may represent infection.

Obliteration of most of the airway lumen by collapse of the normal laryngeal structure is known as *laryngeal collapse* (Fig. 17.5). With prolonged upper airway obstruction, the soft tissues are sucked into the lumen by the increased negative pressure created as the dog or cat struggles to get air into its lungs. Eversion of the laryngeal saccules, thickening and elongation of the soft palate, and inflammation with thickening of the pharyngeal mucosa can occur. The laryngeal cartilages can become soft and deformed, unable to support the soft tissues of the pharynx. It is unclear whether this chondromalacia is a concurrent or secondary component of laryngeal collapse. Collapse most often occurs in dogs with brachycephalic airway syndrome but can also occur with any chronic obstructive disorder.

Suggested Readings

Rudorf H, et al. The role of ultrasound in the assessment of laryngeal paralysis in the dog. *Vet Radiol Ultrasound*. 2001;42:338.

Tobias KM, et al. Effects of doxapram HCl on laryngeal function of normal dogs and dogs with naturally occurring laryngeal paralysis. *Vet Anaesth Analg*. 2004;31:258.

CHAPTER 18

Disorders of the Larynx and Pharynx



LARYNGEAL PARALYSIS

Laryngeal paralysis refers to failure of the arytenoid cartilages to abduct during inspiration, creating extrathoracic (upper) airway obstruction. The abductor muscles are innervated by the left and right recurrent laryngeal nerves. If clinical signs develop, both arytenoid cartilages are usually affected. The disease can affect dogs and cats, but dogs are more often presented with clinical signs.

Etiology

Potential causes of laryngeal paralysis are listed in Box 18.1, with the cause remaining idiopathic in most cases. Historically, dogs with idiopathic laryngeal paralysis were considered to have dysfunction limited to the laryngeal nerve. It is now believed that idiopathic laryngeal paralysis is part of a generalized neuromuscular disorder. A study by Stanley et al. (2010) demonstrated that dogs with idiopathic laryngeal paralysis have esophageal dysfunction detected by swallowing studies. This study further showed that, on the basis of neurologic examination, these dogs will demonstrate signs of generalized neuromuscular disease within a year. Abnormal electrodiagnostic testing and histologic changes in peripheral nerves have also been reported (Thieman et al., 2010). Dogs with overt polyneuropathy-polymyopathy also may present with laryngeal paralysis as the predominant clinical sign. Polyneuropathies in turn have been associated with immune-mediated diseases, endocrinopathies, or other systemic disorders (see Chapter 66).

Congenital laryngeal paralysis has been documented in the Bouvier des Flandres and is suspected in Siberian Huskies and Bull Terriers. A laryngeal paralysis-polyneuropathy complex has been described in young Dalmatians, Rottweilers, and Great Pyrenees. The possibility that a genetic predisposition exists in Labrador Retrievers, even though signs appear later in life, has been proposed on the basis of their overrepresentation in reports of laryngeal paralysis (Shelton, 2010).

Direct damage to the laryngeal nerves or the larynx can also result in paralysis. Trauma or neoplasia involving the ventral neck can damage the recurrent laryngeal nerves directly or through inflammation and scarring. Masses or trauma involving the anterior thoracic cavity can also cause damage to the recurrent laryngeal nerves as they course around the subclavian artery (right side) or the ligamentum arteriosum (left side). These causes are less commonly encountered.

Clinical Features

Laryngeal paralysis can occur at any age and in any breed, although it is most commonly seen in older large-breed dogs. Labrador Retrievers are overrepresented. The disease is uncommon in cats. Clinical signs of respiratory distress and stridor are a direct result of narrowing of the airway at the arytenoid cartilages and vocal folds. The owner may also note a change in voice (i.e., bark or meow). Many patients are presented for acute respiratory distress, in spite of the chronic, progressive nature of this disease. Decompensation occurs as a result of exercise, excitement, or high environmental temperatures, resulting in a cycle of increased respiratory efforts; increased negative airway pressures, which suck the soft tissue into the airway; and pharyngeal edema and inflammation, which lead to further increased respiratory efforts. Cyanosis, syncope, and death can occur. Dogs in respiratory distress require immediate emergency therapy.

Some dogs with laryngeal paralysis exhibit gagging or coughing, often noted particularly with eating or drinking. These signs could be a result of secondary laryngitis, concurrent pharyngeal or esophageal dysfunction, and/or esophageal reflux secondary to upper airway obstruction. Signs of aspiration pneumonia may also be present but are rarely the presenting complaint.

Diagnosis

A definitive diagnosis of laryngeal paralysis is made through laryngoscopy (see Chapter 17). Movement of the arytenoid cartilages is observed during a light plane of anesthesia while the patient is taking deep breaths. In laryngeal paralysis, the arytenoid cartilages and the vocal folds remain in a midline position or are sucked inward (paradoxically)

BOX 18.1

Potential Causes of Laryngeal Paralysis

Idiopathic

Ventral Cervical Lesion

Trauma to nerves
- Direct trauma
- Inflammation
- Fibrosis

Neoplasia
Other inflammatory or mass lesion

Anterior Thoracic Lesion

Neoplasia
Trauma
- Postoperative
- Other

Other inflammatory or mass lesion

Polyneuropathy and Polymyopathy

Idiopathic
Immune mediated
Endocrinopathy
- Hypothyroidism

Other systemic disorder
- Toxicity

Congenital disease

Myasthenia Gravis

BOX 18.2

Diagnostic Evaluation of Dogs and Cats With Confirmed Laryngeal Paralysis

Underlying Cause

Thoracic radiographs
Cervical radiographs
Serum biochemical panel
Thyroid hormone evaluation
Ancillary tests in select cases
- Evaluation for polyneuropathy-polymyopathy
  - Electromyography
  - Nerve conduction measurements
- Antinuclear antibody test
- Antiacetylcholine receptor antibody test

Concurrent Pulmonary Disease

Thoracic radiographs

Concurrent Pharyngeal Dysfunction

Evaluation of gag reflex
Observation of patient swallowing food and water
Fluoroscopic observation of barium swallow

Concurrent Esophageal Dysfunction

Thoracic radiographs
Contrast-enhanced esophagram
Fluoroscopic observation of barium swallow

during inspiration and may open slightly during expiration. The larynx does not exhibit the normal coordinated movement associated with breathing, opening on inspiration and closing on expiration. Additional laryngoscopic findings may include laryngeal edema and inflammation. The larynx and the pharynx are also examined for neoplasia, foreign bodies, or other disorders that might interfere with normal function and for laryngeal collapse (see Chapter 17).

Once a diagnosis of laryngeal paralysis has been established, additional diagnostic tests should be considered to identify underlying or associated diseases (particularly if the patient is an atypical breed), to identify concurrent aspiration pneumonia, and identify concurrent pharyngeal and esophageal motility problems (Box 18.2).

Treatment

In animals with respiratory distress, emergency medical therapy to relieve upper airway obstruction is indicated (see Chapter 25). Following stabilization and a thorough diagnostic evaluation, surgery is usually the treatment of choice. Even when specific therapy can be directed at an associated disease (e.g., hypothyroidism), complete resolution of clinical signs of laryngeal paralysis is rarely seen.

Various laryngoplasty techniques have been described, including arytenoid lateralization (tie-back) procedures, partial laryngectomy, and castellated laryngoplasty. The goal of surgery is to provide an adequate opening for the flow of air but not one so large that the animal is predisposed to aspiration and the development of pneumonia. Several operations to gradually enlarge the glottis may be necessary to minimize the chance of subsequent aspiration. The recommended initial procedure for most dogs and cats is unilateral arytenoid lateralization.

If surgery is not an option, medical management consisting of antiinflammatory doses of short-acting glucocorticoids (e.g., prednisone, 0.5 mg/kg given orally q12h initially) and cage rest may reduce secondary inflammation and edema of the pharynx and larynx and enhance airflow. For long-term management, situations resulting in prolonged or increased breathing efforts, such as heavy exercise, and high ambient temperatures are avoided. Exercise may need to be limited to leash walks or other routines where the intensity of activity is controlled. Trazadone can be considered for highly excitable dogs.

Prognosis

The overall prognosis for dogs with laryngeal paralysis treated surgically is fair to good, despite evidence for progressive, generalized disease, esophageal dysfunction, or aspiration pneumonia. Wilson et al. (2016) showed that

outcome following surgical intervention was not related to presurgical esophageal dysfunction. In this study, 232 dogs that underwent unilateral lateralization procedures had 1-, 2-, 3-, and 4-year survival rates of 94%, 89%, 84%, and 75%, respectively. These numbers are quite positive, particularly considering the median age and body weights of these dogs were 10.6 years and 35 kg. At 1-, 3-, and 4-year follow-up, aspiration pneumonia occurred in 19%, 32%, and 32% of dogs. Risk factors for aspiration pneumonia were postoperative megaesophagus and postoperative administration of opioid analgesics before discharge. In contrast to previously held conventional wisdom, preoperative aspiration pneumonia was not a negative prognostic indicator. A good prognosis was reported for a small number of cats undergoing unilateral arytenoid lateralization (Thunberg et al., 2010).

BRACHYCEPHALIC AIRWAY SYNDROME

The term *brachycephalic airway syndrome,* or *brachycephalic airway obstruction syndrome (BOAS),* refers to the multiple anatomic abnormalities commonly found in brachycephalic dogs and, to a lesser extent, in short-faced cats such as Himalayans. The predominant, readily identified, anatomic abnormalities include stenotic nares, elongated soft palate, and, in Bulldogs, hypoplastic trachea. However, with the common use of computed tomography and rhinoscopy, it is now known that abnormal, obstructing nasal turbinates contribute significantly to the breathing abnormalities of dogs with this conformation (Oechtering, 2010; Oechtering et al., 2016). Prolonged upper airway obstruction resulting in increased inspiratory efforts may lead to eversion of the laryngeal saccules and, ultimately, to laryngeal collapse (see Fig. 17.5). The severity of these abnormalities varies, and one or any combination of these abnormalities may be present in any given brachycephalic dog or short-faced cat (Fig. 18.1).

Concurrent gastrointestinal signs such as ptyalism, regurgitation, and vomiting are common in dogs with brachycephalic airway syndrome (Poncet et al., 2005) Underlying gastrointestinal disease may be a concurrent problem in these breeds of dogs or may result from or may be exacerbated by increased intrathoracic pressures generated in response to the upper airway obstruction.

Clinical Features

Abnormalities associated with the brachycephalic airway syndrome impair the flow of air through the extrathoracic (upper) airways and cause clinical signs of upper airway obstruction, including loud breathing sounds, stertor, increased inspiratory efforts, cyanosis, and syncope. Clinical signs are exacerbated by exercise, excitement, and high environmental temperatures. The increased inspiratory effort commonly associated with this syndrome may cause secondary edema and inflammation of the laryngeal and pharyngeal mucosae and may enhance eversion of the laryngeal saccules or laryngeal collapse, further narrowing the glottis, exacerbating the clinical signs, and creating a vicious cycle.

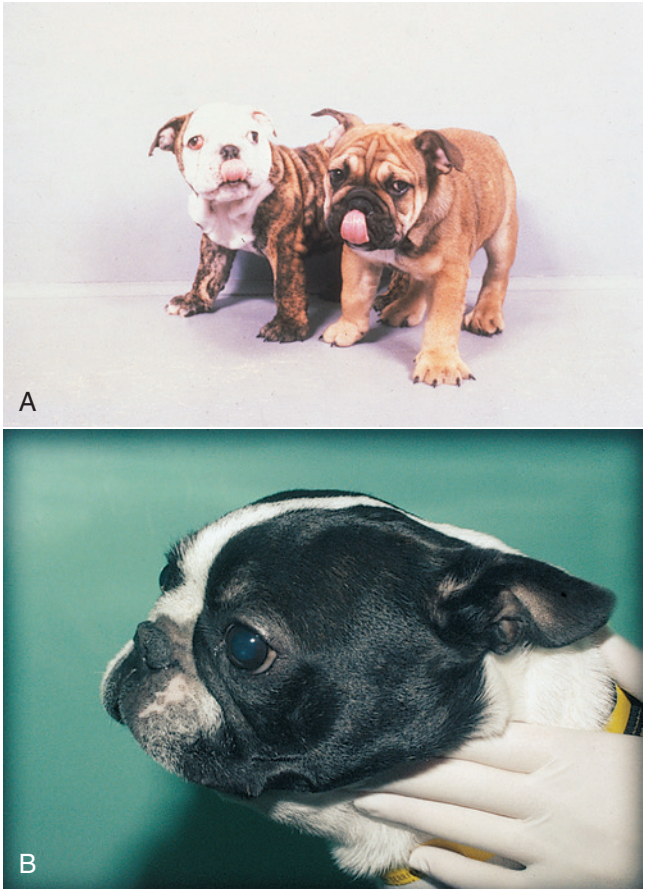


FIG 18.1
Two Bulldog puppies **(A)** and a Boston Terrier **(B)** with brachycephalic airway syndrome. Abnormalities can include stenotic nares, elongated soft palate, everted laryngeal saccules, laryngeal collapse, and hypoplastic trachea. Abnormal nasal turbinate development contributes significantly to obstruction.

As a result, some dogs may be presented with life-threatening upper airway obstruction that requires immediate emergency therapy. Concurrent gastrointestinal signs are commonly reported.

Diagnosis

A tentative diagnosis is made on the basis of breed, clinical signs, and appearance of the external nares (Fig. 18.2). Stenotic nares are generally bilaterally symmetric, and the alar folds may be sucked inward during inspiration, thereby worsening the obstruction to airflow. Laryngoscopy (see Chapter 17) and radiographic evaluation of the trachea (see Chapter 20) are necessary to fully assess the extent and severity of abnormalities. Computed tomography and rhinoscopy would be required to fully assess the turbinates; however, availability of treatment by laser turbinectomy is currently limited. Most other causes of upper airway obstruction (see Chapter 25 and Boxes 16.1 and 16.2) can also be ruled in or out on the basis of the results of these diagnostic tests.

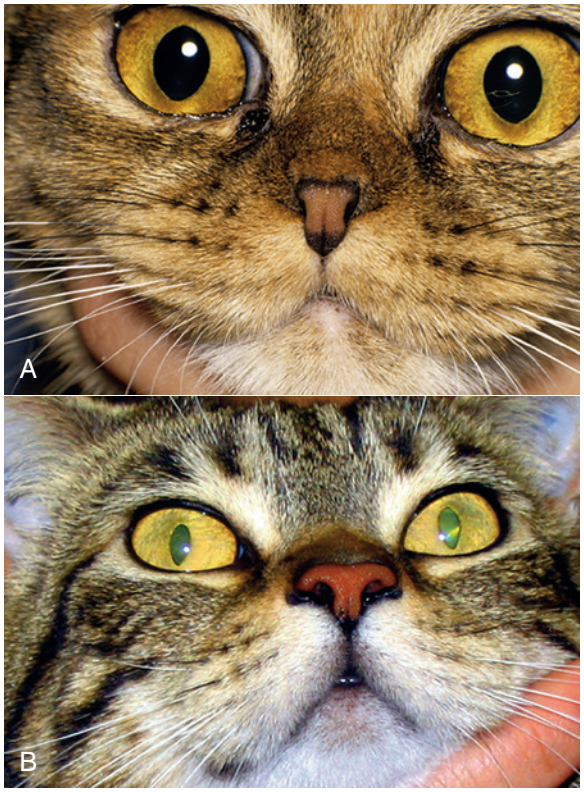


FIG 18.2
Cat with severely stenotic nares **(A)** as compared with the nares of a normal cat **(B).** Early correction of stenotic nares and other amenable upper airway obstructions, such as an elongated soft palate, is highly recommended.

Treatment

Therapy should be designed to enhance the passage of air through the upper airways and to minimize the factors that exacerbate clinical signs (e.g., excessive exercise and excitement, overheating). Surgical correction of anatomic defects is the treatment of choice. The specific surgical procedure selected depends on the nature of the existing problems and can include widening of the external nares and removal of excessive soft palate and everted laryngeal saccules. Laser turbinectomy has proven successful in improving quality of life but is technically difficult and not readily available (Schuenemann and Oechtering, 2014).

Correction of stenotic nares is a simple procedure and can lead to a surprising alleviation of signs in affected patients. Stenotic nares can be safely corrected at 3 to 4 months of age, *ideally before clinical signs develop*. The soft palate should be evaluated at the same time and corrected if elongated. Such early relief of obstruction should decrease the amount of negative pressure placed on pharyngeal and laryngeal structures during inspiration and may decrease progression of disease.

Medical management consisting of the administration of short-acting glucocorticoids (e.g., prednisone, 0.5 mg/kg given orally q12h initially) and cage rest may reduce the secondary inflammation and edema of the pharynx and larynx and enhance airflow, but it will not eliminate the problem. Emergency therapy may be required to alleviate the upper airway obstruction in animals presenting in respiratory distress (see Chapter 25).

Weight management and concurrent treatment for gastrointestinal disease should not be neglected in patients with brachycephalic airway syndrome.

Prognosis

The prognosis depends on the severity of the abnormalities at the time of diagnosis and the ability to surgically correct them. Clinical signs will progressively worsen if the underlying problems go uncorrected. The prognosis after early surgical correction of the abnormalities is good for many animals. Laryngeal collapse is generally considered a poor prognostic indicator, although even dogs with severe laryngeal collapse can respond well to surgical intervention (Torrez et al., 2006). Permanent tracheostomy can be considered as a salvage procedure in animals with severe collapse that are not responsive. A hypoplastic trachea is not surgically correctable, but there is no clear relationship between the degree of hypoplasia and morbidity or mortality. Using the objective measurement of tracheal diameter:thoracic inlet distance, six English Bulldog puppies (2-6 months of age) had improvement in relative tracheal diameter when reevaluated radiographically after 6 months or longer (Clarke et al., 2011). These findings suggest partial resolution is possible in some puppies as they develop.

OBSTRUCTIVE LARYNGITIS

Nonneoplastic infiltration of the larynx with inflammatory cells can occur in dogs and cats, causing irregular proliferation, hyperemia, and swelling of the larynx. Clinical signs of an upper airway obstruction may result. The larynx may appear grossly neoplastic during laryngoscopy but is differentiated from neoplasia on the basis of the histopathologic evaluation of biopsy specimens. Inflammatory infiltrates can be granulomatous, pyogranulomatous, or lymphocytic-plasmacytic. Etiologic agents have not been identified.

This syndrome is poorly characterized and probably includes several different diseases. Some animals respond to glucocorticoid therapy. Prednisone or prednisolone (1 mg/kg given orally q12h) is used initially. Once the clinical signs have resolved, the dose of prednisone can be tapered to the lowest amount that effectively maintains remission of clinical signs. Conservative excision of the tissue obstructing the airway may be necessary in animals with severe signs of upper airway obstruction or large granulomatous masses.

The prognosis varies, depending on the size of the lesion, the severity of laryngeal damage, and the responsiveness of the lesion to glucocorticoid therapy.

LARYNGEAL NEOPLASIA

Neoplasms originating from the larynx are uncommon in dogs and cats. More commonly, tumors originating in tissues adjacent to the larynx, such as thyroid carcinoma and lymphoma, compress or invade the larynx and distort normal laryngeal structures. Clinical signs of extrathoracic (upper) airway obstruction result. Laryngeal tumors include carcinoma (squamous cell, undifferentiated, and adenocarcinoma), lymphoma, melanoma, mast cell tumors and other sarcomas, and benign neoplasia. Lymphoma is the most common tumor in cats.

Clinical Features

The clinical signs of laryngeal neoplasia are similar to those of other laryngeal diseases and include noisy respiration, stridor, increased inspiratory efforts, cyanosis, syncope, and a change in bark or meow. Mass lesions can also cause concurrent dysphagia, aspiration pneumonia, or visible or palpable masses in the ventral neck.

Diagnosis

Extralaryngeal mass lesions are often identified by palpation of the neck. Primary laryngeal tumors are rarely palpable and are best identified by laryngoscopy. Laryngeal radiographs, ultrasonography, or computed tomography can be useful in assessing the extent of disease. Differential diagnoses include obstructive laryngitis, nasopharyngeal polyp, foreign body, traumatic granuloma, and abscess. Cytologic examination of fine-needle mass aspirates may provide a diagnosis. Yield and safety are increased with ultrasound guidance. A definitive diagnosis of neoplasia requires histologic examination of a biopsy specimen of the mass. A diagnosis of malignant neoplasia should not be made on the basis of gross appearance alone.

Treatment

The therapy used depends on the type of tumor identified histologically. Benign tumors should be excised surgically, if possible. Complete surgical excision of malignant tumors is rarely possible, although ventilation may be improved and time may be gained to allow other treatments such as radiation or chemotherapy to become effective. Complete laryngectomy and permanent tracheostomy may be considered in select animals.

Prognosis

The prognosis in animals with benign tumors is excellent if the tumors can be totally resected. Malignant neoplasms are associated with a poor prognosis.

Suggested Readings

Clarke DL, Holt DE, King LG. Partial resolution of hypoplastic trachea in six English bulldog puppies with bronchopneumonia. *J Am Anim Hosp Assoc*. 2011;47:329.

Gabriel A, et al. Laryngeal paralysis-polyneuropathy complex in young related Pyrenean mountain dogs. *J Small Anim Pract*. 2006;47:144.

Jakubiak MJ, et al. Laryngeal, laryngotracheal, and tracheal masses in cats: 27 cases (1998-2003). *J Am Anim Hosp Assoc*. 2005;41:310.

Lodato DL, et al. Brachycephalic airway syndrome: pathophysiology and diagnosis. *Compend Contin Educ Vet*. 2012;34:E1.

Oechtering GU. Brachycephalic syndrome—new information on an old congenital disease. *Vet Focus*. 2010;20:2.

Oechtering GU, et al. A novel approach to brachycephalic syndrome. 1. Evaluation of anatomical intranasal airway obstruction. *Vet Surg*. 2016;45:165.

Poncet CM, et al. Prevalence of gastrointestinal tract lesions in 73 brachycephalic dogs with upper respiratory syndrome. *J Small Anim Pract*. 2005;46:273.

Riecks TW, et al. Surgical correction of brachycephalic airway syndrome in dogs: 62 cases (1991-2004). *J Am Vet Med Assoc*. 2007;230:1324.

Schachter S, et al. Laryngeal paralysis in cats: 16 cases (1990-1999). *J Am Vet Med Assoc*. 2000;216:1100.

Schuenemann R, Oechtering G. Inside the brachycephalic nose: conchal regrowth and mucosal contact points after laser-assisted turbinectomy. *J Am Anim Hosp Assoc*. 2014;50:237.

Shelton DG. Acquired laryngeal paralysis in dogs: evidence accumulating for a generalized neuromuscular disease. *Vet Surg*. 2010;39:137.

Stanley BJ, et al. Esophageal dysfunction in dogs with idiopathic laryngeal paralysis: a controlled cohort study. *Vet Surg*. 2010;39:139.

Thieman KM, et al. Histopathological confirmation of polyneuropathy in 11 dogs with laryngeal paralysis. *J Am Anim Hosp Assoc*. 2010;46:161.

Thunberg B, et al. Evaluation of unilateral arytenoid lateralization for the treatment of laryngeal paralysis in 14 cats. *J Am Anim Hosp Assoc*. 2010;46:418.

Torrez CV, et al. Results of surgical correction of abnormalities associated with brachycephalic airway syndrome in dogs in Australia. *J Small Anim Pract*. 2006;47:150.

Wilson D, et al. Risk factors for the development of aspiration pneumonia after unilateral arytenoid lateralization in dogs with laryngeal paralysis: 232 cases (1987-2012). *J Am Vet Med Assoc*. 2016;248:188.

CHAPTER 19

Clinical Manifestations of Lower Respiratory Tract Disorders



CLINICAL SIGNS

In this discussion, the term *lower respiratory tract disorders* refers to diseases of the trachea, bronchi, bronchioles, alveoli, interstitium, and vasculature of the lung (Box 19.1). Dogs and cats with diseases of the lower respiratory tract are commonly seen for evaluation of cough. Lower respiratory tract diseases that interfere with the oxygenation of blood can result in respiratory distress, exercise intolerance, weakness, cyanosis, or syncope. Nonlocalizing signs such as fever, anorexia, weight loss, and depression also occur and are the only presenting sign in some animals. Auscultation and thoracic radiography help localize the disease to the lower respiratory tract in these animals. The two major presenting signs in animals with lower respiratory tract disease—cough and respiratory distress—can be further characterized by a careful history and physical examination.

COUGH

A cough is an explosive release of air from the lungs through the mouth. It is generally a protective reflex to expel material from the airways, although inflammation or compression of the airways can also stimulate cough. Cough is sometimes caused by disease outside of the lower respiratory tract. Chylothorax and laryngeal disease can cause cough. Although not well documented in dogs or cats, gastroesophageal reflux and postnasal drip are common causes of cough in people.

Classically in human medicine, differential diagnoses for cough are divided into those that cause productive cough and those that cause nonproductive cough. A productive cough results in the delivery of mucus, exudate, edema fluid, or blood from the airways into the oral cavity, whereas a nonproductive cough is a dry cough. This distinction is readily made in people because they can report their experience. However, in veterinary medicine, many patients with productive diseases do not appear to have a productive cough, despite careful observation and auscultation. Therefore, if a cough can be identified as productive the list of differential diagnoses can be narrowed (Box 19.2). *However, not hearing or seeing evidence of productivity does not rule out the possibility of its presence, and these differentials should remain under consideration.*

Productive coughs are most commonly caused by inflammatory or infectious diseases involving the airways or alveoli and by heart failure. A moist sound can often be heard during the cough. Animals rarely expectorate the fluid, but swallowing can often be seen after a coughing episode. If expectoration occurs, clients may confuse the cough with vomiting. Cough in cats can be confused with attempts to vomit a hairball. Cats that never produce a hairball are likely coughing (Video 19.1).

Hemoptysis is the coughing up of blood. Blood-tinged saliva may be observed within the oral cavity or dripping from the commissures of the mouth after a cough. Hemoptysis is an unusual clinical sign that most commonly occurs in animals with heartworm disease or pulmonary neoplasia. Less common causes of hemoptysis are mycotic infection, foreign bodies, severe congestive heart failure, thromboembolic disease, lung lobe torsion, and some systemic bleeding disorders, such as disseminated intravascular coagulation (see Box 19.2).

Intensity of cough is useful in prioritizing the differential diagnoses, although exceptions are common. Cough associated with airway inflammation (i.e., bronchitis) or large airway collapse is often loud, harsh, and paroxysmal. The cough associated with tracheal collapse is often described as a "goose-honk." Cough resulting from tracheal disease can usually be induced by palpation of the trachea, although there is often concurrent involvement of the deeper airways. Cough associated with pneumonias and pulmonary edema is often soft.

The association of coughing with temporal events can be helpful. Cough resulting from tracheal disease is exacerbated by pressure on the neck, such as pulling on the animal's collar. Cough caused by heart failure tends to occur more frequently at night, whereas cough caused by airway inflammation (bronchitis) tends to occur more frequently upon rising from sleep or during and after exercise or exposure to cold air. The client's perception of frequency may be biased

BOX 19.1

Differential Diagnoses for Lower Respiratory Tract Disease in Dogs and Cats

Disorders of the Trachea and Bronchi

Canine infectious respiratory disease complex
Canine chronic bronchitis
Tracheobronchomalacia (collapsing trachea and/or bronchi)
Feline bronchitis (idiopathic)
Allergic bronchitis
Bacterial, including *Mycoplasma,* infections
Oslerus osleri infection
Neoplasia
Foreign body
Tracheal tear
Bronchial compression
- Left atrial enlargement
- Hilar lymphadenopathy
- Neoplasia

Disorders of the Pulmonary Parenchyma and Vasculature

Infectious diseases
- Viral pneumonias
  - Canine influenza
  - Canine distemper
  - Calicivirus
  - Feline infectious peritonitis
- Bacterial pneumonia
- Protozoal pneumonia
  - Toxoplasmosis
- Fungal pneumonia
  - Blastomycosis
  - Histoplasmosis
  - Coccidioidomycosis
- Parasitic disease
  - Heartworm disease
  - Pulmonary parasites
    - *Paragonimus* infection
    - *Aelurostrongylus* infection
    - *Capillaria* infection
    - *Crenosoma* infection

Aspiration pneumonia
Eosinophilic lung disease
Idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis

Pulmonary neoplasia
Pulmonary contusions
Pulmonary hypertension
Pulmonary thromboembolism
Pulmonary edema

by the times of day during which they have the most contact with their pets, often in the evenings and during exercise.

It is surprising to note that cats with many of the disorders listed in Box 19.2 do not cough. In cats that cough, the index of suspicion for bronchitis, lung parasites, and heartworm disease is high.

BOX 19.2

Differential Diagnoses for Productive Cough* in Dogs and Cats

Edema

Heart failure
Noncardiogenic pulmonary edema

Mucus or Exudate

Canine infectious respiratory disease complex
Canine chronic bronchitis
Feline bronchitis (idiopathic)†
Allergic bronchitis†
Bacterial infection (bronchitis or pneumonia)
Parasitic disease†
Aspiration pneumonia
Fungal pneumonia (severe)

Blood (Hemoptysis)

Heartworm disease†
Neoplasia
Fungal pneumonia
Thromboembolism
Severe heart failure
Foreign body
Lung lobe torsion
Systemic bleeding disorder

*Because it can be difficult to determine the productive nature of a cough in veterinary medicine, these differential diagnoses should also be considered in patients with nonproductive cough.
†Diseases of the lower respiratory tract most often associated with cough in cats. Cough in cats is rarely identified as productive.

EXERCISE INTOLERANCE AND RESPIRATORY DISTRESS

Diseases of the lower respiratory tract can compromise the lung's function of oxygenating the blood through a variety of mechanisms (see the section on blood gas analysis in Chapter 20). Clinical signs of such compromise begin as mildly increased respirations and subtly decreased activity and progress through exercise intolerance (manifested as reluctance to exercise or respiratory distress with exertion) to overt respiratory distress at rest. Because of compensatory mechanisms, the ability of most pets to self-regulate their activity, and the inability of pets to communicate, many veterinary patients with compromised lung function arrive in overt respiratory distress. Dogs in overt distress will often stand with their neck extended and elbows abducted. Movements of the abdominal muscles may be exaggerated. Healthy cats have minimally visible respiratory efforts. Cats that show noticeable chest excursions or open-mouth breathing are severely compromised. Patients in overt distress require rapid physical assessment and immediate stabilization before further diagnostic testing, as discussed in Chapter 25.

Resting Respiratory Rate

Resting respiratory rate can be used as an objective indicator of pulmonary function in patients that are not yet in respiratory distress. The measurement is ideally made at home by the owner, eliminating the effect of the stress of the veterinary hospital on the respiratory rate. The normal respiratory rate of a dog or cat without stress, at rest, is less than 20 respirations per minute. A rate of up to 30 respirations per minute is generally considered normal during a routine physical examination. Panting is a distinct activity with respiratory rates often exceeding 200 breaths/minute. Panting is primarily associated with the function of heat dissipation but can also be seen as a response to pain or anxiety and in association with hyperadrenocorticism or steroid administration.

Mucous Membrane Color

Cyanosis, in which normally pink mucous membranes are bluish, is a sign of severe hypoxemia and indicates that the increased respiratory effort is not sufficiently compensating for the degree of respiratory dysfunction. Pallor of mucous membranes is a more common sign of acute hypoxemia resulting from respiratory disease.

Breathing Pattern

Patients in respiratory distress resulting from diseases of the lower respiratory tract, excluding the large airways, typically have rapid and often shallow respirations; have increased expiratory or inspiratory efforts, or both; and may have abnormal lung sounds on auscultation. Patients with intrathoracic large airway obstruction (intrathoracic trachea and/or large bronchi) generally have normal to slightly increased respiratory rate; prolonged, labored expiration; and audible or auscultable expiratory sounds (see Chapter 25).

DIAGNOSTIC APPROACH TO DOGS AND CATS WITH LOWER RESPIRATORY TRACT DISEASE

INITIAL DIAGNOSTIC EVALUATION

The initial diagnostic evaluation of dogs or cats with signs of lower respiratory tract disease includes a complete history, physical examination, thoracic radiographs, and complete blood count (CBC). Further diagnostic tests are selected on the basis of information obtained from these procedures; these include tests for specific diseases, the evaluation of specimens collected from the lower respiratory tract, specialized imaging techniques, and pulmonary function tests (Fig. 19.1). Historical information was discussed in previous paragraphs.

Physical Examination

Measurement of respiratory rate, assessment of mucous membrane color, and observation of the breathing pattern

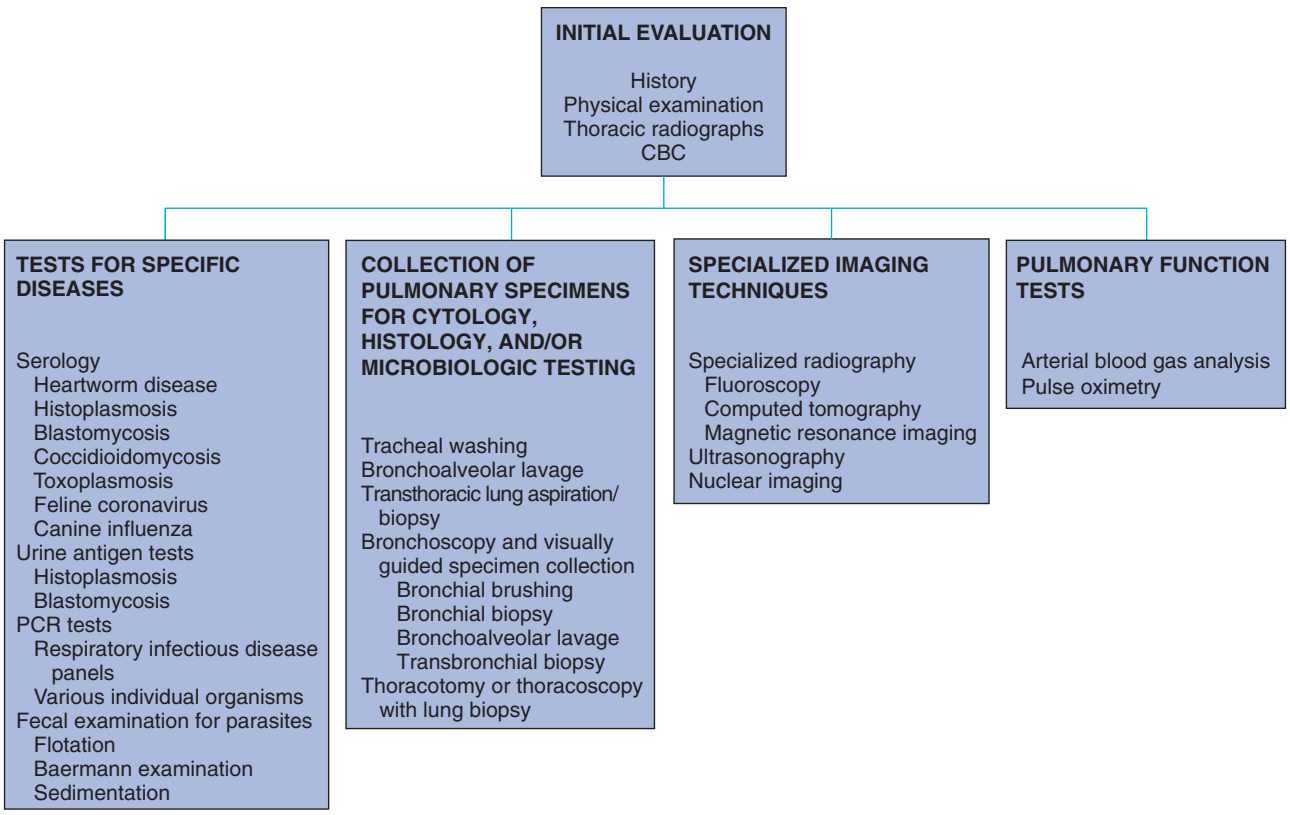


FIG 19.1
Diagnostic approach for dogs and cats with lower respiratory tract disease.

were described in the previous sections. A complete physical examination, including a fundic examination, is warranted to identify signs of disease that may be concurrently or secondarily affecting the lungs (e.g., systemic mycoses, metastatic neoplasia, megaesophagus).

The cardiovascular system should be carefully evaluated. Mitral insufficiency murmurs are frequently auscultated in older small-breed dogs brought to the clinician with the primary complaint of cough. Mitral insufficiency is often an incidental finding, but the clinician must consider both cardiac and respiratory tract diseases as differential diagnoses in these animals. Mitral insufficiency can lead to congestive heart failure with pulmonary edema, and left atrial enlargement itself may contribute to cough. Cough associated with mitral insufficiency has been presumed to be a result of airway compression by an enlarged left atrium, but collapse of the left bronchus appears to be independent of atrial size (Singh et al., 2012). Other factors, such as vibration from a mitral jet or concurrent bronchial inflammation, may be involved. Congestive heart failure most often results in tachypnea or dyspnea, rather than cough (Ferasin et al., 2013), and tachycardia. Other signs of heart disease include prolonged capillary refill time, weak or irregular pulses, abnormal jugular pulses, ascites or subcutaneous edema, gallop rhythms, and pulse deficits. Thoracic radiographs and occasionally echocardiography may be needed before cardiac problems can be comfortably ruled out as a cause of lower respiratory tract signs.

Thoracic auscultation

Careful auscultation of the upper airways and lungs is a critical component of the physical examination in dogs and cats with respiratory tract signs. Auscultation should be performed in a quiet location with the animal calm. Panting and purring do not result in deep inspiration, precluding evaluation of lung sounds. The heart and upper airways should be auscultated first. The clinician can then mentally subtract the contribution of these sounds from the sounds auscultated over the lung fields.

Initially, the stethoscope is placed over the trachea near the larynx (Fig. 19.2). Discontinuous snoring or snorting sounds can be referred from the nasal cavity and pharynx as a result of obstructions stemming from structural abnormalities, such as an elongated soft palate or mass lesions, and excessive mucus or exudate. Collapse of the extrathoracic trachea can also cause coarse sounds. Wheezes, which are continuous high-pitched sounds, occur in animals with obstructive laryngeal conditions, such as laryngeal paralysis, neoplasia, inflammation, and foreign bodies. Discontinuous snoring sounds and wheezes are known as *stertor* and *stridor,* respectively, when they can be heard without a stethoscope. The entire cervical trachea is then auscultated for areas of high-pitched sounds caused by localized airway narrowing. Several breaths are auscultated with the stethoscope in each position, and the phase of respiration in which abnormal sounds occur is noted. Abnormal sounds resulting from extrathoracic disease are generally loudest during inspiration.

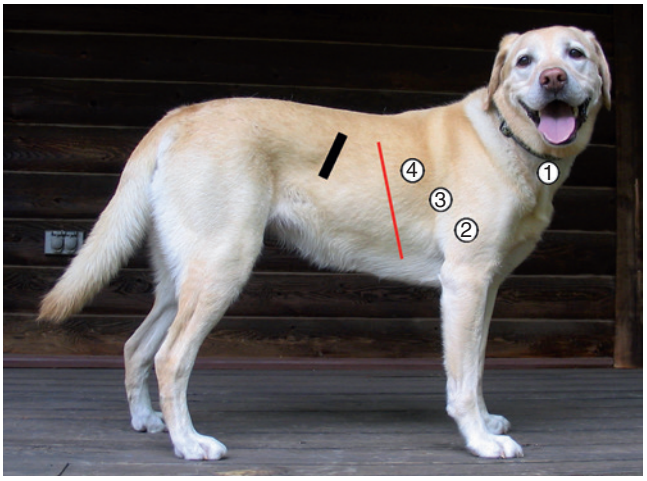


FIG 19.2
Auscultation of the respiratory tract begins with the stethoscope positioned over the trachea (stethoscope position 1). After upper airway sounds are assessed, the stethoscope is positioned to evaluate the cranioventral, central, and dorsal lung fields on both sides of the chest (stethoscope positions 2, 3, and 4). Note that the lung fields extend from the thoracic inlet to approximately the seventh rib along the sternum and to approximately the eleventh intercostal space along the spine *(thin red line)*. Common mistakes are to neglect the cranioventral lung fields, reached by placing the stethoscope between the forelimb and the chest, and to position the stethoscope too far caudally, beyond the lung fields and over the liver. (*Thick black line* indicates position of the thirteenth rib.)

The lungs are auscultated next. Normally, the lungs extend cranially to the thoracic inlet and caudally to about the seventh rib ventrally along the sternum and to approximately the eleventh intercostal space dorsally along the spine (see Fig. 19.2). The cranioventral, central, and dorsal lung fields on both the left and right sides are auscultated systematically. Any asymmetry in the sounds between the left and right sides is abnormal.

Normal lung sounds have been described historically as a mixture of "bronchial or tracheal" and "vesicular" sounds, although all sounds originate from the large airways rather than the alveoli (vesicles). The terms "breath sounds" or "lung sounds" are now preferred. Tracheal and bronchial sounds are louder, harsher, tubular sounds heard over the trachea and, less prominently, in the central regions of the lungs. Over the majority of the lung field, sounds are normally soft and have been likened to a breeze blowing through leaves.

Decreased lung sounds over one or both sides of the thorax occur in dogs and cats with pleural effusion, pneumothorax, diaphragmatic hernia, or mass lesions. It is surprising to note that consolidated lung lobes and mass lesions can result in enhanced lung sounds because of improved transmission of airway sounds from adjacent lobes.

Abnormal lungs sounds are described as increased breath sounds (alternatively, harsh lung sounds), crackles, or wheezes. Increased breath sounds are a nonspecific finding

but are common in patients with pulmonary edema or pneumonia. Crackles are nonmusical, discontinuous noises that sound like paper being crumpled or bubbles popping. Diseases resulting in the formation of edema or an exudate within the airways (e.g., pulmonary edema, infectious or aspiration pneumonia, bronchitis) and some interstitial pneumonias, particularly interstitial fibrosis, can result in crackles. Wheezes are musical, continuous sounds that indicate the presence of airway narrowing. Narrowing can occur as a result of bronchoconstriction, bronchial wall thickening, exudate or fluid within the bronchial lumen, intraluminal masses, or external airway compression. Wheezes are most commonly heard in cats with bronchitis. Wheezes caused by an intrathoracic airway obstruction are loudest during early expiration. Sudden snapping at the end of expiration can be heard in some dogs with intrathoracic tracheal collapse.

Radiography

Thoracic radiographs are indicated in dogs and cats with lower respiratory tract signs. Neck radiographs should also be obtained in animals with suspected tracheal disease. Radiography is perhaps the single most helpful diagnostic tool in the evaluation of dogs and cats with intrathoracic disease. It helps in localizing the problem to an organ system (i.e., cardiac, pulmonary, mediastinal, pleural), identifying the area of involvement within the lower respiratory tract (i.e., vascular, bronchial, alveolar, interstitial), and narrowing the list of potential differential diagnoses. It also helps in the formulation of a diagnostic plan (see Chapter 20). Additional diagnostic tests are necessary in most animals to establish a definitive diagnosis.

Complete Blood Count

The CBC of patients with lower respiratory tract disease may show anemia of inflammatory disease, polycythemia secondary to chronic hypoxia, or a white blood cell response characteristic of an inflammatory process of the lungs. The hematologic changes are insensitive, however, and an absence of abnormalities cannot be used as the basis for ruling out inflammatory lung disease. For instance, only half of dogs with bacterial pneumonia have a neutrophilic leukocytosis and a left shift.

PULMONARY SPECIMENS AND SPECIFIC DISEASE TESTING

On the basis of results of the history, physical examination, thoracic radiographs, and CBC, a prioritized list of differential diagnoses is developed. Additional diagnostic tests (Fig. 19.1) are nearly always required to achieve a definitive diagnosis, which is necessary for optimal therapy and outcome. Selection of appropriate tests is based on the most likely differential diagnoses, the localization of disease within the lower respiratory tract (e.g., diffuse bronchial disease, single mass lesion), the degree of respiratory compromise of the patient, and the client's motivation for optimal care.

Invasive and noninvasive tests are available. Noninvasive tests have the obvious advantage of being nearly risk free but are usually aimed at confirming a specific diagnosis. Patients with persistent lower respiratory tract disease often require collection of a pulmonary specimen for microscopic and microbiologic analysis to further narrow the list of differential diagnoses or to make a definitive diagnosis. Although the procedures for specimen collection from the lung are considered invasive, they carry varying degrees of risk, depending on the procedure used and the degree of respiratory compromise of the patient. The risk is minimal in many instances.

Noninvasive tests include serology, urine antigen tests, and polymerase chain reaction (PCR) tests for pulmonary pathogens, fecal examinations for parasites, and specialized imaging techniques such as fluoroscopy, angiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and nuclear imaging. Techniques for collection of pulmonary specimens that can be performed without specialized equipment include tracheal wash, nonbronchoscopic bronchoalveolar lavage, and transthoracic lung aspiration. Visually guided specimens can be collected during bronchoscopy. Bronchoscopy offers the additional benefit of allowing visual assessment of the airways. If analysis of lung specimens and results of reasonable noninvasive tests do not provide a diagnosis in a patient with progressive disease, thoracoscopy or thoracotomy with lung biopsy is indicated.

Valuable information about patients with lower respiratory tract disease can also be obtained by assessing lung function through arterial blood gas analysis. Results are rarely helpful in making a final diagnosis, but they are useful in determining degree of compromise and in monitoring response to therapy. Pulse oximetry, a noninvasive technique used to measure oxygen saturation of the blood, is particularly valuable in monitoring patients with respiratory compromise during anesthetic procedures or respiratory crises.

Suggested Readings

Bohadan A, et al. Fundamentals of lung auscultation. *N Engl J Med*. 2014;370:744.

Ferasin L, et al. Risk factors for coughing in dogs with naturally acquired myxomatous mitral valve disease. *J Vet Intern Med*. 2013;27:286.

Hamlin RL. Physical examination of the pulmonary system. *Vet Clin N Am Small Anim Pract*. 2000;30:1175.

Hawkins EC, et al. Demographic and historical findings, including exposure to environmental tobacco smoke, in dogs with chronic cough. *J Vet Intern Med*. 2010;24:825.

Sarkar M, et al. Ausculation of the respiratory system. *Ann Thor Med*. 2015;10:158.

Singh MK, et al. Bronchomalacia in dogs with myxomatous mitral valve degeneration. *J Vet Intern Med*. 2012;26:312.

CHAPTER 20

Diagnostic Tests for the Lower Respiratory Tract



THORACIC RADIOGRAPHY

GENERAL PRINCIPLES

Thoracic radiographs play an integral role in the diagnostic evaluation of dogs and cats with clinical signs related to the lower respiratory tract. They are also indicated for the evaluation of animals with vague, nonspecific signs of disease to detect occult pulmonary disease. Thoracic radiographs can be helpful in localizing disease processes, narrowing and prioritizing the differential diagnoses, determining the extent of disease involvement, and monitoring the progression of disease and response to treatment.

A minimum of two views of the thorax should be taken in all dogs and cats, but three views will improve the detection of lesions. Right lateral and ventrodorsal (VD) views are standard. The addition of the left lateral view improves the sensitivity of radiographs in the detection of disease of the right middle lung lobe, single nodules or metastatic disease, and other subtle changes. The side of the lung away from the table is more aerated, thereby providing more contrast for soft tissue opacities, and is slightly magnified compared with the side against the table. Dorsoventral (DV) views are taken to evaluate the dorsal pulmonary arteries in animals with suspected heartworm disease, pulmonary thromboembolism, or pulmonary hypertension to enhance contrast of the dorsally oriented vessels. Patients in respiratory distress are evaluated with DV, rather than VD, views to minimize stress. Horizontal beam lateral radiographs with the animal standing can be used to evaluate animals with suspected cavitary lesions or pleural effusion.

Careful technique is essential to ensure that thoracic radiographs are obtained that yield useful information. Poor technique can lead to underinterpretation or overinterpretation of abnormalities. Appropriate exposure settings should be used and the settings recorded so that the same technique can be used when future images of the patient are obtained; this allows for more critical comparison of progression of disease. Radiographs should be interpreted using a large, high-resolution monitor and dim ambient lighting.

The dog or cat should be restrained adequately to prevent movement, and a short exposure time used. Radiographs should be taken during maximum inspiration. Fully expanded lungs provide the greatest air contrast for soft tissue opacities, and motion is minimized during this phase of the respiratory cycle. Radiographic indications of maximum inspiration include widening of the angle between the diaphragm and the vertebral column (representing maximal expansion of caudal lung lobes); a lucent region in front of the heart shadow (representing maximal expansion of the cranial lung lobes); flattening of the diaphragm; minimal contact between the heart and the diaphragm; and a well-delineated, nearly horizontal vena cava. Radiographs of the lungs obtained during phases of respiration other than peak inspiration are difficult to interpret. Incomplete expansion of the lungs can cause increased pulmonary opacities to be seen that appear pathologic, resulting in misdiagnosis.

Animals that are panting should be allowed to calm down before thoracic radiographs are obtained. It may be necessary to sedate some animals.

All structures of the thorax should be evaluated systematically in every animal to enhance diagnostic accuracy. Extrapulmonary abnormalities may develop secondary to pulmonary disease and may be the only radiographic finding (e.g., subcutaneous emphysema after tracheal laceration). Conversely, pulmonary disease may occur secondary to other evident thoracic diseases, such as mitral valve insufficiency, megaesophagus, and neoplasia of the body wall.

TRACHEA

The trachea and, in young animals, the thymus are recognizable in the cranial mediastinum. Radiographs of the cervical trachea are obtained from dogs and cats with suspected upper airway obstruction or primary tracheal disease, including tracheal collapse (tracheal malacia) in dogs. During evaluation of the trachea, it is important to obtain radiographs of the cervical portion during inspiration and of the thorax during both inspiration and expiration to identify dynamic changes in luminal diameter. As previously discussed, avoid over-reading lung lesions in the expiratory exposures.

Only the inner wall of the trachea should be visible. Visibility of the outer wall of the trachea is suggestive of pneumomediastinum. The trachea normally has a uniform diameter and is straight, deviating ventrally from the vertebral bodies on lateral views as it progresses toward the carina. It may appear elevated near the carina if the heart is enlarged or if pleural effusion is present. Flexion or extension of the neck may cause bowing of the trachea. On VD views, the trachea may deviate to the right of midline in some dogs. The tracheal cartilage becomes calcified in some older dogs and chondrodystrophic breeds.

The overall size and continuity of the tracheal lumen should also be evaluated. The normal tracheal lumen is nearly as wide as the laryngeal lumen. Hypoplastic tracheas are most often found in English Bulldogs and have a lumen less than half the normal size (Fig. 20.1). The ratio of tracheal diameter to thoracic inlet diameter (TD:TI) can be used to more objectively define tracheal size in these patients. If identified in dogs less than 1 year of age, the hypoplasia may partially resolve with maturity (Clarke et al., 2011). Strictures and fractured cartilage rings can cause an abrupt, localized narrowing of the air stripe.

Mass lesions in the tissues adjacent to the trachea can compress the trachea, causing a more gradual, localized narrowing of the air stripe. The air contrast of the trachea sometimes allows foreign bodies or masses to be visualized within the trachea. Most foreign bodies lodge at the level of the carina or within the bronchi. The inability to radiographically identify a foreign body does not rule out the diagnosis, however.

The radiographic diagnosis of tracheobronchomalacia (tracheal collapse) can be challenging, and radiographic signs should be interpreted with some caution. In theory, the diagnosis should be straightforward. In animals with extrathoracic tracheal collapse, the tracheal air stripe would be narrowed in the cervical region during inspiration. In animals with intrathoracic tracheal collapse, the air stripe would be narrowed within the thorax during expiration. In reality, a diagnosis of tracheal collapse may be missed simply because the intra- to extra-airway pressure differential is insufficient for a dog lying on the radiology table to create visible narrowing of the trachea. Further, in the cervical trachea, a soft tissue opacity extending along the dorsal margin of the trachea may represent either abnormal sagging of the dorsal tracheal membrane or overlying esophagus (or other soft tissue). Fluoroscopy, available primarily through referral centers, provides a more sensitive assessment of tracheal collapse.

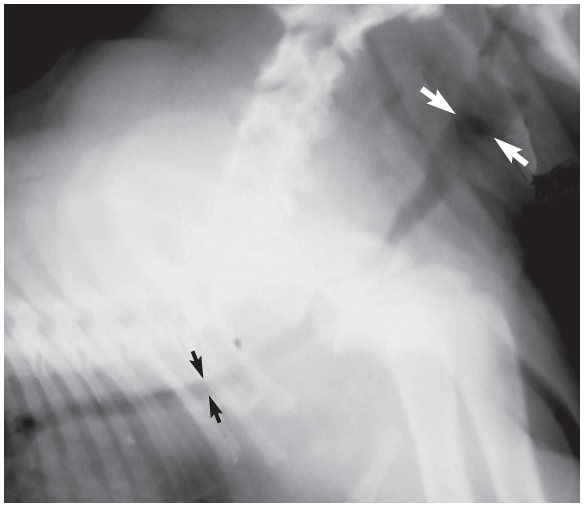


FIG 20.1
Lateral radiograph of a Bulldog with a hypoplastic trachea. The tracheal lumen *(narrow arrows)* is less than half the size of the larynx *(broad arrows)*.

LUNGS

The clinician must be careful not to overinterpret lung abnormalities on thoracic radiographs. A definitive diagnosis is not possible in most animals, and microscopic examination of pulmonary specimens, further evaluation of the heart, or testing for specific diseases is necessary. The lungs are examined for the possible presence of four major abnormal patterns: vascular, bronchial, alveolar, and interstitial. Mass lesions are considered with the interstitial patterns. Lung lobe consolidation, atelectasis, pulmonary cysts, and lung lobe torsions are other potential abnormalities. The distribution of lesions within the lungs is also noted. Diseases of airway origin, such as bronchopneumonia and aspiration pneumonia, typically have more severe radiographic disease affecting the gravity-dependent lung lobes (right middle and cranial, and/or left cranial lobes). Diseases originating from the vasculature or lymphatics, such as metastatic neoplasia and systemic mycoses, may affect the caudal lung lobes more severely. Animals in severe respiratory distress localized to the lungs by history and physical examination and normal thoracic radiograph usually have thromboembolic disease or have suffered a very recent insult to the lungs, such as trauma or aspiration (Box 20.1).

Vascular Pattern

The pulmonary vasculature is assessed by evaluating the vessels to the cranial lung lobes on the lateral view and the vessels to the caudal lung lobes on the VD or DV view. Normally, the blood vessels should taper gradually from the left atrium (pulmonary vein) or the right ventricle (pulmonary arteries) toward the periphery of the lungs. Companion arteries and veins should be similar in size. Arteries and veins have a consistent relationship with each other and with the associated bronchus. On lateral radiographs, the pulmonary artery is dorsal and the pulmonary vein is ventral to the bronchus. On VD or DV radiographs, the pulmonary artery is lateral and the pulmonary vein is medial to the bronchus. Vessels that are pointed directly toward or away from the X-ray beam are "end-on" and appear as circular nodules. They are distinguished from lesions by their association with a linear vessel and adjacent bronchus.

Abnormal vascular patterns generally involve an increase or decrease in the size of arteries or veins (Box 20.2). The

BOX 20.1

Common Lower Respiratory Tract Differential Diagnoses for Dogs and Cats With Respiratory Signs and Normal Thoracic Radiographs

Respiratory Distress

Pulmonary thromboembolism
Acute aspiration
Acute pulmonary hemorrhage
Acute foreign body inhalation

Cough

Canine infectious respiratory disease complex
Canine chronic bronchitis
Collapsing trachea
Feline bronchitis (idiopathic)
Acute foreign body inhalation
Gastroesophageal reflux*

*Gastroesophageal reflux is a common cause of cough in people. Documentation in dogs and cats is limited, but the possibility should be considered.

finding of arteries larger than their companion veins indicates the presence of pulmonary hypertension or thromboembolism, most commonly caused by heartworm disease—a finding seen in both dogs and cats (Fig. 20.2). The pulmonary arteries often appear tortuous and truncated in such animals. Concurrent enlargement of the main pulmonary artery and the right side of the heart may be seen in affected dogs. Interstitial, bronchial, or alveolar infiltrates may also be present in cats and dogs with heartworm disease as a result of concurrent inflammation, edema, or hemorrhage. Infection with *Aelurostrongylus abstrusus* can also cause pulmonary artery enlargement.

Veins larger than their companion arteries indicate the presence of congestion resulting from left-sided heart failure. Pulmonary edema may also be present.

Dilation of both arteries and veins is an unusual finding, except in young animals. The finding of pulmonary overcirculation is suggestive of left-to-right cardiac or vascular shunts, such as patent ductus arteriosus and ventricular septal defects.

The finding of smaller-than-normal arteries and veins may indicate the presence of pulmonary undercirculation or hyperinflation. Undercirculation most often occurs in combination with microcardia resulting from hypoadrenocorticism or other causes of severe hypovolemia. Pulmonic

BOX 20.2

Differential Diagnoses for Dogs and Cats With Abnormal Pulmonary Vascular Patterns on Thoracic Radiographs

Enlarged Arteries

Heartworm disease
Aelurostrongylosis (cats)
Pulmonary thromboembolism
Pulmonary hypertension

Enlarged Veins

Left-sided heart failure

Enlarged Arteries and Veins (Pulmonary Overcirculation)

Left-to-right shunts
- Patent ductus arteriosus
- Ventricular septal defect
- Atrial septal defect

Small Arteries and Veins

Pulmonary undercirculation
- Cardiovascular shock
- Hypovolemia
  - Severe dehydration
  - Blood loss
  - Hypoadrenocorticism
- Pulmonic valve stenosis

Hyperinflation of the lungs
- Feline bronchitis (idiopathic)
- Allergic bronchitis

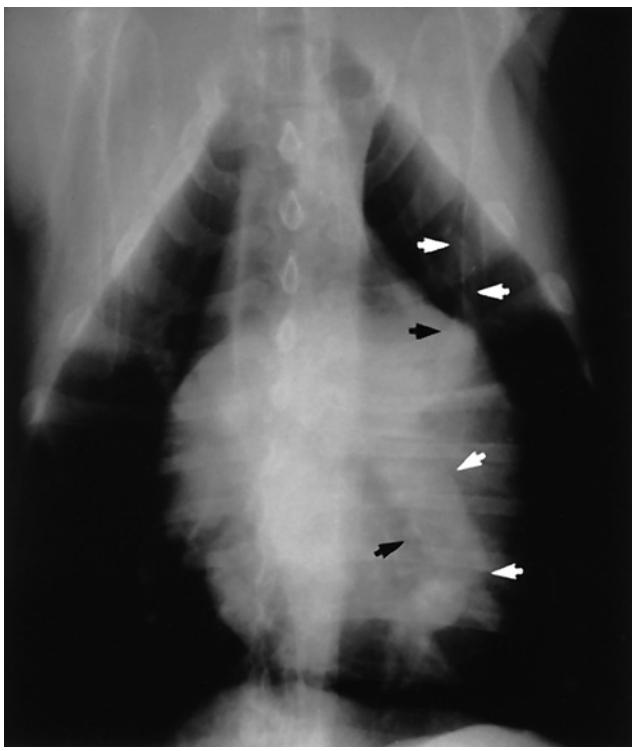


FIG 20.2
Dilation of pulmonary arteries is apparent on this ventrodorsal view of the thorax in a dog with heartworm disease. The artery to the left caudal lung lobe is extremely enlarged. *Arrowheads* delineate the borders of the arteries to the left cranial and caudal lobes.

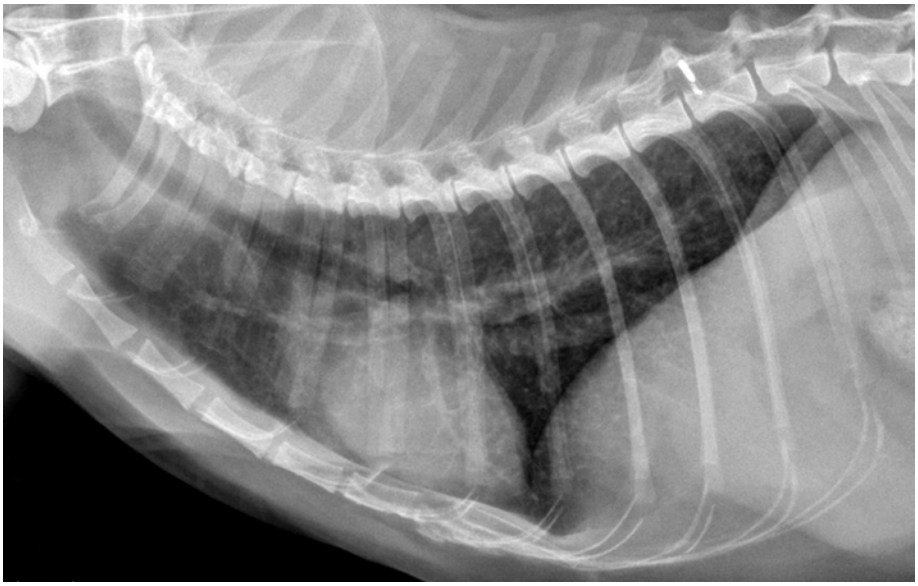


FIG 20.3
A bronchointerstitial pattern is present in this lateral radiograph from a cat with idiopathic bronchitis. The bronchial component results from thickening of the bronchial walls and is characterized by "doughnuts" and "tram lines." In this radiograph, the bronchial changes are most apparent in the caudal lung lobes.

stenosis may also cause radiographically visible undercirculation in some dogs. Hyperinflation is associated with obstructive airway disease, such as allergic or idiopathic feline bronchitis.

Bronchial Pattern

Bronchial walls are most easily discernible at the hilus on radiographs of normal dogs and cats. They should taper and grow thinner as they extend toward the periphery of each lung lobe. Bronchial structures are not normally visible radiographically in the peripheral regions of the lungs. The cartilage may be calcified in older dogs and in chondrodystrophic breeds, making the walls more prominent but still sharply defined.

Thickening of the bronchial walls or bronchial dilation results in a bronchial pattern. Thickened bronchial walls are visible as "tram lines" and "doughnuts" in the peripheral regions of the lung (Fig. 20.3). Tram lines are produced by airways that run transverse to the X-ray beam, causing the appearance of parallel thick lines with an air stripe in between. Doughnuts are produced by airways that are pointing directly toward or away from the beam, causing a thick circle to be seen radiographically, with the airway lumen creating the "hole." The walls of the bronchi tend to be indistinct. The finding of thickened walls indicates the presence of bronchitis and results from an accumulation of mucus or exudate along the walls within the lumens, an infiltration of inflammatory cells within the walls, muscular hypertrophy, epithelial hyperplasia, or a combination of these changes. Potential causes of bronchial disease are listed in Box 20.3.

Chronic bronchial inflammation can result in irreversible dilation of the airways, which is termed *bronchiectasis*. It is identified radiographically by the presence of widened, nontapering airways (Fig. 20.4). Bronchiectasis can be cylindrical (tubular) or saccular (cystic). Cylindrical bronchiectasis is characterized by fairly uniform dilation of the airway. Saccular bronchiectasis additionally has localized dilations peripherally that can lead to a honeycomb appearance. All major bronchi are usually affected, though localized disease can occur.

BOX 20.3

Differential Diagnoses for Dogs and Cats With Bronchial Patterns on Thoracic Radiographs*

Canine chronic bronchitis
Feline bronchitis (idiopathic)
Allergic bronchitis
Canine infectious respiratory disease complex
Bacterial infection
Mycoplasmal infection
Pulmonary parasites

*Bronchial disease can occur in conjunction with parenchymal lung disease. See Boxes 20.4 to 20.6 for additional differential diagnoses if mixed patterns are present.

Alveolar Pattern

Alveoli are not normally visible radiographically. Alveolar patterns occur when the alveoli are filled with fluid-dense material. The fluid opacity may be caused by edema, inflammation, hemorrhage, or neoplastic infiltrates, which generally originate from the interstitial tissues (Box 20.4). The

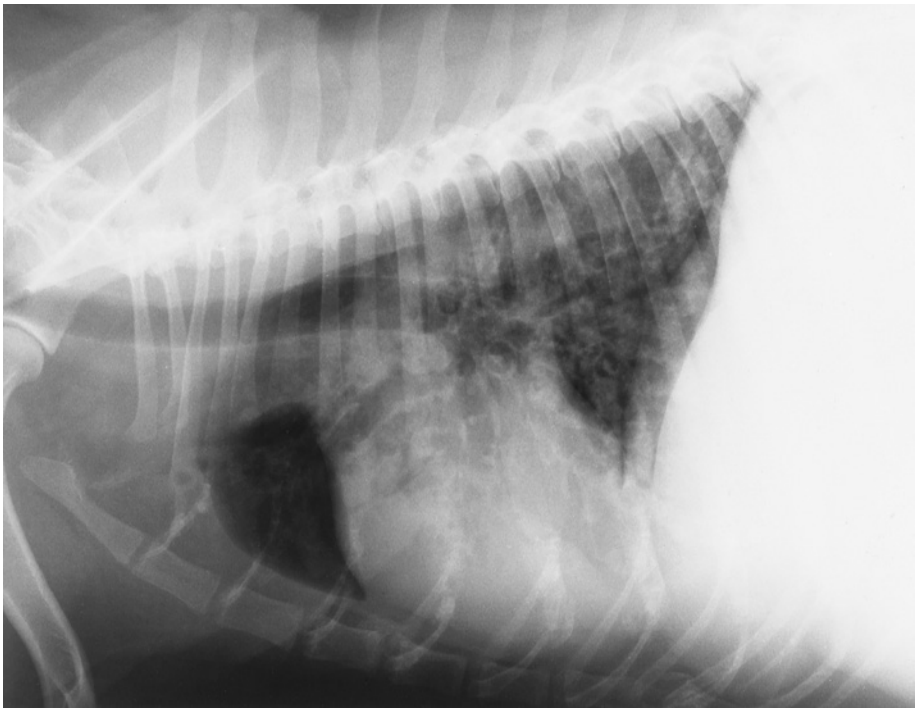


FIG 20.4
Lateral radiograph of a dog with chronic bronchitis and bronchiectasis. The airway lumens are greatly enlarged, and normal tapering of the airway walls is not seen.

BOX 20.4

Differential Diagnoses for Dogs and Cats With Alveolar Patterns on Thoracic Radiographs*

Pulmonary Edema
Severe Inflammatory Disease
- Bacterial pneumonia
- Aspiration pneumonia

Hemorrhage
- Pulmonary contusion
- Pulmonary thromboembolism
- Neoplasia
- Fungal pneumonia
- Systemic coagulopathy

*Any of the differential diagnoses for interstitial patterns (see Boxes 20.5 and 20.6) can cause an alveolar pattern if associated with severe inflammation, edema, or hemorrhage.

fluid-filled alveoli are silhouetted against the walls of the airways they surround. The result is a visible stripe of air from the airway lumen in the absence of definable airway walls. This stripe is an air bronchogram (Fig. 20.5). If fluid continues to accumulate, the airway lumen eventually will also become filled with fluid, resulting in the formation of solid areas of fluid opacity, or consolidation. When fluid-dense regions are located at the edge of the lung lobe, a *lobar sign* occurs. The curvilinear edge of the affected lung lobe is visible in contrast with the adjacent, aerated lobe.

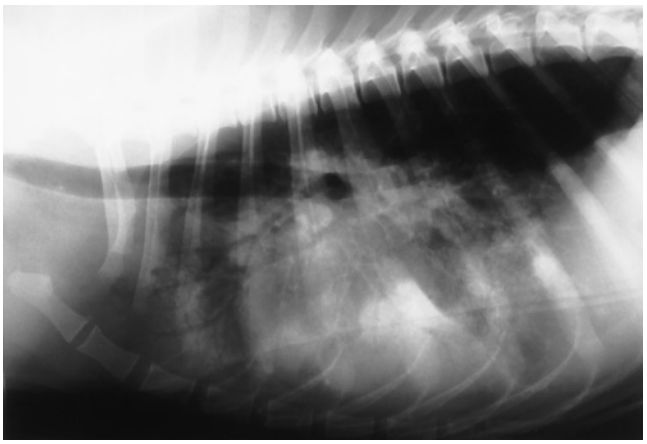


FIG 20.5
Lateral view of the thorax of a dog with aspiration pneumonia. An alveolar pattern is evident by the increased soft tissue opacity with air bronchograms. Air bronchograms are bronchial air stripes without visible bronchial walls. In this radiograph the pattern is most severe in the ventral (dependent) regions of the lung, consistent with bacterial or aspiration pneumonia.

Edema most often results from left-sided heart failure (see Chapter 22). In dogs the fluid initially accumulates in the perihilar region, and eventually the entire lung is affected. In cats patchy areas of edema can be present initially throughout the lung fields. The finding of enlarged pulmonary veins supports the cardiac origin of the infiltrates. Noncardiogenic edema is typically most severe in the caudal lung lobes.

Inflammatory infiltrates can be caused by infectious agents, noninfectious inflammatory disease, or neoplasia. The location of the infiltrative process can often help establish a tentative diagnosis. For example, diseases of airway origin, such as most bacterial and aspiration pneumonias, primarily affect the dependent lung lobes (i.e., the right middle and cranial lobes and the left cranial lobe). In contrast, diseases of vascular origin, such as dirofilariasis, thromboemboli, systemic fungal infection, and bacterial infection of hematogenous origin primarily affect the caudal lung lobes. Localized processes involving only one lung lobe suggest the presence of a foreign body, neoplasia, abscess, granuloma, or lung lobe torsion.

Hemorrhage usually results from trauma. Thromboembolism, neoplasia, coagulopathies, and fungal infections can also cause hemorrhage into the alveoli.

Interstitial Pattern

The pulmonary interstitial tissues confer a fine, lacy pattern to the pulmonary parenchyma of many dogs and cats as they age, in the absence of clinically apparent respiratory disease. They are not normally visible on inspiratory radiographs in young adult animals.

Abnormal interstitial patterns are reticular (unstructured), nodular, or reticulonodular in appearance. A nodular interstitial pattern is characterized by the finding of roughly circular, fluid-dense lesions in one or more lung lobes. However, the nodules must be nearly 1 cm in diameter to be routinely detected. Interstitial nodules may represent active or inactive inflammatory lesions or neoplasia (Box 20.5).

Active inflammatory nodules often have poorly defined borders. Mycotic infections typically result in the formation of multiple, diffuse nodules. The nodules may be small (miliary; Fig. 20.6) or large and coalescing. Parasitic granulomas are often multiple, although paragonimiasis can result in the formation of a single pulmonary nodule. Abscesses can form as a result of foreign bodies or as a sequela to bacterial pneumonia. Nodular patterns may also be seen on the radiographs obtained in animals with some eosinophilic lung diseases and idiopathic interstitial pneumonias.

Inflammatory nodules can persist as inactive lesions after the disease resolves. In contrast to active inflammatory nodules, however, the borders of inactive nodules are often well demarcated. Nodules may become mineralized in some conditions, such as histoplasmosis. Well-defined, small, inactive nodules are sometimes seen in healthy older dogs without a history of disease. Radiographs taken several months later in these animals typically show no change in the size of these inactive lesions.

Neoplastic nodules may be singular or multiple (Fig. 20.7). They are often well defined, although secondary inflammation, edema, or hemorrhage can obscure the margins. No radiographic pattern is diagnostic for neoplasia.

BOX 20.5

Differential Diagnoses for Dogs and Cats With Nodular Interstitial Patterns

- Neoplasia
- Mycotic Infection
  - Blastomycosis
  - Histoplasmosis
  - Coccidioidomycosis
- Pulmonary Parasites
  - *Aelurostrongylus* infection
  - *Paragonimus* infection
- Abscess
  - Bacterial pneumonia
  - Foreign body
- Eosinophilic Lung Disease
- Idiopathic Interstitial Pneumonia
- Inactive Lesions

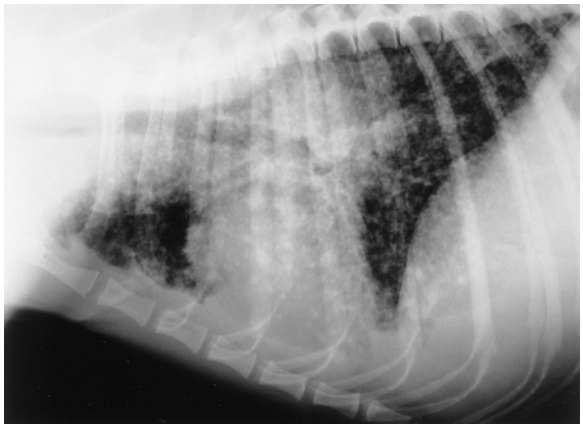


FIG 20.6
Lateral view of the thorax in a dog with blastomycosis. A miliary, nodular interstitial pattern is present. Increased soft tissue opacity above the base of the heart may be the result of hilar lymphadenopathy.

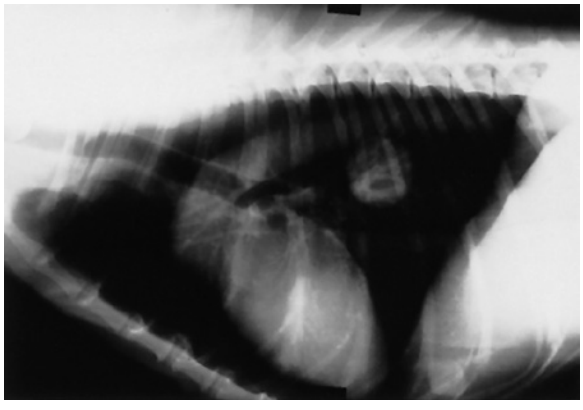


FIG 20.7
Lateral view of the thorax of a dog with malignant neoplasia. A well-circumscribed, solid, circular mass is present in the caudal lung field. Papillary adenocarcinoma was diagnosed after surgical excision.

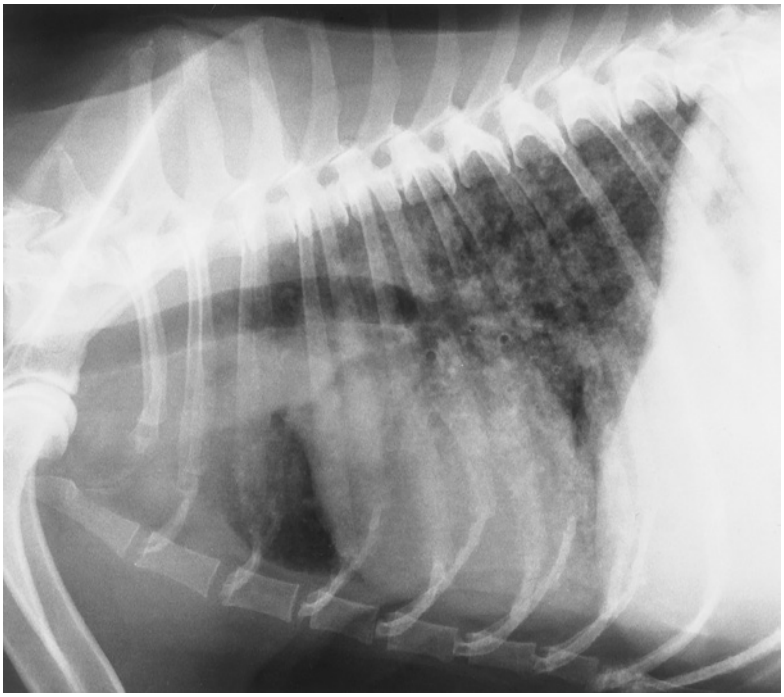


FIG 20.8
Lateral radiograph of a dog with pulmonary carcinoma. An unstructured pattern is present, as is an increased bronchial pattern.

Lesions caused by parasites, fungal infections, and some eosinophilic lung diseases or idiopathic interstitial pneumonias may be indistinguishable from neoplastic lesions. In the absence of strong clinical evidence, malignant neoplasia must be confirmed cytologically or histologically. If this is not possible, radiographs can be obtained again 4 weeks later to evaluate for progression of disease.

Neoplastic involvement of the pulmonary parenchyma cannot be totally excluded on the basis of thoracic radiograph findings because malignant cells are present for a while before lesions reach a radiographically detectable size. The sensitivity of radiography in identifying neoplastic nodules can be improved by obtaining left and right lateral views of the thorax.

The reticular interstitial pattern is characterized by a diffuse, unstructured, lacy increase in the opacity of the pulmonary interstitium, which partially obscures normal vascular and airway markings. Reticular interstitial patterns frequently occur in conjunction with nodular interstitial patterns (also called *reticulonodular patterns*) and alveolar and bronchial patterns (Fig. 20.8).

Increased reticular interstitial opacity can result from edema, hemorrhage, inflammatory cells, neoplastic cells, or fibrosis within the interstitium (Box 20.6). The interstitial space surrounds the airways and vessels, and is normally extremely small in dogs and cats. With continued accumulation of fluid or cells, however, the alveoli can become flooded, which produces an alveolar pattern. Visible focal interstitial accumulations of cells, or nodules, can also develop with time. Any of the diseases associated with alveolar and interstitial nodular patterns can cause a reticular interstitial pattern early in the course of disease (see Boxes 20.4 and 20.5). This pattern is also often seen in older dogs with no clinically apparent disease, presumably as a result of pulmonary fibrosis; this further decreases the specificity of the finding.

BOX 20.6

Differential Diagnoses for Dogs and Cats With Reticular (Unstructured) Interstitial Patterns

Pulmonary Edema (Mild)
Infection
- Viral pneumonia
- Bacterial pneumonia
- Toxoplasmosis
- Mycotic pneumonia
- Parasitic infection (more often bronchial or nodular interstitial pattern)

Neoplasia
Eosinophilic Lung Disease
Idiopathic Interstitial Pneumonia
- Idiopathic pulmonary fibrosis

Hemorrhage (Mild)

Lung Lobe Consolidation

Lung lobe consolidation is characterized by a lung lobe that is entirely of soft tissue opacity (Fig. 20.9, *A*). Consolidation

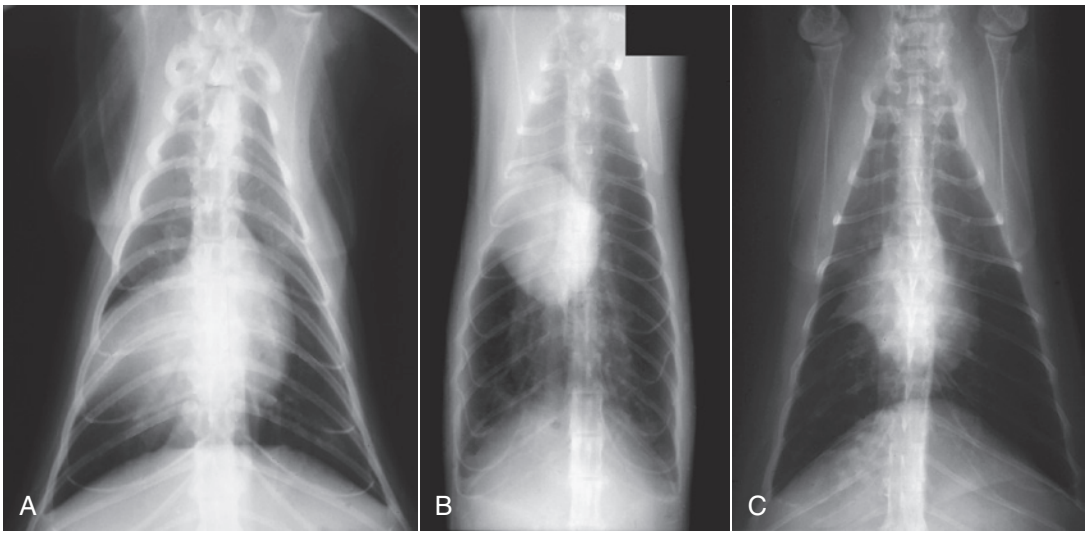


FIG 20.9
Thoracic radiographs from three different patients, ventrodorsal projections. Radiograph A shows consolidation of the right middle lung lobe caused by neoplasia. Note that the soft tissue density of the lung silhouettes with the shadow of the heart. Radiograph B shows atelectasis of the middle region of the right lung and marked hyperinflation of the remaining lungs in a cat with idiopathic bronchitis. Note the shift of the heart shadow toward the collapsed region. Radiograph C shows atelectasis of the right middle lung lobe in another cat with idiopathic bronchitis. In this patient the adjacent lung lobes have expanded into the area previously occupied by the right middle lobe, preventing displacement of the heart.

occurs when an alveolar or interstitial disease process progresses to the point at which the entire lobe is filled with fluid or cells. Common differential diagnoses for lung lobe consolidation are severe bacterial or aspiration pneumonia, neoplasia, lung lobe torsion, and hemorrhage. Inhalation of plant material can also result in consolidation of the involved lung lobe as a result of the inflammatory reaction to foreign material and secondary infection. This differential diagnosis should be considered especially in regions of the country where foxtails are prevalent.

Atelectasis

Atelectasis is also characterized by a lobe that is entirely of soft tissue opacity. In this instance, the lobe is collapsed as a result of airway obstruction. All the air within the lobe has been absorbed and not replaced. It is distinguished from consolidation by the small size of the lobe (see Fig. 20.9, *B*). Often the heart is displaced toward the atelectatic lobe. Atelectasis is most commonly seen involving the right middle lobe of cats with bronchitis (see Fig. 20.9, *C*). Displacement of the heart may not occur in these cats.

Cavitary Lesions

Cavity lesions describe any abnormal air accumulation in the lung. They can be congenital, acquired, or idiopathic. Specific types of cavitary lesions include bullae, which result from ruptured alveoli due to congenital weakness of tissues and/or small airway obstruction, as seen in some cats with idiopathic bronchitis; blebs, which are bullae located within the pleura; and cysts, which are cavitary lesions lined by airway epithelium. Parasitic "cysts" (not lined by epithelium) can form around *Paragonimus* flukes. Thoracic trauma is a common cause of cavitary lesions. Other differential diagnoses include neoplasia, lung infarction (from thromboembolism), abscess, and granuloma. Cavitary lesions may be apparent as localized accumulations of air or fluid, often with a partially visible wall (Fig. 20.10). An air-fluid interface may be visible when standing horizontal beam projections are used. Bullae and blebs are rarely apparent radiographically.

Cavitary lesions may be discovered incidentally or on thoracic radiographs of dogs and cats with spontaneous pneumothorax. If pneumothorax is present, surgical excision of the lesion is usually indicated (see Chapter 24). If inflammatory or neoplastic disease is suspected, further diagnostic testing is indicated. If the lesion is found incidentally, animals can be periodically reevaluated radiographically to determine whether the lesion is progressing or resolving. If the lesion does not resolve during the course of 1 to 3 months, surgical removal is considered for diagnostic purposes and to prevent potentially life-threatening spontaneous pneumothorax.

Lung Lobe Torsion

Lung lobe torsion can develop spontaneously, particularly in deep-chested dogs, or as a complication of pleural effusion

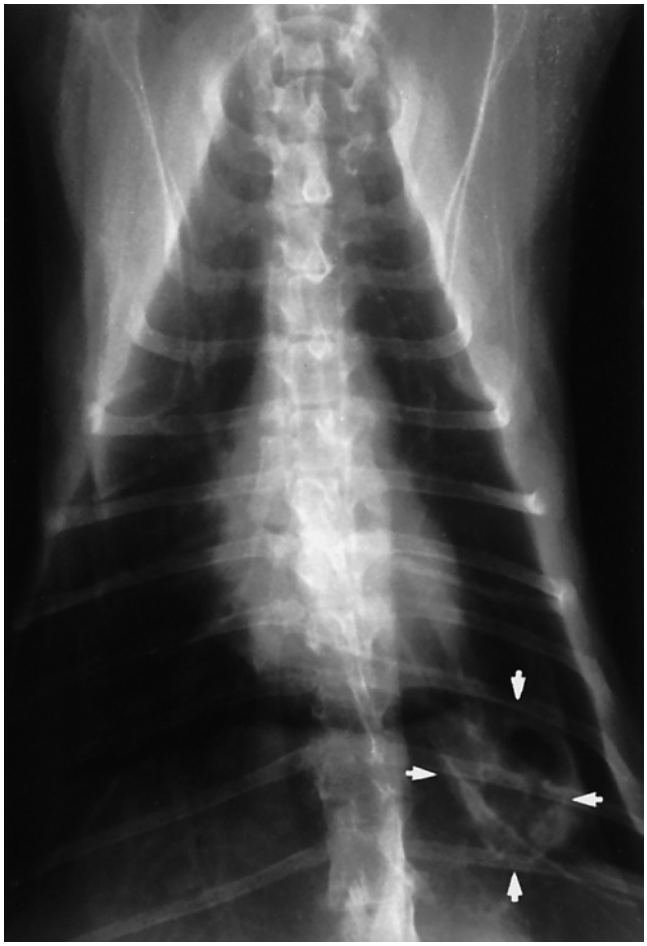


FIG 20.10
Ventrodorsal view of the thorax in a cat showing a cystic lesion *(arrowheads)* in the left caudal lung lobe. Differential diagnoses included neoplasia and *Paragonimus* infection.

or pneumonectomy in dogs and cats. The right middle and left cranial lobes are most commonly involved. The lobe usually twists at the hilus, obstructing the flow of blood into and out of the lung lobe. Venous drainage is obstructed before arterial flow, causing the lung lobe to become congested with blood. Inflammation and necrosis ensue. Over time, air is absorbed from the alveoli and atelectasis can occur.

Lung lobe torsion is difficult to identify radiographically. Severe bacterial or aspiration pneumonia resulting in consolidation of these same lobes is far more common and produces similar radiographic changes. The finding of pulmonary vessels or bronchi traveling in an abnormal direction is strongly suggestive of torsion. Unfortunately, pleural fluid, if not present initially, often develops and obscures the radiographic image of the affected lobe. Ultrasonography is often useful in detecting a torsed lung lobe. Bronchoscopy, bronchography, computed tomography (CT), or thoracotomy is necessary to confirm the diagnosis in some animals.

ULTRASONOGRAPHY

In the emergency setting, thoracic ultrasonography is used for the rapid identification of pleural effusion. Its application in the rapid diagnosis of pulmonary edema and other parenchymal disease is growing. In this setting the acronyms TFAST (Thoracic Focused Assessment with Sonography for Trauma) and VetBLUE (Veterinary Bedside Lung Ultrasound Examination) are used (Lisciandro, 2011; Lisciandro et al., 2014).

In the nonemergent setting, ultrasonography is used to evaluate pulmonary mass lesions adjacent to the body wall, diaphragm, or heart and also consolidated lung lobes (Fig. 20.11). Because air interferes with sound waves, aerated lungs and structures surrounded by aerated lungs cannot be examined. However, some patients with a reticular interstitial pattern on thoracic radiographs have sufficient infiltrates to be visualized where they abut the body wall. The consistency of lesions often can be determined to be solid, cystic, or vascularized. Some solid masses are hypolucent and appear to be cystic on ultrasonograms. Vascular structures may be visible, particularly with Doppler ultrasound, and this can be helpful in identifying lung lobe torsion. Ultrasonography can also be used to guide needles or biopsy instruments into solid masses for specimen collection. It is used in evaluating the heart of animals with clinical signs that cannot be readily localized to the cardiac or the respiratory system. Ultrasonographic evaluation of patients with pleural disorders is discussed in Chapter 23.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

CT and magnetic resonance imaging (MRI) are used routinely in human medicine for the diagnostic evaluation of lung disease. The accessibility of CT in particular has led to its increased use in dogs and cats and it is now used routinely in the diagnostic evaluation of challenging respiratory cases. The resultant three-dimensional images are more sensitive and specific for the identification of certain airway, vascular, and parenchymal diseases as compared with thoracic radiography. In one study of dogs with metastatic neoplasia, only 9% of nodules detected by CT were identified by thoracic radiography (Nemanic et al., 2006). Images are routinely obtained before and after the intravenous injection of a contrast agent, which further enhances the characterization of lesions and allows for the identification of macrothrombi and emboli. Thoracic CT has also become routine for the planning of thoracic surgery. Compared with standard radiography, the extent of mass lesions and their relationship to major vessels and other critical structures is better defined, and multifocal disease is more likely to be identified (e.g., metastatic lesions or multiple cavitary lesions). The risks associated with CT scanning are minimal except that light, general anesthesia is required to eliminate patient motion and to allow for breath-holding

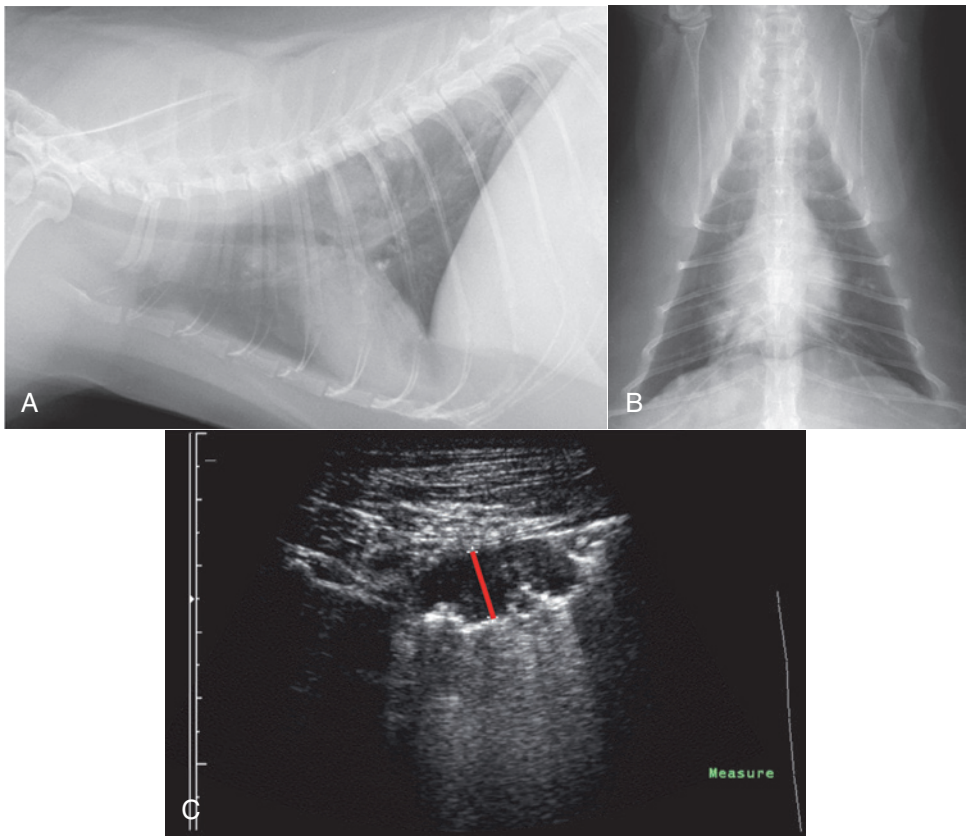


FIG 20.11
Multiple pulmonary nodules are easily visible on the lateral radiograph **(A)** from a cat with a 1-year history of cough and recent episodes of respiratory distress with wheezing. Nodules do not obviously extend to the chest wall as seen on the ventrodorsal radiograph. **(B)** However, a 1-cm mass was found on ultrasonographic examination of the right thorax; **(C)** a *red line* has been positioned between ultrasound markers to indicate site of measurement. An ultrasound-guided aspirate was performed. The presence of eosinophils in the aspirate prompted the performance of fecal examinations for pulmonary parasites, and a diagnosis of paragonimiasis was made through identification of characteristic ova.

during image exposure. For unstable patients for which results of a noncontrast enhanced CT are considered to be critical, heavy sedation and physical restraints can be used.

NUCLEAR IMAGING

Mucociliary clearance can be measured by placing a drop of technetium-labeled albumin at the carina and observing its movement with a gamma camera to assist in the diagnosis of ciliary dyskinesia. Nuclear imaging can be used for the relatively noninvasive measurement of pulmonary perfusion and ventilation, valuable for the diagnosis of pulmonary thromboembolism. Restrictions for handling radioisotopes and the need for specialized recording equipment limit the availability of these tools to specialty centers.

PARASITOLOGY

Parasites involving the lower respiratory tract are identified by direct observation, blood tests, cytologic analysis of respiratory tract specimens, or fecal examination. *Oslerus osleri* reside in nodules near the carina, which can be identified bronchoscopically. Rarely, other parasites may be seen. Blood tests are often used to diagnose heartworm disease (see Chapter 10).

Larvae that may be present in fluid from tracheal or bronchial washings include *O. osleri, Aelurostrongylus abstrusus* (Fig. 20.12, *A*), and *Crenosoma vulpis* (Fig. 20.12, *B*). Eggs that may be present include those of *Capillaria (Eucoleus) aerophila* and *Paragonimus kellicotti* (Fig. 20.12, *C* and *D*). Larvated eggs or larvae from *Filaroides hirthi* or *Aelurostrongylus milksi* can be present but are rarely associated with clinical signs. The more common organisms are described in Table 20.1.

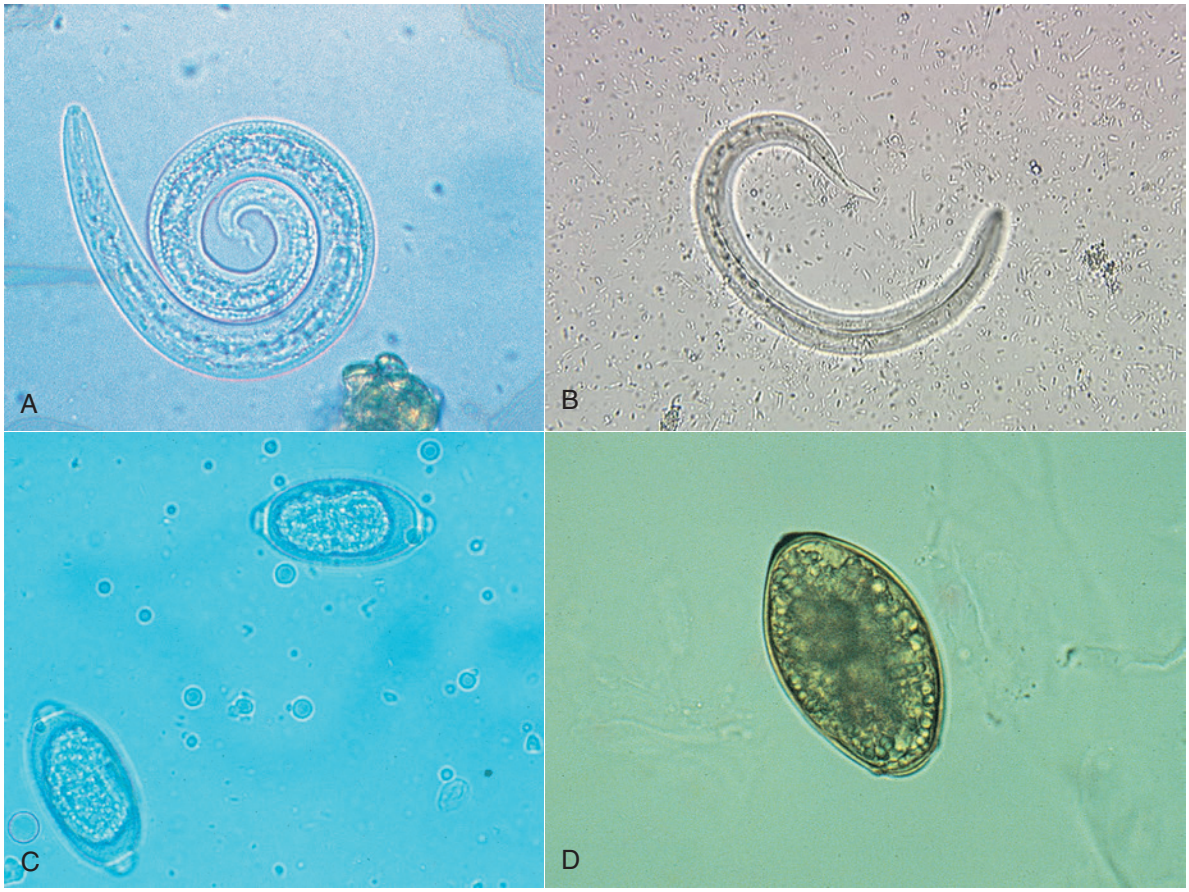


FIG 20.12
(A) Larva of *Aelurostrongylus abstrusus*. **(B)** Larva of *Crenosoma vulpis*. **(C)** Double operculated ova of *Capillaria* sp. **(D)** Single operculated ova of *Paragonimus kellicotti*.

TABLE 20.1

Characteristics of Eggs or Larvae From Respiratory Parasites

PARASITE	HOST	STAGE	SOURCE	DESCRIPTION
Capillaria aerophila	Dog and cat	Eggs	Routine flotation of feces, airway specimens	Barrel-shaped, yellow, with prominent, transparent, asymmetric bipolar plugs; slightly smaller than Trichuris eggs; 60-80 µm × 30-40 µm
Paragonimus kellicotti	Dog and cat	Eggs	High-density flotation or sedimentation of feces, airway specimens	Oval, golden-brown, single, operculated; operculum flat with prominent shoulders; 75-118 µm × 42-67 µm
Aelurostrongylus abstrusus	Cat	Larvae	Baermann technique of feces, airway specimens	Larvae with S-shaped tail; dorsal spine present; 350-400 µm × 17 µm; eggs or larvated eggs may be seen in airway specimens
Oslerus osleri	Dog	Larvae, eggs	Tracheal wash, bronchial brushing of nodules, zinc-sulfate flotation of feces	Larvae have S-shaped tail without dorsal spine; rarely found eggs are thin-walled, colorless, and larvated; 80 µm × 50 µm
Crenosoma vulpis	Dog	Larvae	Baermann technique of feces, airway specimens	Larvae have tapered tail without severe kinks or spines; 250-300 µm; larvated eggs may be seen in airway specimens

The hosts of lung parasites generally cough up and swallow the eggs or larvae, which then are passed in the feces to infect the next host or an intermediate host. Fecal examination for eggs or larvae is a simple, noninvasive tool for the diagnosis of such infestations. However, because shedding is intermittent, parasitic disease cannot be included solely on the basis of negative fecal examination findings. Multiple (at least three) examinations should be performed in animals that are highly suspected of having parasitic disease. If possible, several days should be allowed to elapse between collections of feces.

Routine fecal flotation can be used to concentrate eggs from *C. aerophila*. High-density fecal flotation (specific gravity [s.g.], 1.30 to 1.35) can be used to concentrate *P. kellicotti* eggs. Sedimentation techniques are preferred for concentrating and identifying *P. kellicotti* eggs, particularly if few eggs are present. Larvae are identified through the use of the Baermann technique. However, *O. osleri* larvae are insufficiently motile for reliable identification with this technique, and zinc sulfate (s.g., 1.18) flotation is recommended. Even so, false-negative results are common in cases with *O. osleri*.

All of these techniques can be readily performed in-house at minimal expense, but the infrequent identification of respiratory parasites in small-animal patients makes submission of feces to an external laboratory with greater experience in organism identification appealing. However, timing should be carefully arranged to ensure that fresh feces are available for prompt evaluation by laboratory personnel.

Toxoplasma gondii occasionally causes pneumonia in dogs and cats. Dogs do not shed *Toxoplasma* organisms in the feces, but cats may. However, the shedding of eggs is part of the direct life cycle of the organisms and does not correlate with the presence of systemic disease resulting from the indirect cycle. Infection is therefore diagnosed by the finding of tachyzoites in pulmonary specimens or indirectly on the basis of serologic findings.

Migrating intestinal parasites can cause transient pulmonary signs in young animals. Migration most often occurs before the mature adults develop in the intestine, thus eggs may not be found in feces. Migration of *Toxocara cati* has been implicated as a cause of idiopathic feline bronchitis in adult cats, but no practical means of diagnosis exists (Dillon et al., 2013).

SEROLOGY

Serologic tests can detect a variety of pulmonary pathogens. Antibody tests provide only indirect evidence of infection, however. In general, they should be used only to confirm a suspected diagnosis, not to screen for disease. Whenever possible, identification of infectious organisms is the preferred method of diagnosis. Tests available for common pulmonary pathogens include those for *Histoplasma, Blastomyces, Coccidiodomyces, Toxoplasma,* and feline coronavirus. These tests are discussed fully in Chapter 97. Antibody tests for canine influenza are discussed further in Chapter 22. Serum antigen tests for *Cryptococcus* (see Chapter 97) and adult heartworms are also available (see Chapter 10). Antibody tests for dirofilariasis are available and are used primarily to support the diagnosis of feline heartworm disease (see Chapter 10).

URINE ANTIGEN TESTS

Urine antigen tests for the detection of *Histoplasma* and *Blastomyces* antigens are available. The test for *Blastomyces* is more sensitive than serum antibody testing by agar gel immunodiffusion for the diagnosis of blastomycosis (Spector et al., 2008). See Chapter 97 for further discussion.

POLYMERASE CHAIN REACTION TESTS

Molecular diagnostic tests are available for identification of a wide range of individual respiratory pathogens. Panels of tests are commercially available for multiple agents commonly involved in acute respiratory tract infection in dogs or cats. Specimens that can be tested include swabs from the oropharynx, nasal cavity, or conjunctiva; tracheal wash or bronchoalveolar lavage specimens; airway brushings; and tissue. Best results are obtained when the timing and the site of collection are chosen on the basis of the pathophysiology of the target organism. For collection of material by swab, polyester swabs should be used. Consultation with the diagnostic laboratory is recommended for specimen collection and handling to maximize results.

TRACHEAL WASH

Indications and Complications

Tracheal wash can yield valuable diagnostic information in animals with cough or respiratory distress resulting from disease of the airways or pulmonary parenchyma and in animals with vague presenting signs and pulmonary abnormalities detected on thoracic radiographs (i.e., most animals with lower respiratory tract disease). Tracheal wash is generally performed after results of the history, physical examination, thoracic radiography, and other routine components of the database are known.

Tracheal wash provides fluid and cells that can be used to identify diseases involving the major airways while bypassing the normal flora and debris of the oral cavity and pharynx. Representative specimens are often obtained from patients with disease of the small airways (e.g., bronchitis) or alveoli (e.g., bacterial pneumonia or aspiration pneumonia) because diagnostic material is carried to the major airways by mucociliary clearance, cough, or the extension of disease (Table 20.2). The fluid obtained is evaluated cytologically and microbiologically and therefore should be collected before antibiotic treatment is initiated, whenever possible.

TABLE 20.2

Comparisons of Techniques for Collecting Specimens From the Lower Respiratory Tract

TECHNIQUE	SITE OF COLLECTION	SPECIMEN SIZE	ADVANTAGES	DISADVANTAGES	INDICATIONS
Tracheal wash	Large airways Small airway and alveoli (through mucociliary clearance, cough, and extension)	Moderate	Simple technique Minimal expense No special equipment Complications rare Volume adequate for cytology and culture	Airways must be involved for specimen to represent disease May induce bronchospasm in patients with hyperreactive airways, particularly cats	Bronchial and alveolar disease (particularly bacterial bronchopneumonia and aspiration pneumonia) Because of safety and ease, consider for any lung disease Less likely to be representative of interstitial or small focal processes
Bronchoalveolar lavage	Small airways, alveoli, sometimes interstitium	Large	Nonbronchoscopic technique requires no special equipment and minimal expense Bronchoscopic technique allows airway evaluation and directed sampling Resultant hypoxemia is transient and responsive to oxygen supplementation Safe for animals in stable condition Large volume of lung sampled High cytologic quality Large volume for analysis	General anesthesia required Special equipment and expertise required for bronchoscopic collection Generally not recommended for animals with tachypnea, increased respiratory efforts, or respiratory distress Capability to provide oxygen supplementation for an hour or more is required May induce bronchospasm in patients with hyperreactive airways, particularly cats	Primarily diffuse interstitial disease; also small airway and alveolar disease. Routine during bronchoscopy
Lung aspirate	Interstitium, alveoli when flooded	Small	Simple technique Minimal expense No special equipment Solid masses adjacent to body wall: excellent representation with minimal risk	Potential for complications: pneumothorax, hemothorax, pulmonary hemorrhage Relatively small area of lung sampled Specimen adequate only for cytology Specimen blood contaminated	Solid masses adjacent to chest wall (for solitary/localized disease, see also Thoracotomy or Thoracoscopy with Lung Biopsy) Diffuse interstitial disease
Thoracotomy or thoracoscopy with lung biopsy	Small airways, alveoli, interstitium	Large	Ideal specimen Allows histologic examination in addition to culture	Relatively expensive Requires expertise Requires general anesthesia Major surgical procedure	Localized process where excision may be therapeutic as well as diagnostic Any progressive disease not diagnosed by less invasive methods

Tracheal wash is less likely to provide representative material from interstitial and focal disease processes. However, the procedure is inexpensive and minimally invasive, and this makes it reasonable to perform in most animals with lower respiratory tract disease if the risks of other methods of specimen collection are deemed too great.

Potential complications are rare and include tracheal laceration, subcutaneous emphysema, and pneumomediastinum. Bronchospasm may be induced by the procedure in patients with hyperreactive airways, particularly cats with bronchitis.

TECHNIQUES

Tracheal wash is performed with the use of transtracheal or endotracheal techniques. Transtracheal wash is performed by passing a catheter into the trachea to the level of the carina through the cricothyroid ligament or between the tracheal rings in an awake or sedated animal. Endotracheal wash is performed by passing a catheter through an endotracheal tube in an anesthetized animal. The endotracheal technique is preferred in cats and very small dogs, although either technique can be used in any animal. Patients with airways that may be hyperreactive, particularly cats, are treated with bronchodilators (see the section on endotracheal technique).

Transtracheal Technique

Transtracheal wash fluid is collected by inserting a short, large bore over-the-needle catheter through the cricothyroid ligament or between tracheal rings; removing the needle; passing a long, smaller bore, flushing catheter through the catheter into the trachea to reach just cranial to the carina; then performing the saline wash. Options for catheters include a prepackaged kit containing a 14-gauge introduction catheter and a 10- to 28-inch flushing catheter (Mila International, Inc., Florence, Kentucky) or a 14-gauge over-the-needle catheter and a 3.5F polypropylene male dog urinary catheter. For the latter, the ability to pass a specific brand of urinary catheter through a specific over-the-needle catheter should be tested before use, as the fit may be too tight in some instances. Alternatively, a 12-inch-long, 18- to 22-gauge through-the-needle intravenous catheter can be used, but in our area, these catheters are no longer commercially available. The flushing catheter should be long enough to reach the carina, which is located at approximately the level of the fourth intercostal space.

The dog can sit or lie down, depending on what position is more comfortable for the animal and the clinician. The dog is restrained with its nose pointing toward the ceiling at about 45 degrees from horizontal (Fig. 20.13, *A*). Overextension of the neck causes the animal to be more resistant. Dogs that cannot be restrained should be tranquilized. If tranquilization is needed, premedication with atropine or glycopyrrolate is considered to minimize contamination of the trachea with oral secretions. Narcotics are avoided to preserve the cough reflex, which can facilitate the retrieval of fluid.

The cricothyroid ligament is identified by palpating the trachea in the ventral cervical region and following it dorsally toward the larynx to the raised, smooth, narrow band of the cricoid cartilage. Immediately above the cricoid cartilage is a depression, where the cricothyroid ligament is located (see Fig. 20.13, *B*). If the trachea is entered above the cricothyroid ligament, the catheter is passed dorsally into the pharynx and a nondiagnostic specimen is obtained. Such dorsal passage of the catheter often results in excessive gagging and retching but may go unrecognized in sedate patients.

Lidocaine is always injected subcutaneously at the site of entry. The skin over the cricothyroid ligament is prepared surgically, and sterile gloves are worn to pass the catheter. The over-the-needle catheter is held with the bevel of the needle facing ventrally. The skin over the ligament is then tented, and the needle is passed through the skin. The larynx is stabilized with the nondominant hand. To properly stabilize it, the clinician should grasp at least 180 degrees of the circumference of the airway between the fingers and the thumb. Failure to hold the airway firmly is the most common technical mistake. Next, the tip of the needle is rested against the cricothyroid ligament and inserted through the ligament with a quick, short motion. The syringe end of the catheter is raised without withdrawing the needle, and the catheter is threaded down the trachea. The hand stabilizing the trachea is then used to pinch the hub at the skin, with the hand kept firmly in contact with the neck, while the needle is removed. By keeping the hand holding the hub of the catheter against the neck of the animal so that the hand, needle, and neck can move as one, the clinician prevents laceration of the larynx or trachea and inadvertent removal of the catheter from the trachea.

The flushing catheter is then threaded through the over-the-needle catheter. Threading the catheter provokes coughing. Little or no resistance to passage of the catheter should be noted. Elevating the hub of the over-the-needle catheter slightly so that the tip points more ventrally facilitates passage of the flushing catheter if it is abutting the opposite tracheal wall. Once the catheter has been completely threaded into the airway, the head can be restrained in a natural position

Note that if the flushing catheter will not pass despite adjustments in position of the over-the-needle catheter, the over-the-needle catheter *must be completely removed* and the procedure repeated from the beginning. Attempting to reinsert the needle into the over-the-needle catheter while it is within the patient is dangerous as it can result in a piece of the catheter being sheared off and lost deep within the airways.

It is convenient to have six to eight 12-mL syringes ready, each filled with 3 to 5 mL of 0.9% sterile preservative-free sodium chloride solution. The entire bolus of saline in one syringe is injected into the flushing catheter. Immediately after this, many aspiration attempts are made. After each aspiration, the syringe must be disconnected from the catheter and the air evacuated without loss of any of the retrieved fluid. Attachment of a three-way stopcock between the

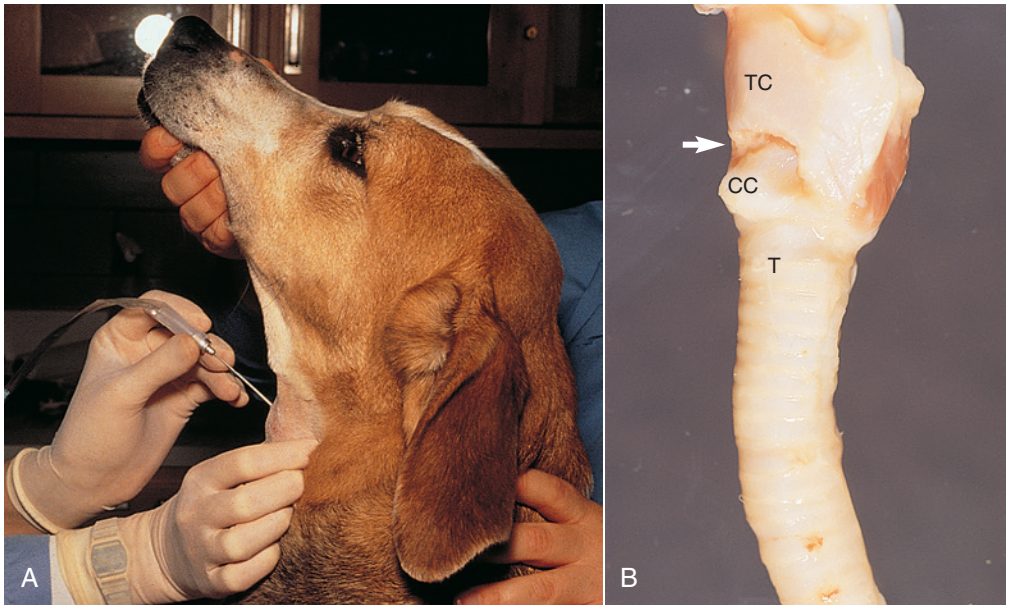


FIG 20.13
(A) When a transtracheal wash is performed, the animal is restrained in a comfortable position with the nose pointed toward the ceiling. The ventral neck is clipped and scrubbed, and the clinician wears sterile gloves. The cricothyroid ligament is identified as described in **(B).** After an injection of lidocaine, the needle of the catheter (whether a through-the-needle catheter as is shown here, or an over-the-needle catheter as described in the text) is placed through the skin. The larynx is grasped firmly with the fingers and the thumb at least 180 degrees around the airway. The needle can then be inserted through the cricothyroid ligament into the airway lumen. **(B)** The lateral view of this anatomic specimen demonstrates the trachea and larynx in a position similar to that of the dog in **(A).** The cricothyroid ligament *(arrow)* is identified by palpating the trachea *(T)* from ventral to dorsal until the raised cricoid cartilage *(CC)* is palpated. The cricothyroid ligament is the first depression above the cricoid cartilage. The cricothyroid ligament attaches cranially to the thyroid cartilage *(TC)*. The palpable depression above the thyroid cartilage *(not shown)* should not be entered.

catheter and the syringe can make it easier to connect and disconnect the syringe. Aspirations should be forceful and should be repeated at least five or six times, so that small volumes of airway secretions that have been aspirated into the catheter are pulled the entire length of the catheter into the syringe.

The procedure is repeated using additional boluses of saline until a sufficient amount of fluid is retrieved for analysis. A total of 2 to 3 mL of turbid fluid is adequate in most instances. The clinician does not need to be concerned about "drowning" the animal with infusion of the modest volumes of fluid described because the fluid is rapidly absorbed into the circulation. Failure to retrieve adequate volumes of visibly turbid fluid can be the result of several technical difficulties, as outlined in Fig. 20.14.

The catheter is removed after sufficient fluid is collected. A sterile gauze sponge with antiseptic ointment is then immediately placed over the catheter site, and a light bandage is wrapped around the neck. This bandage is left in place for several hours while the animal rests quietly in a cage. These precautions minimize the likelihood that subcutaneous emphysema or pneumomediastinum will develop.

Endotracheal Technique

The endotracheal technique is performed by passing a 5F red rubber or male dog urinary catheter through a sterilized endotracheal tube. The length of the catheter must be sufficient to extend beyond the end of the endotracheal tube by several centimeters and to nearly reach the carina.

The animal is anesthetized with a short-acting intravenous agent to a sufficient depth to allow intubation. Propofol or, in cats, a combination of ketamine and acepromazine or diazepam is effective. Premedication with atropine, particularly in cats, is considered to minimize contamination of the trachea with saliva. Cats with lower respiratory tract disease may have airway hyperreactivity and generally should be administered a bronchodilator before the tracheal wash. Terbutaline (0.01 mg/kg) can be given subcutaneously to cats not already receiving oral bronchodilators. It is also prudent to keep a metered dose inhaler of albuterol at hand to be administered through the endotracheal tube or by mask if breathing becomes labored or wheezes are auscultated.

A sterilized endotracheal tube should be passed without dragging the tip through the oral cavity. The animal's mouth is opened wide with the tongue pulled out, a laryngoscope

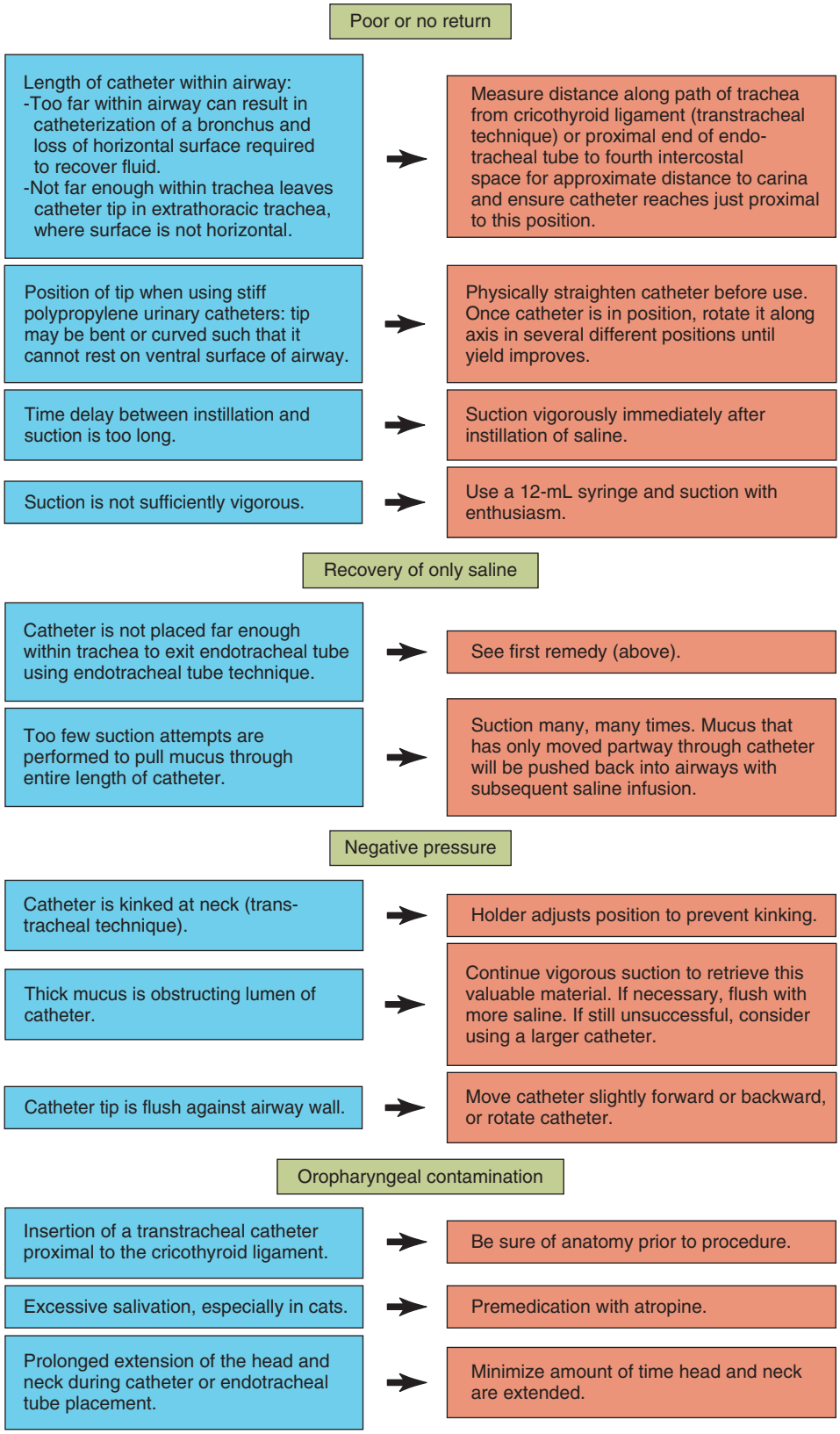


FIG 20.14
Overcoming problems with tracheal wash fluid collection. *Green boxes* indicate problems, *blue boxes* indicate possible causes, and *orange boxes* indicate remedies.

is used, and, in cats, sterile topical lidocaine is applied to the laryngeal cartilages to ease passage of the tube with minimal contamination. The tip of the endotracheal tube should be positioned beyond the larynx but sufficiently in front of the carina to allow the flushing catheter to rest against the floor of the trachea.

The catheter is passed through the endotracheal tube to just proximal to the level of the carina (approximately the fourth intercostal space), while sterile technique is maintained. The wash procedure is performed as described for the transtracheal technique. Slightly larger boluses of saline may be required, however, because of the larger volume of the catheter. Use of a catheter larger than 5F seems to reduce the yield of the wash, except when secretions are extremely viscous.

SPECIMEN HANDLING

The cells collected in the wash fluid are fragile. The fluid is ideally processed within 30 minutes of collection, with minimal manipulation. Bacterial culture is performed on at least 0.5 to 1 mL of fluid. Fungal cultures can be performed if mycotic disease is a differential diagnosis, and *Mycoplasma* culture or polymerase chain reaction (PCR) testing is considered for cats and dogs with signs of bronchitis. Cytologic preparations are made both from the fluid and from any mucus within the fluid. Both fluid and mucus are examined because infectious agents and inflammatory cells can be concentrated in the mucus, but the proteinaceous material causes cells to clump and interferes with evaluation of the cell morphology. Mucus is retrieved with a needle, and squash preparations are made. Direct smears of the fluid itself can be made, but such specimens are usually hypocellular. Sediment or cytocentrifuge preparations are generally necessary to make adequate interpretation possible. Straining the fluid through gauze to remove the mucus is discouraged because infectious agents may be lost in the process. Routine cytologic stains are used.

Microscopic examination of slides includes identification of cell types, qualitative evaluation of cells, and examination for infectious agents. Cells are evaluated qualitatively for evidence of macrophage activation, neutrophil degeneration, lymphocyte reactivity, and characteristics of malignancy. Epithelial hyperplasia secondary to inflammation should not be overinterpreted as neoplasia, however. Infectious agents such as bacteria, protozoa *(Toxoplasma gondii),* fungi (*Histoplasma, Blastomyces,* and *Cryptococcus* organisms), and parasitic larvae or eggs may be present (see Fig. 20.12, and Figs. 20.15 through 20.17). Because only one or two organisms may be present on an entire slide, a thorough evaluation of each slide is indicated.

INTERPRETATION OF RESULTS

Normal tracheal wash fluid contains primarily respiratory epithelial cells. Few other inflammatory cells are present (Fig. 20.18). Occasionally, macrophages are retrieved from the small airways and alveoli because the catheter was extended into the lungs beyond the carina, or because relatively large volumes of saline were used. Most macrophages are not activated. In these instances the presence of macrophages does not indicate disease but rather reflects the acquisition of material from the deep lung (see the section on nonbronchoscopic bronchoalveolar lavage).

Slides are examined for evidence of overt oral contamination, which can occur during transtracheal washing if the catheter needle was inadvertently inserted proximal to the cricothyroid ligament. Rarely, dogs can cough up the catheter into the oropharynx. Oral contamination can also result from drainage of saliva into the trachea, which usually occurs in cats that hypersalivate or dogs that are heavily sedated,

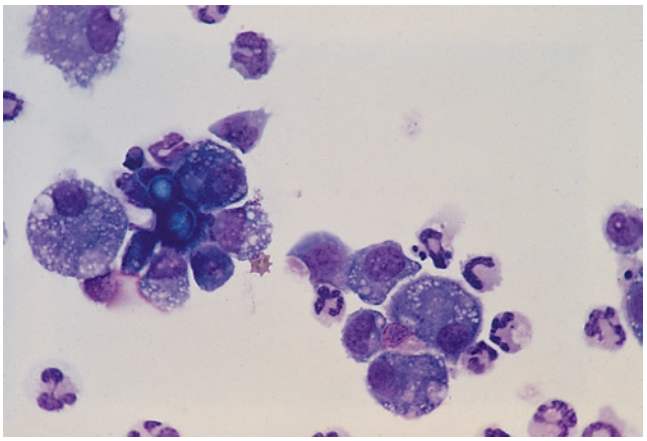


FIG 20.15
Photomicrograph of a *Blastomyces* organism from the lungs of a dog with blastomycosis. The organisms stain deeply basophilic, are 5 to 15 µm in diameter, and have a thick refractile cell wall. Often, as in this figure, broad-based budding forms are seen. The cells present are alveolar macrophages and neutrophils. (Bronchoalveolar lavage fluid, Wright stain.)

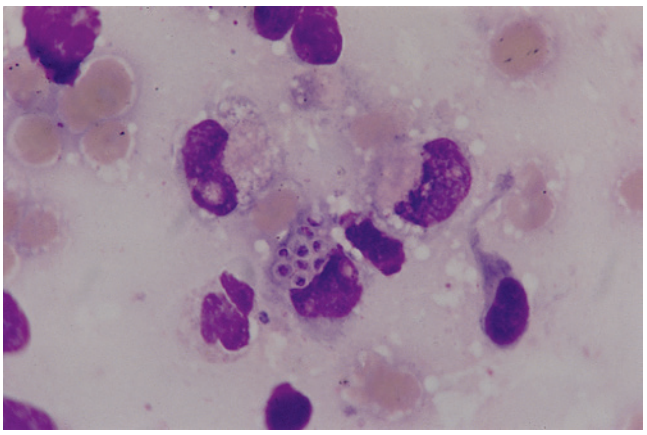


FIG 20.16
Photomicrograph of *Histoplasma* organisms from the lungs of a dog with histoplasmosis. The organisms are small (2-4 µm) and round, with a deeply staining center and a lighter-staining halo. They are often found within phagocytic cells—in this figure, an alveolar macrophage. (Bronchoalveolar lavage fluid, Wright stain.)

particularly if the head and neck are extended more than briefly for passage of the endotracheal tube or transtracheal catheter. Oral contamination is indicated by the finding of numerous squamous epithelial cells, often coated with bacteria, and *Simonsiella* organisms (Fig. 20.19). *Simonsiella* organisms are large basophilic rods that are frequently found stacked uniformly on top of one another along their broad side. Specimens with overt oral contamination may not provide accurate information about the airways, particularly with regard to bacterial infection.

Cytologic results of tracheal wash fluid are most useful when pathogenic organisms or malignant cells are identified. The presence of pathogens such as *Toxoplasma gondii,* systemic fungal organisms, and parasites provides a definitive

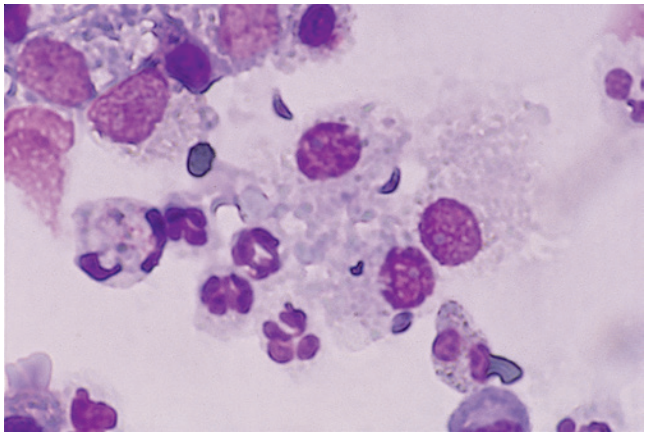


FIG 20.17
Photomicrograph of *Toxoplasma gondii* tachyzoites from the lungs of a cat with acute toxoplasmosis. The extracellular tachyzoites are crescent shaped with a centrally placed nucleus. They are approximately 6 µm in length. (Bronchoalveolar lavage fluid, Wright stain.)

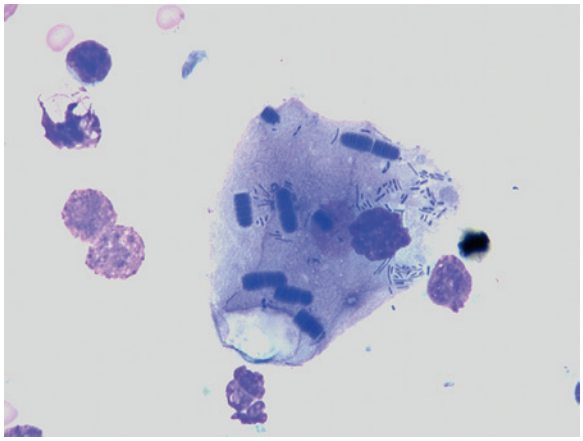


FIG 20.19
Tracheal wash fluid showing evidence of oropharyngeal contamination. The numerous, uniformly stacked basophilic rods are *Simonsiella* organisms—normal inhabitants of the oral cavity. These organisms, as well as many other bacteria, are adhering to a squamous epithelial cell. Squamous epithelium is another indication of contamination from the oral cavity.

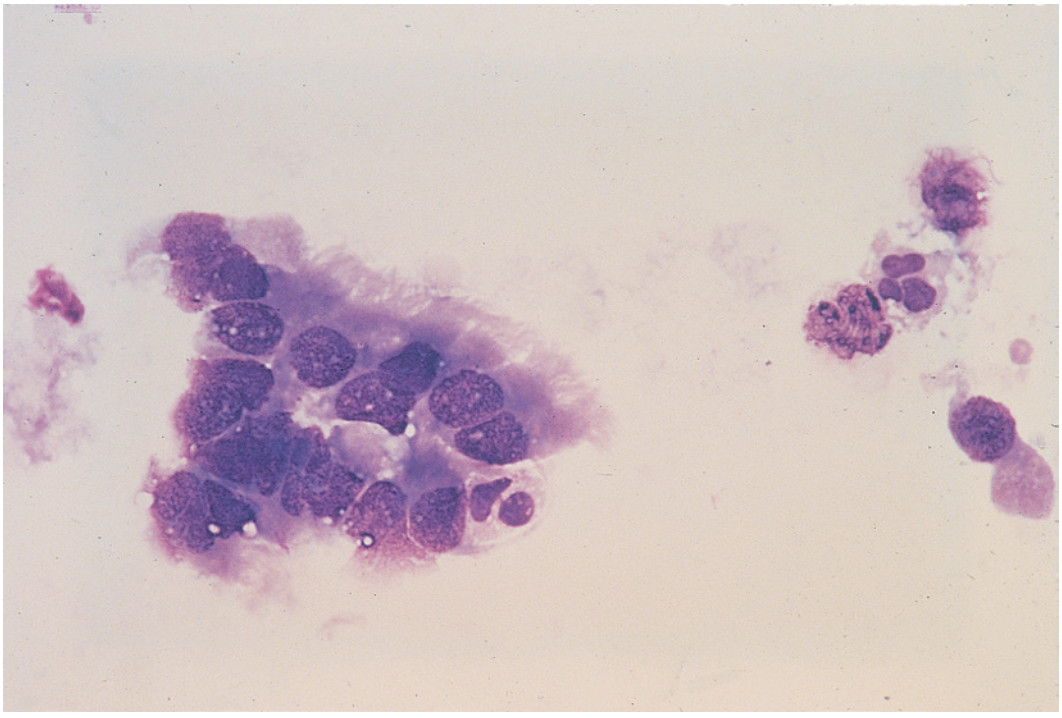


FIG 20.18
Tracheal wash fluid from a healthy dog showing ciliated epithelium and few inflammatory cells.

diagnosis. The finding of intracellular bacterial organisms in cytologic preparations without evidence of oral contamination indicates the presence of infection. The growth of any of the systemic mycotic agents in culture is also clinically significant, whereas the growth of bacteria in culture may or may not be significant because low numbers of bacteria can be present in the large airways of healthy animals. In general, the cytologic identification of bacteria and their growth in culture without multiplication in enrichment broth are significant findings.

Bacteria that are not seen cytologically and that grow only after incubation in enrichment media can result from several situations. For example, the bacteria may be causing infection without being present in high numbers because of the prior administration of antibiotics, or because of the collection of a nonrepresentative specimen. The bacteria may also be clinically insignificant and represent normal tracheal inhabitants, or they may result from contamination during collection. Other clinical data must therefore be considered when such findings are interpreted.

The role of *Mycoplasma* spp. in respiratory disease of the dog and cat is not well understood. These organisms cannot be seen on cytologic preparations and are difficult to grow in culture. Specific transport media are necessary. Growth of *Mycoplasma* organisms from tracheal wash fluid may indicate primary or secondary infection or may be an insignificant finding. Testing for *Mycoplasma* by PCR is also available. Treatment is generally recommended if inflammation was documented cytologically.

Criteria of malignancy for making a diagnosis of neoplasia must be interpreted with extreme caution. Overt characteristics of malignancy must be present in many cells in the absence of concurrent inflammation for a definitive diagnosis to be made.

The type of inflammatory cells present in tracheal wash fluid can assist in narrowing the differential diagnoses, although a mixed inflammatory response is common. Neutrophilic (suppurative) inflammation is common in bacterial infections. Before antibiotic therapy is initiated, the neutrophils may be (but are not always) degenerative, and organisms can often be seen. Neutrophilic inflammation may be a response to a variety of other diseases. For instance, it can be caused by other infectious agents or seen in patients with canine chronic bronchitis, idiopathic pulmonary fibrosis, or other idiopathic interstitial pneumonias, or even neoplasia. Some cats with idiopathic bronchitis have neutrophilic inflammation rather than the more classic eosinophilic response (see Chapter 21). The neutrophils in these instances are generally nondegenerative.

Eosinophilic inflammation reflects a hypersensitivity response, and diseases commonly resulting in eosinophilic inflammation include allergic bronchitis, parasitic disease, and eosinophilic lung disease. Parasites that affect the lung include primary lungworms or flukes, migrating intestinal parasites, and heartworms. Over time, mixed inflammation can occur in patients with hypersensitivity. It is occasionally possible for nonparasitic infection or neoplasia to cause eosinophilia, usually as part of a mixed inflammatory response.

Macrophagic (granulomatous) inflammation is characterized by the finding of increased numbers of activated macrophages, generally present as a component of mixed inflammation, along with increased numbers of other inflammatory cells. Activated macrophages are vacuolated and have increased amounts of cytoplasm. This response is nonspecific unless an etiologic agent can be identified.

Lymphocytic inflammation alone is uncommon. Viral or rickettsial infection, idiopathic interstitial pneumonia, and lymphoma are considerations.

True hemorrhage can be differentiated from a traumatic specimen collection by the presence of erythrophagocytosis and hemosiderin-laden macrophages. An inflammatory response is also usually present. Hemorrhage can be caused by neoplasia, mycotic infection, heartworm disease, thromboembolism, foreign body, lung lobe torsion, or coagulopathies. Evidence of hemorrhage is seen occasionally in animals with congestive heart failure or severe bacterial pneumonia. Of note is that hemosiderosis is found in tracheal wash fluid collected from cats with a wide range of diseases, including idiopathic bronchitis.

NONBRONCHOSCOPIC BRONCHOALVEOLAR LAVAGE

Indications and Complications

Nonbronchoscopic bronchoalveolar lavage (NB-BAL) is considered for the diagnostic evaluation of patients with lung disease involving the interstitium, small airways, or alveoli that are not tachypneic or otherwise showing signs of respiratory distress (see Table 20.2). This author prefers tracheal wash for patients with diffuse airway disease, bacterial bronchopneumonia, or aspiration pneumonia because tracheal wash carries less risk and can be expected to result in a representative specimen in these situations. Further, NB-BAL using a catheter for dogs as described in the following text will usually sample a caudal lung lobe and could bypass the exudate from pneumonia of airway origin. Therefore NB-BAL is considered primarily for patients with diffuse interstitial lung disease. Bronchoscopically guided BAL is performed as a routine part of bronchoscopy and is indicated when focal disease is present.

A large volume of lung is sampled by BAL (Figs. 20.20 and 20.21). The collected specimens are of large volume, providing more than adequate material for routine cytology, cytology involving special stains (e.g., Gram stains, acid-fast stains), multiple types of cultures (e.g., bacterial, fungal, mycoplasmal), or other specific tests that might be helpful in particular patients (e.g., flow cytometry, PCR). Cytologic preparations from BAL fluid are of excellent quality and consistently provide large numbers of well-stained cells for examination.

Although general anesthesia is required, the procedure is associated with few complications in *stable* patients. The

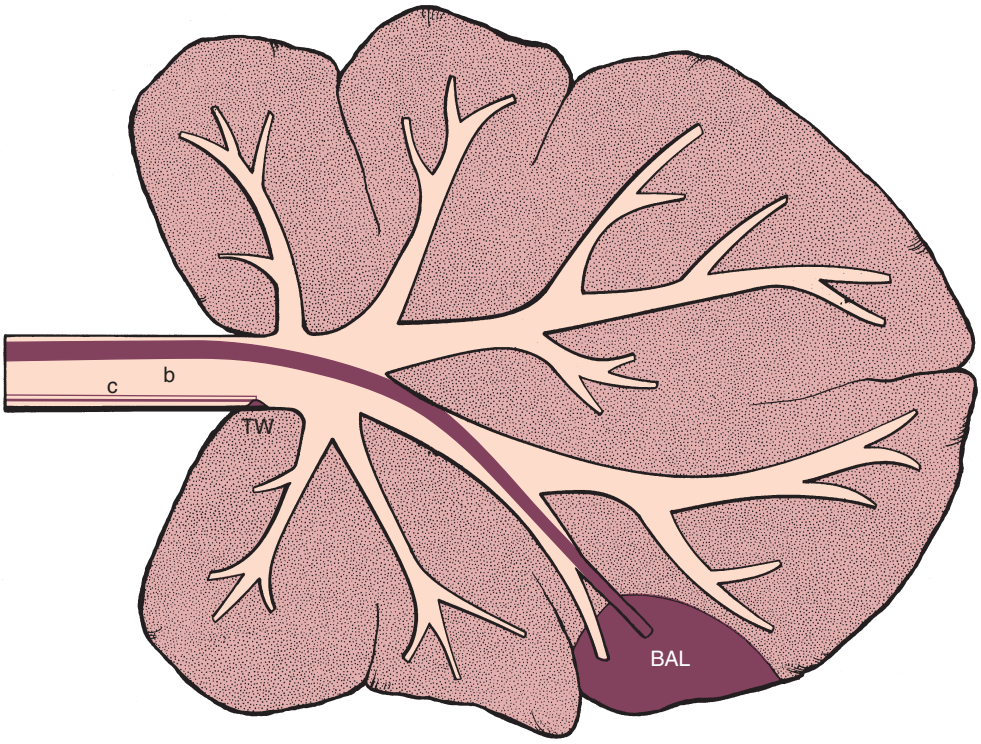


FIG 20.20
The region of the lower respiratory tract that is sampled by bronchoalveolar lavage *(BAL)* in comparison with the region sampled by tracheal wash *(TW)*. The solid line *(b)* within the airways represents a bronchoscope or a modified feeding tube. The open lines *(c)* represent the tracheal wash catheter. Bronchoalveolar lavage yields fluid representative of the deep lung, whereas tracheal wash yields fluid representative of processes involving major airways, including diffuse bronchitis, bacterial bronchopneumonia, and aspiration pneumonia.

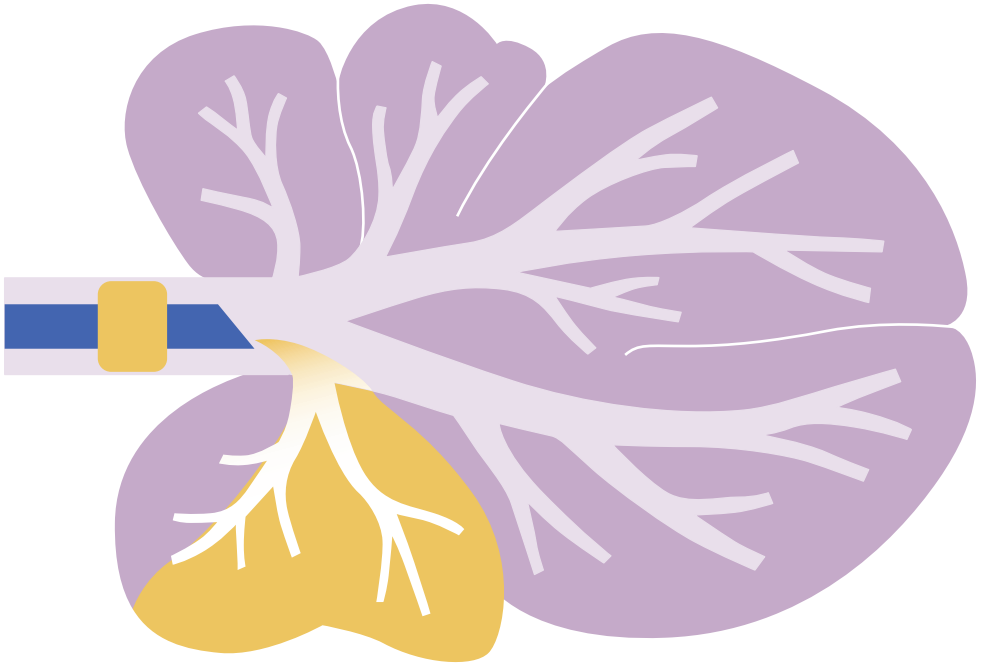


FIG 20.21
The region of the lower respiratory tract presumed to be sampled by nonbronchoscopic bronchoalveolar lavage in cats using an endotracheal tube.

primary complication of BAL is hypoxemia. Hypoxemia generally can be corrected with oxygen supplementation, but animals exhibiting increased respiratory efforts or respiratory distress in room air are not good candidates for this procedure. Patients may have poor lung function without overt signs, so the ability to provide oxygen supplementation for an hour or longer is necessary to minimize the risk of patient decompensation. Patients with hyperreactive airways, particularly cats, are treated with bronchodilators, as described previously for endotracheal washing.

In addition to the methods described, other techniques for NB-BAL have been reported in which a long, thin, sterile catheter is passed through a sterile endotracheal tube until the catheter is lodged in a distal airway, and relatively small volumes of saline are infused and recovered. Foster and Martin (2011) used a 6F to 8F dog urinary catheter and two 5- to 10-mL aliquots of sterile saline. Such methods likely result in less hypoxemia than those described here but would be expected to sample a smaller portion of lung. Critical evaluation of different techniques for BAL in disease states has not been performed.

TECHNIQUE FOR NB-BAL IN CATS

A sterile endotracheal tube and a syringe adapter are used in cats to collect lavage fluid (Fig. 20.22; see also Fig. 20.21). Cats, particularly those with signs of bronchitis, should be treated with bronchodilators before the procedure, as described previously for tracheal wash (endotracheal technique), to decrease the risk of bronchospasm. The cat may be premedicated with atropine (0.05 mg/kg subcutaneously) to minimize oral secretions, and is anesthetized with ketamine and acepromazine or diazepam, given intravenously. The endotracheal tube is passed as cleanly as possible through the larynx to minimize oral contamination. To achieve sufficient cleanliness, the tip of the tongue is pulled out, a laryngoscope is used, and sterile lidocaine is applied topically to the laryngeal mucosa. The cuff is then inflated sufficiently to create a seal, but overinflation is avoided to prevent tracheal rupture (i.e., use a 3-mL syringe and inflate the cuff in 0.5-mL increments only until no leak is audible when gentle pressure is placed on the oxygen reservoir bag).

The cat is placed in lateral recumbency with the most diseased side, as determined by physical and radiographic findings, against the table. Oxygen (100%) is administered for several minutes through the endotracheal tube. The anesthetic adapter then is removed from the endotracheal tube and replaced with a sterile syringe adapter, with caution to avoid contamination of the end of the tube or adapter. Immediately, a bolus of warmed, sterile 0.9% saline solution (5 mL/kg body weight) is infused through the tube over approximately 3 seconds. Immediately after infusion, suction is applied by syringe. Air is eliminated from the syringe, and several aspiration attempts are made until fluid is no longer recovered. The procedure is repeated using a total of two or three boluses of saline solution. The cat is allowed to expand its lungs between infusions of saline solution. After the last infusion, the syringe adapter is removed (because it greatly interferes with ventilation) and excess fluid is drained from the large airways and endotracheal tube by elevating the caudal half of the cat a few inches off of the table. At this point, the cat is cared for as described in the section on recovery of patients after BAL.

TECHNIQUE FOR NB-BAL IN DOGS

An inexpensive 122-cm 16F Levin-type polyvinyl chloride stomach tube can be used in dogs to collect lavage fluid. The tube must be modified for best results. Sterile technique is maintained throughout. The distal end of the tube is cut off for removal of the side openings. The proximal end is cut off for removal of the flange and shortening of

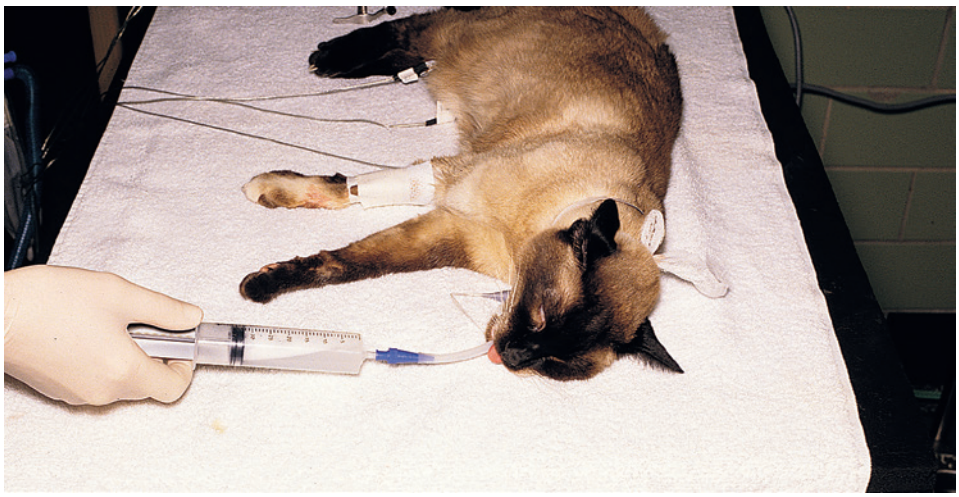


FIG 20.22
Bronchoalveolar lavage using an endotracheal tube in a cat. The fluid retrieved is grossly foamy because of the surfactant present. The procedure is performed quickly because the airway is completely occluded during infusion and aspiration of fluid.

the tube to a length slightly greater than the distance from the open end of the dog's endotracheal tube to the last rib. A syringe adapter is placed within the proximal end of the tube (Fig. 20.23).

Recovery of BAL fluid can be improved by tapering the distal end of the tube. Tapering is readily achieved using a metal, single-blade, handheld pencil sharpener that has been autoclaved and is used only for this purpose (see Fig. 20.23, *A* and *B*).

The dog may be premedicated with atropine (0.05 mg/kg subcutaneously) or glycopyrrolate (0.005 mg/kg subcutaneously) to minimize oral secretions and is anesthetized using a short-acting protocol that will allow intubation, such as with propofol, a short-acting barbiturate, or the combination of medetomidine and butorphanol. If the dog is of sufficient size to accept a size 6 or larger endotracheal tube, the dog is intubated with a sterile endotracheal tube placed as cleanly as possible to minimize oral contamination of the specimen. The modified stomach tube will not fit through a smaller endotracheal tube, so the technique must be performed without an endotracheal tube, or a smaller stomach tube must be used. If no endotracheal tube is used, extreme care must be taken to minimize oral contamination in passing the modified stomach tube, and an appropriately sized endotracheal tube should be available to gain control of the airway in case of complications and for recovery.

Oxygen (100%) is provided through the endotracheal tube or by face mask for several minutes. The modified stomach tube is passed through the endotracheal tube using sterile technique until resistance is felt. The goal is to wedge the tube snugly into an airway rather than have it abut an airway division. Therefore the tube is withdrawn slightly, then is passed again, until resistance is consistently felt at the same depth. Rotating the tube slightly during passage may help achieve a snug fit. Remember that if the endotracheal tube is not much larger than the stomach tube, ventilation is restricted at this point and the procedure should be completed expediently.

For medium-size dogs and larger, two 35-mL syringes are prepared in advance, each with 25 mL of saline and 5 mL of air. While the modified stomach tube is held in place, a 25-mL bolus of saline is infused through the tube, followed by the 5 mL of air, by holding the syringe upright during infusion (Fig. 20.24). Gentle suction is applied immediately after infusion, using the same syringe. It may be necessary to withdraw the tube slightly if negative pressure is felt. The tube should not be withdrawn more than a few millimeters. If it is withdrawn too far, air will be recovered instead of fluid. The second bolus of saline is infused and recovered in the same manner, with the tube in the same position. The dog is cared for as described in the next section.

In very small dogs, it is prudent to reduce the volume of saline used in each bolus, particularly if a smaller-diameter stomach tube is used. Overinflation of the lungs with excessive fluid volumes should be avoided.

RECOVERY OF PATIENTS AFTER BAL

Regardless of the method used, BAL causes a transient decrease in the arterial oxygen concentration. In most patients this hypoxemia responds to oxygen supplementation. Patients are monitored with pulse oximetry (discussed later in this chapter) before and throughout the procedure and during recovery. Immediately after the procedure, 100% oxygen is provided through an endotracheal tube for as long as the dog or cat will allow intubation. Several gentle "sighs" are performed with the anesthesia bag to help expand any collapsed portions of lung. Bronchospasms are a reported

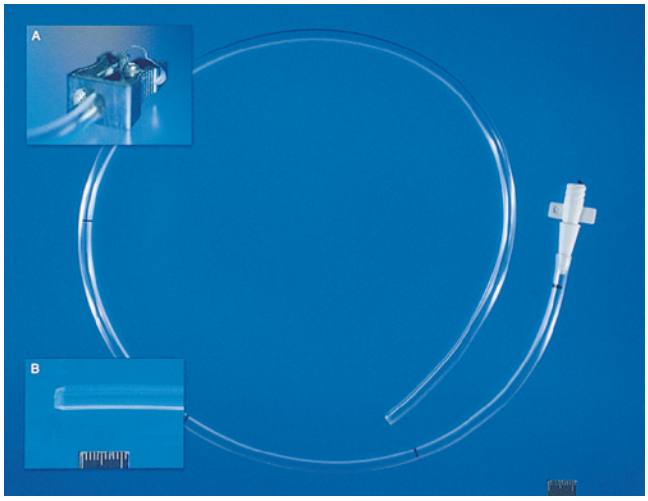


FIG 20.23
The catheter used for nonbronchoscopic bronchoalveolar lavage in dogs is a modified 16F Levin-type stomach tube. The tube is shortened by cutting off both ends. A simple pencil sharpener *(inset A)* is used to taper the distal end of the tube *(inset B)*. A syringe adapter is added to the proximal end. Sterility is maintained throughout.

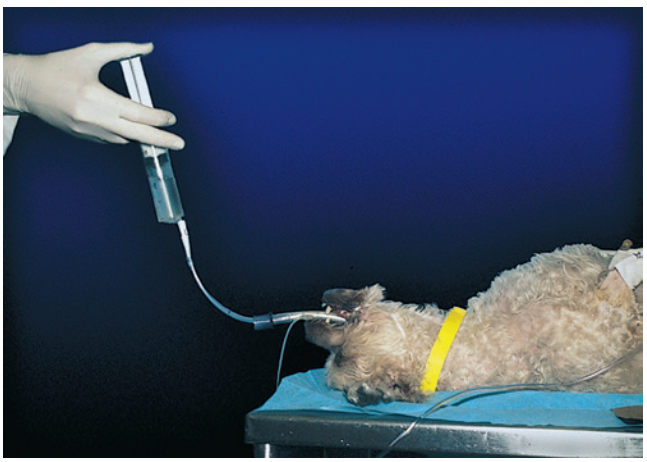


FIG 20.24
Bronchoalveolar lavage using a modified stomach tube in a dog. The tube is passed through a sterile endotracheal tube and is lodged in a bronchus. A syringe preloaded with saline and air is held upright during infusion so that saline is infused first, followed by air.

complication of BAL in people, and increased airway resistance has been documented in cats after bronchoscopy and BAL (Kirschvink et al., 2005). Albuterol in a metered dose inhaler should be on hand to administer through the endotracheal tube or by spacer and mask if needed.

After extubation the mucous membrane color, pulses, and the character of respirations are monitored closely. Crackles can be heard for several hours after BAL and are not cause for concern. Treatment with oxygen supplementation is continued by mask, oxygen cage, or nasal catheter if there are any indications of hypoxemia. Oxygen supplementation is rarely necessary for longer than 10 to 15 minutes after BAL in patients that were stable in room air before the procedure; however, the ability to provide supplementation for an hour or longer is a prerequisite for performance of this procedure, in case decompensation occurs. Considerations for patients who continue to require oxygen supplementation or whose condition deteriorates include pneumothorax, resulting from rupture of a bulla or other cavitary lesion; aspiration, as a complication of anesthesia; or cardiogenic edema from fluid overload.

SPECIMEN HANDLING

Successful BAL yields fluid that is grossly foamy, as a result of surfactant from the alveoli. Approximately 50% to 80% of the total volume of saline instilled is expected to be recovered. Less will be obtained from dogs with tracheobronchomalacia (collapsing airways). The fluid is placed on ice immediately after collection and is processed as soon as possible, with minimum manipulation to decrease cell lysis. For convenience, retrieved boluses can be combined for analysis; however, fluid from the first bolus usually contains more cells from the larger airways, and fluid from later boluses is more representative of the alveoli and interstitium.

BAL fluid is analyzed cytologically and microbiologically. Nucleated cell counts are performed on undiluted fluid using a hemocytometer. Cells are concentrated onto slides for differential cell counts and qualitative analysis using cytocentrifugation or sedimentation techniques. Slides then are stained using routine cytologic procedures. Differential cell counts are performed by counting at least 200 nucleated cells. Slides are scrutinized for evidence of macrophage activation, lymphocyte reactivity, neutrophil degeneration, and criteria of malignancy. All slides are examined thoroughly for possible etiologic agents, such as fungi, protozoa, parasites, and bacteria (see Figs. 20.12 and 20.15 to 20.17). As described for tracheal wash, visible strands of mucus can be examined for etiologic agents by squash preparation.

Approximately 5 mL of fluid is used for bacterial culture. Additional fluid is submitted for fungal culture if mycotic disease is among the differential diagnoses. *Mycoplasma* cultures or PCR are considered in cats and dogs with signs of bronchitis.

INTERPRETATION OF RESULTS

Normal cytologic values for BAL fluid are inexact because of inconsistency in the techniques used and variability among individual animals of the same species. In general, total nucleated cell counts in normal animals are less than 400 to 500/µL. Differential cell counts from healthy dogs and cats are listed in Table 20.3. Note that the provided values are means from groups of healthy animals. *Values from individual patients should not be considered abnormal unless the values are at least one or two standard deviations above these*

TABLE 20.3

Mean (±Standard Deviation [SD] or Standard Error [SE]) of Differential Cell Counts From Bronchoalveolar Lavage Fluid From Normal Animals[a]

	BRONCHOSCOPIC BAL		NONBRONCHOSCOPIC BAL	
CELL TYPE	**CANINE (%)***	**FELINE (%)†**	**CANINE (%)‡**	**FELINE (%)§**
Macrophages	70 ± 11	71 ± 10	81 ± 11	78 ± 15
Lymphocytes	7 ± 5	5 ± 3	2 ± 5	0.4 ± 0.6
Neutrophils	5 ± 5	7 ± 4	15 ± 12	5 ± 5
Eosinophils	6 ± 6	16 ± 7	2 ± 3	16 ± 14
Epithelial cells	1 ± 1	—	—	—
Mast cells	1 ± 1	—	—	—

[a]The provided values are means. Normal ranges can be expected to extend two standard deviations from the mean. See text for further discussion.

*Mean ± SD, 6 clinically and histologically normal dogs. (From Kuehn NF: *Canine bronchoalveolar lavage profile.* Thesis for masters of science degree, West Lafayette, Indiana, 1987, Purdue University.)

†Mean ± SE, 11 clinically normal cats. (From King RR et al.: Bronchoalveolar lavage cell populations in dogs and cats with eosinophilic pneumonitis. In *Proceedings of the Seventh Veterinary Respiratory Symposium,* Chicago, 1988, Comparative Respiratory Society.)

‡Mean ± SD, 9 clinically normal dogs. (From Hawkins EC et al.: Use of a modified stomach tube for bronchoalveolar lavage in dogs, *J Am Vet Med Assoc* 215:1635, 1999.)

§Mean ± SD, 34 specific pathogen–free cats. (From Hawkins EC et al.: Cytologic characterization of bronchoalveolar lavage fluid collected through an endotracheal tube in cats, *Am J Vet Res* 55:795, 1994.)

mean values. **In our canine studies we have used values of ≥12% neutrophils, 14% eosinophils, or 16% lymphocytes as indicative of inflammation.**

Interpretation of BAL fluid cytology and cultures is essentially the same as that described for tracheal wash fluid, although the specimens are more representative of the deep lung than the airways. In addition, the normal cell population of macrophages must not be misinterpreted as being indicative of macrophagic or chronic inflammation (Fig. 20.25). As for all cytologic specimens, definitive diagnoses are made through identification of organisms or abnormal cell populations. Fungal, protozoal, or parasitic organisms may be present in extremely low numbers in BAL specimens; therefore the entire concentrated slide preparation must be carefully scanned. Profound epithelial hyperplasia can occur in the presence of an inflammatory response and should not be confused with neoplasia.

If quantitative bacterial culture is available, growth of organisms at greater than 1.7×10^3 colony-forming units (CFUs)/mL has been reported to indicate infection (Peeters et al., 2000). In the absence of quantitative numbers, growth of organisms on a plate directly inoculated with BAL fluid is considered significant, whereas growth from fluid that occurs only after multiplication in enrichment broth may be a result of normal inhabitants or contamination. Patients that are already receiving antibiotics at the time of specimen collection may have significant infection with few or no bacteria by culture.

DIAGNOSTIC YIELD

A retrospective study of BAL fluid cytologic analysis in dogs at referral institutions showed that BAL findings served as the basis for a definitive diagnosis in 25% of cases and were supportive of the diagnosis in an additional 50%. Only dogs in which a definitive diagnosis was obtained by any means were included. Definitive diagnoses were possible on the basis of BAL only in those animals in which infectious organisms were identified, or in those cases in which overtly malignant cells were present in specimens in the absence of marked inflammation. BAL has been shown to be more sensitive than radiographs in identifying pulmonary involvement with lymphosarcoma. Carcinoma was definitively identified in 57% of cases, and other sarcomas were not found in BAL fluid. Fungal pneumonia was confirmed in only 25% of cases, although organisms were found in 67% of cases in a previous study of dogs with overt fungal pneumonia.

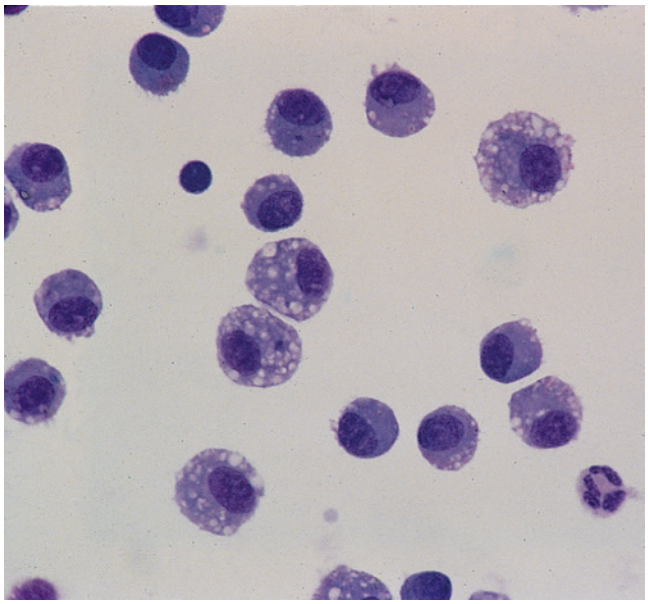


FIG 20.25
Bronchoalveolar lavage fluid from a normal dog. Note that alveolar macrophages predominate.

TRANSTHORACIC LUNG ASPIRATION AND BIOPSY

Indications and Complications

Pulmonary parenchymal specimens can be obtained by transthoracic needle aspiration or biopsy. Although only a small region of lung is sampled by these methods, collection can be guided by radiographic findings or ultrasonography to improve the likelihood of obtaining representative specimens. As with tracheal wash and BAL, a definitive diagnosis will be possible in patients with infectious or neoplastic disease. Patients with noninfectious inflammatory diseases require thoracoscopy or thoracotomy with lung biopsy for a definitive diagnosis.

Potential complications of transthoracic needle aspiration or biopsy include pneumothorax, hemothorax, and pulmonary hemorrhage. These procedures are not recommended in animals with suspected cysts, abscesses, pulmonary hypertension, or coagulopathies. Severe complications are uncommon, but these procedures should not be performed unless the clinician is prepared to place a chest tube and otherwise support the animal if necessary.

Lung aspirates and biopsy specimens are indicated for the nonsurgical diagnosis of intrathoracic mass lesions that are in contact with the thoracic wall. The risk of complications in these animals is relatively low because the specimens can be collected without disrupting aerated lung. Obtaining aspirates or biopsy specimens from masses that are far from the body wall and near the mediastinum carries the additional risk of lacerating important mediastinal organs, vessels, or nerves. If a solitary localized mass lesion is present, thoracotomy and biopsy should be considered rather than transthoracic sampling because this permits both the diagnosis of the problem and the potentially therapeutic benefits of complete excision.

Transthoracic lung aspirates can be obtained in animals with a diffuse interstitial radiographic pattern. In some of these patients, solid areas of infiltrate in lung tissue immediately adjacent to the body wall can be identified ultrasonographically even though they are not apparent on thoracic radiographs (see Fig. 20.11). Ultrasound guidance of the

aspiration needle into the areas of infiltrate should improve diagnostic yield and safety. If areas of infiltrate cannot be identified ultrasonographically, BAL should be considered before lung aspiration in animals that can tolerate the procedure because it yields a larger specimen for analysis and, in this author's opinion, carries less risk than unguided transthoracic aspiration in patients that are not experiencing increased respiratory efforts or distress. Tracheal wash and appropriate ancillary tests are also considered before lung aspiration in these patients because they carry little risk.

TECHNIQUES

The site of collection in animals with localized disease adjacent to the body wall is best identified with ultrasonography. If ultrasonography is not available, or if the lesion is surrounded by aerated lung, the site is determined on the basis of two radiographic views. The location of the lesion during inspiration in all three dimensions is identified by its relationship to external landmarks: the nearest intercostal space or rib, the distance from the costochondral junctions, and the depth into the lungs from the body wall. If available, fluoroscopy or CT also can be used to guide the needle or biopsy instrument.

The site of collection in animals with diffuse disease is a caudal lung lobe. The needle is inserted between the seventh and ninth intercostal spaces, approximately two thirds of the distance from the costochondral junctions to the spine.

The animal must be restrained for the procedure, and sedation or anesthesia is necessary in some. Anesthesia is avoided, if possible, because the hemorrhage created by the procedure is not cleared as readily from the lungs in an anesthetized dog or cat. The skin at the site of collection is shaved and surgically prepared. Lidocaine is injected into subcutaneous tissues and intercostal muscles to provide local anesthesia.

Lung aspiration can be performed with an injection needle, a spinal needle, or a variety of thin-walled needles designed specifically for lung aspiration in people. Spinal needles are readily available in most practices, are sufficiently long to penetrate through the thoracic wall, and have a stylet. A 22-gauge, 1.5- to 3.5-inch (3.75- to 8.75-cm) spinal needle is usually adequate.

The clinician wears sterile gloves. The needle with stylet is advanced through the skin several rib spaces from the desired biopsy site. The needle and skin are then moved to the biopsy site. This is done because air is less likely to enter the thorax through the needle tract after the procedure if the openings in the skin and chest wall are not aligned. The needle is then advanced through the body wall to the pleura. The stylet is removed, and the needle hub is immediately covered by a finger to prevent pneumothorax until a 12-mL syringe can be placed on the hub. During inspiration the needle is thrust into the chest to a depth predetermined from the radiographs, usually about 1 inch (2.5 cm), while suction is applied to the syringe (Fig. 20.26). To keep from inserting the needle too deeply, the clinician may pinch the needle shaft with the thumb and forefinger of the nondominant hand at the desired maximum depth of insertion. During insertion, the needle can be twisted along its long axis in an attempt to obtain a core of tissue. The needle is then immediately withdrawn to the level of the pleura. Several quick stabs into the lung can be made along different lines to increase the yield.



FIG 20.26
Transthoracic lung aspiration performed with a spinal needle. Note that sterile technique is used. The needle shaft can be pinched with finger and thumb at the maximum depth to which the needle should be passed. The finger and thumb thus act as a guard to prevent overinsertion of the needle. Although this patient is under general anesthesia, this is not usually indicated.

Each stab should take only a second. Prolonging the time that the needle is within the lung tissue increases the likelihood of complications. The lung tissue will be moving with respirations, resulting in laceration of tissue, even if the needle is held steady.

The needle is withdrawn from the body wall with a minimal amount of negative pressure maintained by the syringe. It is unusual for the specimen to be large enough to have entered the syringe. The needle is removed from the syringe, the syringe is filled with air and reattached to the needle, and the contents of the needle are then forced onto one or more slides. Grossly, the material is bloody in most cases. Squash preparations are made. Slides are stained using routine procedures and then are evaluated cytologically. Increased numbers of inflammatory cells, infectious agents, or neoplastic cell populations are potential abnormalities. Alveolar macrophages are normal findings in parenchymal specimens and should not be interpreted as representing chronic inflammation. They should be carefully examined for evidence of phagocytosis of bacteria, fungi, or red blood cells and for signs of activation. Epithelial hyperplasia can

occur in the presence of inflammation and should not be confused with neoplasia. Sometimes the liver is aspirated inadvertently, particularly in deep-chested dogs, yielding a population of cells that may resemble those from adenocarcinoma. However, hepatocytes typically contain bile pigment. Bacterial culture is indicated in some animals, although the volume of material obtained is quite small.

Transthoracic lung core biopsies can be performed in animals with mass lesions immediately adjacent to the chest wall. Specimens are collected after an aspirate has proved to be nondiagnostic. Needle biopsy instruments can be used (e.g., EZ Core biopsy needles, Products Group International, Lyons, Colorado). Smaller-bore, thin-walled lung biopsy instruments can be obtained from medical suppliers for human patients. These instruments collect smaller pieces of tissue but are less disruptive to normal lung. Ideally, sufficient material is collected for histologic evaluation. If not, squash preparations are made for cytologic studies.

BRONCHOSCOPY

Indications

Bronchoscopy is indicated for the evaluation of the major airways in animals with suspected structural abnormalities, for visual assessment of airway inflammation or pulmonary hemorrhage, and as a means of collecting specimens in animals with undiagnosed lower respiratory tract disease. Bronchoscopy can be used to identify structural abnormalities of the major airways, such as tracheal collapse, mass lesions, tears, strictures, lung lobe torsions, bronchiectasis, bronchial collapse, and external airway compression. Foreign bodies or parasites may be identified. Hemorrhage or inflammation involving or extending to the large airways may also be seen and localized.

Specimen collection techniques performed in conjunction with bronchoscopy are valuable diagnostic tools because they can be used to obtain specimens from deeper regions of the lung than is possible with the tracheal wash technique, and visually directed sampling of specific lesions or lung lobes is also possible. Animals undergoing bronchoscopy must receive general anesthesia, and the presence of the scope within the airways compromises ventilation. Therefore bronchoscopy is contraindicated in animals with severe respiratory tract compromise unless the procedure is likely to be therapeutic (e.g., foreign body removal).

TECHNIQUE

Bronchoscopy is technically more demanding than most other endoscopic techniques. The patient is often experiencing some degree of respiratory compromise, which poses increased anesthetic and procedural risks. Airway hyperreactivity may be exacerbated by the procedure, particularly in cats. A small-diameter, flexible endoscope is needed and should be sterilized before use. The bronchoscopist should be thoroughly familiar with normal airway anatomy to ensure that every lobe is examined. BAL is routinely performed as part of diagnostic bronchoscopy after thorough visual examination of the airways. The reader is referred elsewhere for details about performing bronchoscopy and bronchoscopic BAL (Dear and Johnson, 2013; Hawkins, 2004; McKiernan, 2005; Padrid, 2011). Bronchoscopic images of normal airways are shown in Fig. 20.27. Reported cell counts from bronchoscopically collected BAL fluid are provided in Table 20.3.

Abnormalities that may be observed during bronchoscopy, and their common clinical correlations are listed in Table 20.4. A definitive diagnosis is rarely possible on the basis of the findings yielded by gross examination alone. Specimens are collected through the biopsy channel for cytologic, histopathologic, and microbiologic analysis. Bronchial specimens are obtained by bronchial washing, bronchial brushing, or pinch biopsy. Material for bacterial culture can be collected with guarded culture swabs. The deeper lung is sampled by BAL or transbronchial biopsy. Foreign bodies are removed with retrieval forceps.

THORACOTOMY OR THORACOSCOPY WITH LUNG BIOPSY

Thoracotomy and surgical biopsy are performed in animals with progressive clinical signs of lower respiratory tract disease that has not been diagnosed using less invasive means. Although thoracotomy carries a greater risk than the previously mentioned diagnostic techniques, the modern anesthetic agents, surgical techniques, and monitoring capabilities now available have made this procedure routine in many veterinary practices. Analgesic drugs are used to manage postoperative pain, and complication-free animals are discharged as soon as 2 to 3 days after surgery. Surgical biopsy provides excellent-quality specimens for histopathologic analysis, culture, PCR, and other specific tests for infectious diseases or neoplasia. Abnormal lung tissue and accessible lymph nodes are biopsied.

Excisional biopsy of abnormal tissue can be therapeutic in animals with localized disease. Removal of localized neoplasms, abscesses, cysts, and foreign bodies can be curative. The removal of large localized lesions can improve the matching of ventilation and perfusion, even in animals with evidence of diffuse lung involvement, thereby improving the oxygenation of blood and reducing clinical signs.

In practices where thoracoscopy is available, this less invasive technique can be used for initial assessment of intrathoracic disease. Similarly, a "mini" thoracotomy can be performed through a relatively small incision. If disease is obviously disseminated throughout the lungs such that surgical intervention will not be therapeutic, biopsy specimens of abnormal tissue can be obtained with these methods via small incisions. If access by thoracoscopy or "mini" thoracotomy is insufficient based on initial findings, these procedures can be transitioned to a full thoracotomy during the same anesthesia.

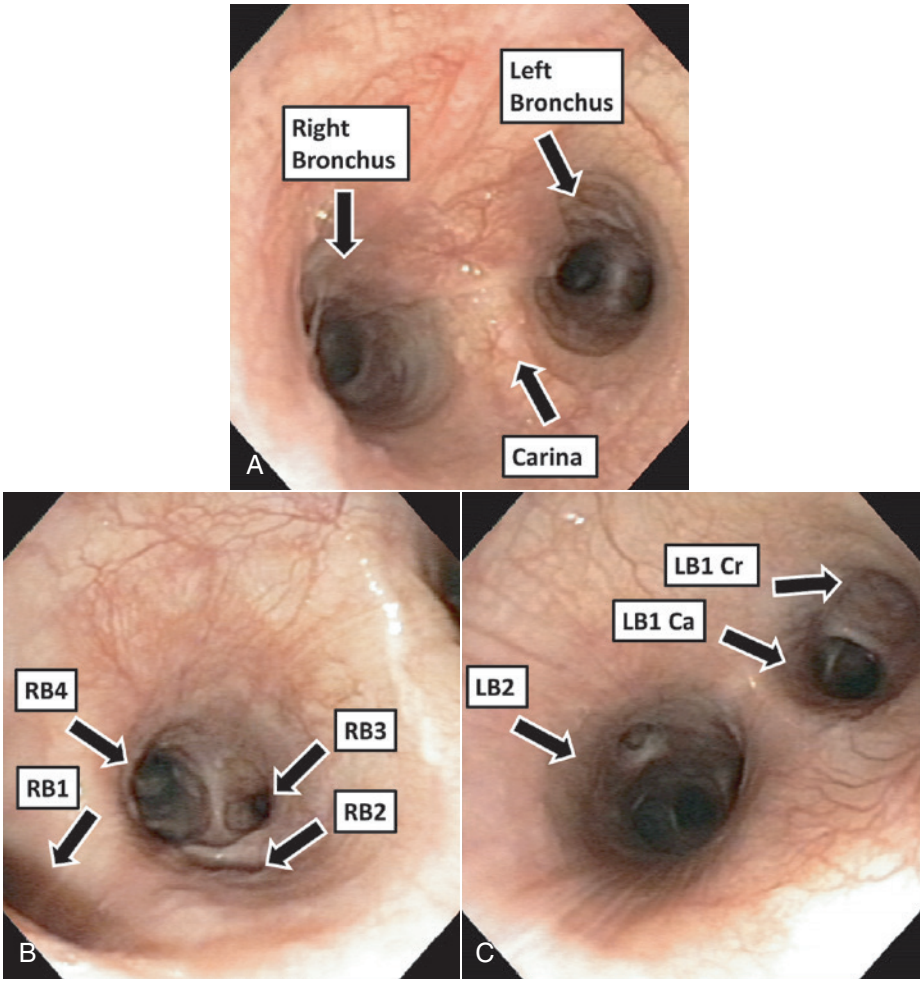


FIG 20.27
Bronchoscopic images of normal airways. The labels for the lobar bronchi are derived from a useful nomenclature system for the major airways and their branches presented by Amis et al. (1986). **(A)** Carina, the division between the right and left mainstem bronchi. **(B)** Right mainstem bronchus. The carina is off the right side of the image. Openings to the right cranial *(RB1),* right middle *(RB2),* accessory *(RB3),* and right caudal *(RB4)* bronchi are visible. **(C)** Left mainstem bronchus. The carina is off the left side of the image. The openings to the left cranial *(LB1)* and left caudal *(LB2)* bronchi are visible. The left cranial lobe *(LB1)* divides immediately into cranial *(Cr)* and caudal *(Ca)* branches. (From Amis TC et al.: Systematic identification of endobronchial anatomy during bronchoscopy in the dog, *Am J Vet Res* 47:2649, 1986.)

BLOOD GAS ANALYSIS

Indications

Measurement of partial pressures of oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) in arterial blood specimens provides information about pulmonary function. Venous blood analysis is less useful because venous blood oxygen pressures are greatly affected by cardiac function and peripheral circulation. Arterial blood gas measurements are indicated to document pulmonary failure, to differentiate hypoventilation from other causes of hypoxemia, to help determine the need for supportive therapy, and to monitor the response to therapy. Respiratory compromise must be severe for abnormalities to be measurable because the body has tremendous compensatory mechanisms.

TECHNIQUES

Arterial blood is collected in a heparinized syringe. Dilution of specimens with liquid heparin can alter blood gas results. Therefore commercially available syringes preloaded with lyophilized heparin are recommended. Alternatively, 0.5 mL of liquid sodium heparin is drawn into a 3-mL syringe with a 25-gauge needle. The plunger is drawn back to the 3 mL mark. All air is then expelled from the syringe. This procedure for expelling air and excess heparin is repeated three times.

TABLE 20.4

Bronchoscopic Abnormalities and Their Clinical Correlations

ABNORMALITY	CLINICAL CORRELATION
Trachea	
Hyperemia, loss of normal vascular pattern, excess mucus, exudate	Inflammation
Redundant tracheal membrane	Usually associated with flattened rings
Flattened cartilage rings	Tracheomalacia
Uniform narrowing	Hypoplastic trachea
Strictures	Prior trauma
Mass lesions	Fractured rings, foreign body granuloma, neoplasia
Tears	Usually caused by excessive endotracheal tube cuff pressure
Carina	
Widened	Hilar lymphadenopathy, extraluminal mass
Multiple raised nodules	*Oslerus osleri*
Foreign body	Foreign body
Bronchi	
Hyperemia, excess mucus, exudate	Inflammation
Collapse of airway during expiration	Chronic inflammation, bronchomalacia
Collapse of airway, inspiration and expiration, ability to pass scope through narrowed airway	Chronic inflammation, bronchomalacia
Collapse of airway, inspiration and expiration, inability to pass scope through narrowed airway	Extraluminal mass lesions (neoplasia, granuloma, abscess)
Collapse of airway with "puckering" of mucosa	Lung lobe torsion
Hemorrhage	Neoplasia, fungal infection, heartworm, thromboembolic disease, coagulopathy, trauma (including foreign body related)
Single mass lesion	Neoplasia
Multiple polypoid masses	Usually chronic bronchitis; at carina, *Oslerus*
Foreign body	Foreign body

The femoral artery is commonly used (Fig. 20.28). The animal is placed in lateral recumbency. The upper rear limb is abducted, and the rear limb resting on the table is restrained in a partially extended position. The femoral artery is palpated in the inguinal region, close to the abdominal wall, using two fingers. The needle is advanced into the artery between these fingers. The artery is thick-walled and loosely attached to adjacent tissues; thus the needle must be sharp and positioned exactly on top of the artery. A short, jabbing motion facilitates entry.

The dorsal pedal artery is useful for arterial collection in medium-size and large dogs. The position of the artery is illustrated in Fig. 20.29.

Once the needle has penetrated the skin, suction is applied. On entry of the needle into the artery, blood should enter the syringe quickly, sometimes in pulses. Unless the animal is severely compromised, the blood will be bright red compared with the dark red of venous blood. Dark red blood or blood that is difficult to draw into the syringe may be obtained from a vein. Mixed samples from both the artery and the vein can be collected accidentally, particularly from the femoral site.

After removal of the needle, pressure is applied to the puncture site for 5 minutes to prevent hematoma formation. Pressure is applied even after unsuccessful attempts if there is any possibility that the artery was entered.

All air bubbles are eliminated from the syringe. The needle is covered by a cork or rubber stopper, and the entire syringe is placed in crushed ice unless the blood specimen is to be analyzed immediately. Specimens should be analyzed as soon as possible after collection. Minimal alterations occur in specimens stored on ice during the few hours required to transport the specimen to a human hospital if a blood gas analyzer is not available on site. Because of the availability of reasonably priced blood gas analyzers, point-of-care testing is now possible.

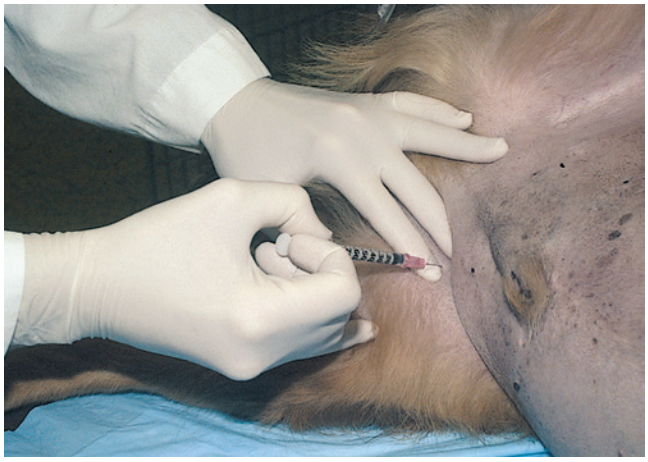


FIG 20.28
Position for obtaining an arterial blood specimen from the femoral artery. The dog is in left lateral recumbency. The right rear limb is being held perpendicular to the table to expose the left inguinal area. The pulse is palpated in the femoral triangle between two fingers to accurately locate the artery. The needle is laid directly on top of the artery, then is stabbed into it with a short, jabbing motion.

TABLE 20.5

Approximate Ranges of Arterial Blood Gas Values for Normal Dogs and Cats Breathing Room Air

MEASUREMENT	ARTERIAL BLOOD
Pa_{O_2} (mm Hg)	85-100
Pa_{CO_2} (mm Hg)	35-45
H_{CO_3} (mmol/L)	21-27
pH	7.35-7.45



FIG 20.29
Position for obtaining an arterial blood specimen from the dorsal pedal artery. The dog is in left lateral recumbency, with the medial surface of the left leg exposed. A pulse is palpated just below the tarsus on the dorsal surface of the metatarsus between the midline and the medial aspect of the distal limb.

INTERPRETATION OF RESULTS

Approximate arterial blood gas values for normal dogs and cats are provided in Table 20.5. More exact values should be obtained for normal dogs and cats using the actual analyzer.

Pa_{O_2} and Pa_{CO_2}

Abnormal Pa_{O_2} and Pa_{CO_2} values can result from technical error. The animal's condition and the collection technique are considered in the interpretation of blood gas values. For example, an animal in stable condition with normal mucous membrane characteristics evaluated for exercise intolerance is unlikely to have a resting Pa_{O_2} of 45 mm Hg. The collection of venous blood is a more likely explanation for this abnormal value.

Hypoxemia is present if the Pa_{O_2} is below the normal range. The oxyhemoglobin dissociation curve describing the relationship between the saturated hemoglobin level and Pa_{O_2} is sigmoid in shape, with a plateau at higher Pa_{O_2} values (Fig. 20.30). Normal hemoglobin is almost totally saturated with oxygen when the Pa_{O_2} is greater than 80 to 90 mm Hg, and clinical signs are unlikely in animals with such values. The curve begins to decrease more quickly at lower Pa_{O_2} values. A value of less than 60 mm Hg corresponds to a hemoglobin saturation that is considered dangerous, and treatment for hypoxemia is indicated. (See the section on oxygen content, delivery, and utilization later in this chapter.)

In general, animals become cyanotic when the Pa_{O_2} reaches 50 mm Hg or less, which results in a concentration of nonoxygenated (unsaturated) hemoglobin of 5 g/dL or more. Cyanosis occurs as a result of the increased concentration of nonoxygenated hemoglobin in the blood and is not a direct reflection of the Pa_{O_2}. The development of cyanosis depends on the total concentration of hemoglobin, as well as on the oxygen pressure; cyanosis develops more quickly in animals with polycythemia than in animals with anemia. Acute hypoxemia resulting from lung disease more often

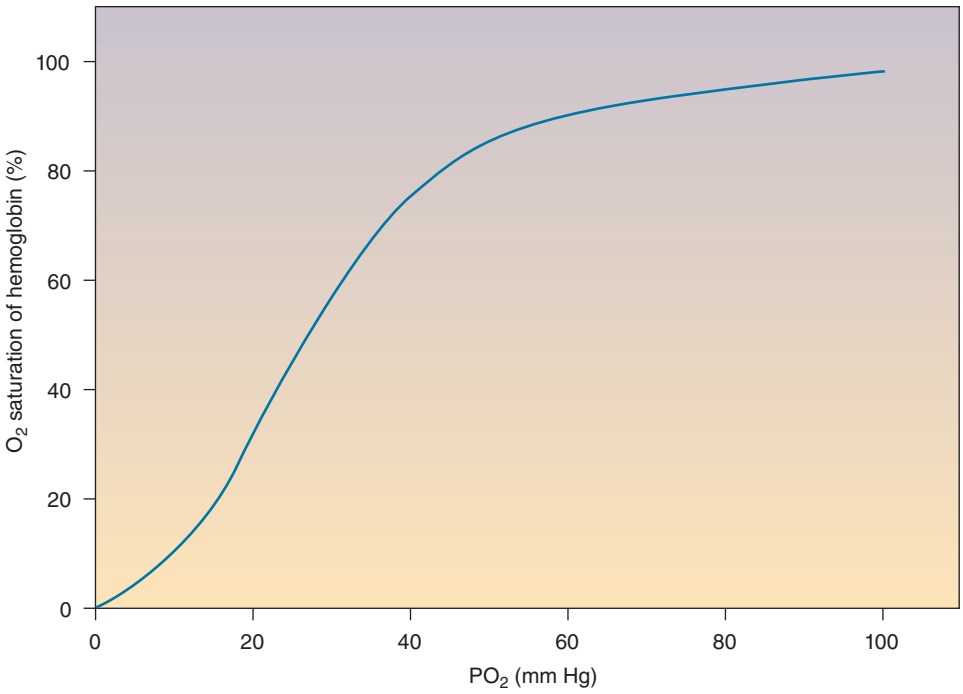


FIG 20.30
Oxyhemoglobin dissociation curve (approximation).

produces pallor in an animal than cyanosis. Treatment for hypoxemia is indicated for all animals with cyanosis.

Determining the mechanism of hypoxemia is useful in selecting appropriate supportive therapy. These mechanisms include hypoventilation, inequality of ventilation and perfusion within the lung, and diffusion abnormality. Hypoventilation is the inadequate exchange of gases between the outside of the body and the alveoli. Both Pa_{O_2} and Pa_{CO_2} are affected by lack of gas exchange, and hypercapnia occurs in conjunction with hypoxemia. Causes of hypoventilation are listed in Box 20.7.

The ventilation and perfusion of different regions of the lung must be matched for the blood leaving the lung to be fully oxygenated. The relationship between ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) can be described as a ratio ($\dot{V}/\dot{Q}$). Hypoxemia can develop if regions of lung have a low or a high $\dot{V}/\dot{Q}$.

Poorly ventilated portions of lung with normal blood flow have a low $\dot{V}/\dot{Q}$. Regionally decreased ventilation occurs in most pulmonary diseases for reasons such as alveolar flooding, alveolar collapse, or small airway obstruction. The flow of blood past totally nonaerated tissue is known as a venous admixture or shunt ($\dot{V}/\dot{Q}$ of zero). The alveoli may be unventilated as a result of complete filling or collapse, resulting in physiologic shunts, or the alveoli may be bypassed by true anatomic shunts. Unoxygenated blood from these regions then mixes with oxygenated blood from ventilated portions of the lung. The immediate result consists of decreased Pa_{O_2} and increased Pa_{CO_2}. The body responds to hypercapnia by increasing ventilation, effectively returning the Pa_{CO_2} to normal or even lower than normal. However,

BOX 20.7

Clinical Correlations of Blood Gas Abnormalities

Decreased Pa_{O_2} and Increased Pa_{CO_2} (Normal A-a Gradient)

Venous specimen
Hypoventilation
- Airway obstruction
- Decreased ventilatory muscle function
  - Anesthesia
  - Central nervous system disease
  - Polyneuropathy
  - Polymyopathy
  - Neuromuscular junction disorders (myasthenia gravis)
  - Extreme fatigue (prolonged distress)
- Restriction of lung expansion
  - Thoracic wall abnormality
  - Excessive thoracic bandage
  - Pneumothorax
  - Pleural effusion
- Increased dead space (low alveolar ventilation)
  - Severe chronic obstructive pulmonary disease/emphysema

End-stage severe pulmonary parenchymal disease
Severe pulmonary thromboembolism

Decreased Pa_{O_2} and Normal or Decreased Pa_{CO_2} (Wide A-a Gradient)

Ventilation/perfusion ($\dot{V}/\dot{Q}$) abnormality
- Most lower respiratory tract diseases (see Box 19.1)

increased ventilation cannot correct the hypoxemia because blood flowing by ventilated alveoli is already maximally saturated.

Except where shunts are present, the Pao_2 can be improved in dogs and cats with lung regions with low $\dot{V}/\dot{Q}$ by providing supplemental oxygen therapy administered by face mask, oxygen cage, or nasal catheter. Positive-pressure ventilation may be necessary to combat atelectasis (see Chapter 25).

Ventilation of areas of lung with decreased circulation (high $\dot{V}/\dot{Q}$) occurs in dogs and cats with thromboembolism. Initially there may be little effect on arterial blood gas values because blood flow is shifted to unaffected regions of the lung. However, blood flow in normal regions of the lungs increases with increasing severity of disease, and $\dot{V}/\dot{Q}$ is decreased enough in those regions that a decreased Pao_2 and a normal or decreased $Paco_2$ may occur, as described previously. Both hypoxemia and hypercapnia are seen in the setting of extremely severe embolization.

Diffusion abnormalities alone do not result in clinically significant hypoxemia but can occur in conjunction with $\dot{V}/\dot{Q}$ mismatching in diseases such as idiopathic pulmonary fibrosis and noncardiogenic pulmonary edema. Gas is normally exchanged between the alveoli and the blood by diffusion across the respiratory membrane. This membrane consists of fluid lining the alveolus, alveolar epithelium, alveolar basement membrane, interstitium, capillary basement membrane, and capillary endothelium. Gases must also diffuse through plasma and red blood cell membranes. Functional and structural adaptations that facilitate diffusion between alveoli and red blood cells provide an efficient system for this process, which is rarely affected significantly by disease.

A-a Gradient

Hypoventilation is differentiated from $\dot{V}/\dot{Q}$ abnormalities by evaluation of the $Paco_2$ in conjunction with the Pao_2. Qualitative differences are described in the preceding paragraphs. Hypoventilation is associated with hypoxemia and hypercapnia, and $\dot{V}/\dot{Q}$ abnormalities are generally associated with hypoxemia and normocapnia or hypocapnia. It is possible to quantify this relationship by calculating the alveolar-arterial oxygen gradient (*A-a* gradient), which factors out the effects of ventilation and the inspired oxygen concentration on Pao_2 (Table 20.6).

TABLE 20.6

Relationships of Arterial Blood Gas Measurements

FORMULA	DISCUSSION
$Pao_2 \propto Sao_2$	Relationship is defined by sigmoid oxyhemoglobin dissociation curve. Curve plateaus at greater than 90% Sao_2 with Pao_2 values greater than 80 mm Hg. Curve is steep at Pao_2 values of between 20 and 60 mm Hg (assuming normal hemoglobin, pH, temperature, and 2,3-diphosphoglycerate concentrations).
$Cao_2 = (Sao_2 \times Hgb \times 1.34) + (0.003 \times Pao_2)$	Total oxygen content of blood is greatly influenced by Sao_2 and hemoglobin concentration. In health, more than 60 times more oxygen is delivered by hemoglobin than is dissolved in plasma (Pao_2).
$Paco_2 = PAco_2$	These values are increased with hypoventilation at alveolar level and are decreased with hypoventilation.
$PAo_2 = Flo_2 (P_B - PH_2O) - Paco_2/R$ On room air at sea level: $PAo_2 = 150$ mm Hg $- Paco_2/0.8$	Partial pressure of oxygen in alveolar air available for exchange with blood changes directly with inspired oxygen concentration and inversely with $Paco_2$. R is assumed to be 0.8 for fasting animals. With normally functioning lungs (minimal $\dot{V}/\dot{Q}$ mismatch), alveolar hyperventilation results in increased PAo_2 and subsequently increased Pao_2, whereas hypoventilation results in decreased PAo_2 and decreased Pao_2.
A-a = $PAo_2 - Pao_2$	*A-a* gradient quantitatively assesses $\dot{V}/\dot{Q}$ mismatch by eliminating contribution of alveolar ventilation and inspired oxygen concentration to measured Pao_2. Low Pao_2, with a normal *A-a* gradient (10 mm Hg in room air) indicates hypoventilation alone. Low Pao_2 with a wide *A-a* gradient (>15 mm Hg in room air) indicates a component of $\dot{V}/\dot{Q}$ mismatch.
$Paco_2 \propto 1/pH$	Increased $Paco_2$ causes respiratory acidosis; decreased $Paco_2$ causes respiratory alkalosis. Actual pH depends on metabolic (Hco_3) status as well.

A-a, Alveolar-arterial oxygen gradient (mm Hg); *Cao_2,* oxygen content of arterial blood (mL of O_2/dL); *Flo_2,* fraction of oxygen in inspired air (%); *Hgb,* hemoglobin concentration (g/dL); *$Paco_2$,* partial pressure of CO_2 in arterial blood (mm Hg); *$PAco_2$,* partial pressure of O_2 in alveolar air (mm Hg); *Pao_2,* partial pressure of O_2 in arterial blood (mm Hg); *PAo_2,* partial pressure of O_2 in alveolar air (mm Hg); *P_B,* barometric (atmospheric) pressure (mm Hg); *PH_2O,* partial pressure of water in alveolar air (100% humidified) (mm Hg); *pH,* negative logarithm of H^+ concentration (decreases with increased H^+); *R,* respiratory exchange quotient (ratio of O_2 uptake per CO_2 produced); *Sao_2,* amount of hemoglobin saturated with oxygen (%); *$\dot{V}/\dot{Q}$,* ratio of ventilation to perfusion of alveoli.

The premise of the *A-a* gradient is that Pa_{O_2} *(a)* is nearly equal (within 10 mm Hg in room air) to the partial pressure of oxygen in the alveoli, PA_{O_2} *(A),* in the absence of a diffusion abnormality or $\dot{V}/\dot{Q}$ mismatch. In the presence of a diffusion abnormality or a $\dot{V}/\dot{Q}$ mismatch, the difference widens (greater than 15 mm Hg in room air). Examination of the equation reveals that hyperventilation, resulting in a lower Pa_{CO_2}, leads to a higher PA_{O_2}. Conversely, hypoventilation, resulting in a higher Pa_{CO_2}, leads to a lower PA_{O_2}. Physiologically the Pa_{O_2} can never exceed the PA_{O_2}, however, and the finding of a negative value indicates an error. The error may be found in one of the measured values or in the assumed R value (see Table 20.6).

Clinical examples of the calculation and interpretation of the *A-a* gradient are provided in Box 20.8.

Oxygen Content, Delivery, and Utilization

The commonly reported blood gas value Pa_{O_2} reflects the pressure of oxygen dissolved in arterial blood. This value is critical for assessing lung function. However, the clinician must remember that other variables are involved in oxygen delivery to the tissues besides Pa_{O_2}, and that tissue hypoxia can occur in spite of a normal Pa_{O_2}. The formula for calculating the total oxygen content of arterial blood (Ca_{O_2}) is provided in Table 20.6. The greatest contribution to Ca_{O_2} in health is oxygenated hemoglobin. In a normal dog (Pa_{O_2}, 100 mm Hg; hemoglobin, 15 g/dL), oxygenated hemoglobin accounts for 20 mL of O_2/dL, whereas dissolved oxygen accounts for only about 0.3 mL of O_2/dL.

The quantity of hemoglobin is routinely appraised by the complete blood count. It can also be estimated on the basis of the packed cell volume (by dividing the packed cell volume by 3). The oxygen saturation of hemoglobin (Sa_{O_2}) is dependent on the Pa_{O_2}, as depicted by the sigmoid shape of the oxyhemoglobin dissociation curve (see Fig. 20.30). However, the Sa_{O_2} is also influenced by other variables that can shift the oxyhemoglobin dissociation curve to the left or right (e.g., pH, temperature, 2,3-diphosphoglycerate concentrations) or interfere with oxygen binding with hemoglobin (e.g., carbon monoxide toxicity, methemoglobinemia). Some laboratories measure Sa_{O_2}.

Oxygen must be successfully delivered to the tissues, and this depends on cardiac output and local circulation. Ultimately, the tissues must be able to effectively use the oxygen—a process interfered with in the presence of toxicities such as carbon monoxide or cyanide poisoning. Each of these processes must be considered when the blood gas values in an individual animal are interpreted.

Acid-Base Status

The acid-base status of an animal can be assessed using the same blood sample that is used to measure blood gases. Acid-base status is influenced by the respiratory system (see Table 20.6). Respiratory acidosis results if carbon dioxide is retained as a result of hypoventilation. If the problem persists for several days, compensatory retention of bicarbonate by the kidneys occurs. Excess removal of carbon dioxide by the lungs caused by hyperventilation results in respiratory alkalosis. Hyperventilation is usually an acute phenomenon, potentially caused by shock, sepsis, severe anemia, anxiety, or pain; therefore compensatory changes in the bicarbonate concentration are rarely seen.

The respiratory system partially compensates for primary metabolic acid-base disorders, and this can occur quickly. Hyperventilation and a decreased Pa_{CO_2} occur in response to metabolic acidosis. Hypoventilation and an increased Pa_{CO_2} occur in response to metabolic alkalosis.

In most cases, acid-base disturbances can be identified as primarily respiratory or primarily metabolic in nature on the basis of the pH. The compensatory response will never be excessive and alter the pH beyond normal limits. An animal with acidosis (pH of less than 7.35) has a primary respiratory acidosis if the Pa_{CO_2} is increased and a compensatory respiratory response if the Pa_{CO_2} is decreased. An animal with alkalosis (pH of greater than 7.45) has a primary respiratory alkalosis if the Pa_{CO_2} is decreased and a compensatory respiratory response if the Pa_{CO_2} is increased.

If both the Pa_{CO_2} and the bicarbonate concentration are abnormal, such that both contribute to the same alteration in pH, a mixed disturbance is present. For instance, an animal with acidosis, an increased Pa_{CO_2}, and a decreased HCO_3 has a mixed metabolic and respiratory acidosis.

BOX 20.8

Calculation and Interpretation of *A-a* Gradient: Clinical Examples

Example 1: A healthy dog breathing room air has a Pa_{O_2} of 95 mm Hg and a Pa_{CO_2} of 40 mm Hg. His calculated PA_{O_2} is 100 mm Hg. ($PA_{O_2} = FI_{O_2}[P_B - PH_2O] - Pa_{CO_2}/R = 0.21\ [765\ mm\ Hg - 50\ mm\ Hg] - [40\ mm\ Hg/0.8]$.) The *A-a* gradient is 100 mm Hg – 95 mm Hg = 5 mm Hg. This value is normal.

Example 2: A dog with respiratory depression due to an anesthetic overdose has a Pa_{O_2} of 72 mm Hg and a Pa_{CO_2} of 56 mm Hg in room air. His calculated PA_{O_2} is 80 mm Hg. The *A-a* gradient is 8 mm Hg. His hypoxemia can be explained by hypoventilation.

Later the same day, the dog develops crackles bilaterally. Repeat blood gas analysis shows a PaO_2 of 60 mm Hg and a $PaCO_2$ of 48 mm Hg. His calculated PAO_2 is 90 mm Hg. The *A-a* gradient is 30 mm Hg. Hypoventilation continues to contribute to the hypoxemia, but hypoventilation has improved. The widened *A-a* gradient indicates $\dot{V}/\dot{Q}$ mismatch. This dog has aspirated gastric contents into his lungs.

PULSE OXIMETRY

Indications

Pulse oximetry is a method of monitoring the oxygen saturation of blood. The saturation of hemoglobin with oxygen is

related to the Pa_{O_2} by the sigmoid oxyhemoglobin dissociation curve (see Fig. 20.30). Pulse oximetry is noninvasive, can be used to continuously monitor a dog or cat, provides immediate results, and is affordable for most practices. It is a particularly useful device for monitoring animals with respiratory disease that must undergo procedures requiring anesthesia. It can also be used in some cases to monitor the progression of disease or the response to therapy. More and more clinicians are using these devices for routine monitoring of animals under general anesthesia.

METHOD

Most pulse oximeters have a probe attached to a fold of tissue, such as the tongue, lip, ear flap, inguinal skin fold, toe, or tail (Fig. 20.31). This probe measures light absorption through the tissues. Other models measure reflected light and can be placed on mucous membranes or within the esophagus or rectum. Artifacts resulting from external light sources are minimized in the latter sites. Arterial blood is identified by the oximeter as that component which changes in pulses. Nonpulsatile absorption is considered background.

INTERPRETATION

Values provided by the pulse oximeter must be interpreted with care. The instrument must record a pulse that matches the palpable pulse of the animal. Any discrepancy between actual pulse and the pulse received by the oximeter indicates an inaccurate reading. Common problems that can interfere with the accurate detection of pulses include the position of the probe, animal motion (e.g., respirations, shivering), and weak or irregular pulse pressures (e.g., tachycardia, hypovolemia, hypothermia, arrhythmias).

The value measured indicates the saturation of hemoglobin in the local circulation. However, this value can be affected by factors other than pulmonary function, such as vasoconstriction, low cardiac output, and local stasis of blood. Other intrinsic factors that can affect oximetry readings include anemia, hyperbilirubinemia, carboxyhemoglobinemia, and methemoglobinemia. External lights and the location of the probe can also influence results. Pulse oximetry readings of oxygen saturation are less accurate when values are below 80%.

These sources for error should not discourage the clinician from using this technology, however, because changes in saturation in an individual animal provide valuable information. Rather, results must be interpreted critically.

Examination of the oxyhemoglobin dissociation curve (see Fig. 20.30) in normal dogs and cats shows that animals with Pa_{O_2} values exceeding 85 mm Hg will have a hemoglobin saturation greater than 95%. If Pa_{O_2} values decrease to 60 mm Hg, the hemoglobin saturation will be approximately 90%. Any further decrease in Pa_{O_2} results in a precipitous decrease in hemoglobin saturation, as illustrated by the steep portion of the oxyhemoglobin dissociation curve. Ideally, then, hemoglobin saturation should be maintained at greater than 90% by means of oxygen supplementation or ventilatory support (see Chapter 25) or specific treatment of the underlying disease. However, because of the many variables associated with pulse oximetry, such strict guidelines are not always valid. In practice, a baseline hemoglobin saturation value is measured, and subsequent changes in that value are then used to assess improvement or deterioration in oxygenation. Ideally, the baseline value is compared with the Pa_{O_2} obtained from an arterial blood sample collected concurrently to ensure the accuracy of the readings.



FIG 20.31
Monitoring oxygen saturation in a cat under general anesthesia using a pulse oximeter with a probe *(P)* clamped onto the tongue *(T)*.

Suggested Readings

Armbrust LJ. Comparison of three-view thoracic radiography and computed tomography for detection of pulmonary nodules in dogs with neoplasia. *J Am Vet Med Assoc*. 2012;240:1088.

Balakrishnan A, King LG. Updates on pulmonary function testing in small animals. *Vet Clin Small Anim*. 2014;44:1.

Bowman DD, et al. *Georgis' parasitology for veterinarians*. 9th ed. St Louis: Saunders Elsevier; 2009.

Clarke DA, et al. Partial resolution of hypoplastic trachea in six English bulldog puppies with bronchopneumonia. *J Am Anim Hosp Assoc*. 2011;47:329.

Dear JD, Johnson LR. Lower respiratory tract endoscopy in the cat. *J Fel Med Surg*. 2013;15:1019.

DeHeer HL, McManus P. Frequency and severity of tracheal wash hemosiderosis and association with underlying disease in 96 cats: 2002-2003. *Vet Clin Path*. 2005;34:17.

Dillon AR, et al. Lung histopathology, radiography, high-resolution computed tomography, and bronchio-alveolar lavage cytology are altered by Toxocara cati infection in cats and is independent of development of adult intestinal parasites. *Vet Parasitol*. 2013;193:413.

Foster S, Martin P. Lower respiratory tract infections in cats: reaching beyond empirical therapy. *J Fel Med Surg*. 2011;13:313.

Hawkins EC. Bronchoalveolar lavage. In: King LG, ed. *Textbook of respiratory disease in dogs and cats*. St Louis: Elsevier; 2004.

Hopper K, et al. Assessment of the effect of dilution of blood samples with sodium heparin on blood gas, electrolyte, and lactate measurements in dogs. *Am J Vet Res*. 2005;66:656.

Johnson LR, et al. Agreement among radiographs, fluoroscopy and bronchoscopy in documentation of airway collapse in dogs. *J Vet Intern Med*. 2015;29:1619.

Kirschvink N, et al. Bronchodilators in bronchoscopy-induced airflow limitation in allergen-sensitized cats. *J Vet Intern Med*. 2005;19:161.

Lacorcia L, et al. Comparison of bronchoalveolar lavage fluid examination and other diagnostic techniques with the Baermann technique for detection of naturally occurring *Aelurostrongylus abstrusus* infection in cats. *J Am Vet Med Assoc*. 2009;235:43.

Larson MM. Ultrasound of the thorax (noncardiac). *Vet Clin Small Anim*. 2009;39:733.

Lindl BJ, et al. Comparison of the radiographic and tracheoscopic appearance of the dorsal tracheal membrane in large and small breed dogs. *Vet Radiol Ultrasound*. 2015;56:602.

Lisciandro GR. Abdominal and thoracic focused assessment with sonography for trauma, triage, and monitoring in small animals. *J Vet Emerg Crit Care*. 2011;21:104.

Lisciandro GR, et al. Frequency and number of ultrasound lung rockets (B-lines) using a regionally based lung ultrasound examination named vet BLUE (veterinary bedside lung ultrasound exam) in dogs with radiographically normal lung findings. *Vet Radiol Ultrasound*. 2014;55:315.

McKiernan BC. Bronchoscopy. In: McCarthy TC, et al., eds. *Veterinary endoscopy for the small animal practitioner*. St Louis: Elsevier; 2005.

Neath PJ, et al. Lung lobe torsion in dogs: 22 cases (1981-1999). *J Am Vet Med Assoc*. 2000;217:1041.

Nemanic S, et al. Comparison of thoracic radiographs and single breath-hold helical CT for detection of pulmonary nodules in dogs with metastatic neoplasia. *J Vet Intern Med*. 2006;20:508.

Norris CR, et al. Use of keyhole lung biopsy for diagnosis of interstitial lung diseases in dogs and cats: 13 cases (1998-2001). *J Am Vet Med Assoc*. 2002;221:1453.

Padrid PA. Laryngoscopy and tracheobronchoscopy of the dog and cat. In: Tams TR, et al., eds. *Small animal endoscopy*. 3rd ed. St Louis: Elsevier Mosby; 2011.

Peeters DE, et al. Quantitative bacterial cultures and cytological examination of bronchoalveolar lavage specimens from dogs. *J Vet Intern Med*. 2000;14:534.

Sherding RG. Respiratory parasites. In: Bonagura JD, et al., eds. *Kirk's current veterinary therapy XIV*. St Louis: Saunders Elsevier; 2009.

Spector D, et al. Antigen and antibody testing for the diagnosis of blastomycosis in dogs. *J Vet Intern Med*. 2008;22:839.

Taylor SM. *Small animal clinical techniques*. 2nd ed. St Louis: Elsevier; 2016.

Thrall D. *Textbook of veterinary diagnostic radiography*. 6th ed. St Louis: Saunders Elsevier; 2013.

CHAPTER 21

Disorders of the Trachea and Bronchi



GENERAL CONSIDERATIONS

Common diseases of the trachea and bronchi include canine infectious respiratory disease complex (CIRDC), canine chronic bronchitis, feline bronchitis, collapsing trachea, and allergic bronchitis. *Oslerus osleri* infection is an important consideration in young dogs.

Other diseases may involve the airways, either primarily or concurrently with pulmonary parenchymal disease. These diseases, such as viral and bacterial pneumonia, other parasitic infections, and neoplasia are discussed in Chapter 22. Feline bordetellosis can cause signs of bronchitis (e.g., cough) but is more often associated with signs of upper respiratory disease (see the section on feline upper respiratory infection in Chapter 15) or bacterial pneumonia (Chapter 22).

CANINE INFECTIOUS RESPIRATORY DISEASE COMPLEX, INCLUDING CANINE INFLUENZA

Etiology and Client Communication Challenges

CIRDC, also known as *canine infectious tracheobronchitis* or "kennel cough," is a highly contagious, acute disease involving the airways. In most dogs, CIRDC is self-limiting, with resolution of clinical signs in approximately 2 weeks. Many different viral and bacterial pathogens can cause this syndrome (Box 21.1). The role of *Mycoplasma* spp. in respiratory infection of any kind is likely complex, with frequent isolation of organisms from apparently healthy individuals. However, several studies strongly support a role for *Mycoplasma cynos*, in particular, in CIRDC. Co-infection with two or more of the organisms listed in Box 21.1 is common and may result in more severe clinical signs.

Some dogs infected with organisms of CIRDC will develop pneumonia. The pneumonia can be a direct effect of the CIRDC organism, particularly with infections with *B. bronchiseptica* and canine influenza. Secondary bacterial infection can also occur, enabled by damage to host defenses. For instance, *Bordetella* organisms infect ciliated respiratory epithelium (Fig. 21.1) and decrease mucociliary clearance. Pneumonias are discussed further in Chapter 22.

Many clients have the misunderstanding that kennel cough equals infection with *Bordetella bronchiseptica*. They believe that the "kennel cough" vaccine (meaning, a *Bordetella* vaccine) prevents the disease and that antibiotics should cure the disease. They are confused by conflicting information about canine influenza virus infections. Some have read about devastating pneumonia, some have been told by boarding facilities that they must vaccinate their dog before they can use the facility, and some have been told by their veterinarian that vaccination is not indicated.

An effective means of educating clients is to emphasize the similarities between CIRDC and colds and flu in people (Box 21.2). The human medical profession has made strong efforts to educate the public on influenza in the context of vaccination, and colds in the context of the overuse of antibiotics. Further, most people have direct personal experience with colds and flu.

In both CIRDC and "colds and flu," many different agents are involved. Being infected with one agent does not preclude being infected with another. A person is more likely to develop infection if he, she, or family members regularly find themselves in group settings (e.g., daycare, working environments with large staff, interaction with the public), just as dogs are more likely to be infected with frequent exposure to other dogs (e.g., boarding or grooming facilities, dog parks, dog shows and trials, pet stores, shelters). Most people and dogs recover without antibiotics or supportive care, and, in fact, viruses will not respond to antibacterial drugs, but some people and dogs develop pneumonia and require aggressive treatment. Rarely, people and dogs die from their infection or its consequences. Vaccines for specific agents involved in CIRDC do not prevent infection, and none is completely effective in preventing signs, just as the influenza vaccine does not prevent all infections or signs in people. People and dogs are more likely to become seriously ill if they are compromised in some way before infection, but sometimes a particularly virulent strain of organism will arise with severe consequences for even healthy people or dogs.

BOX 21.1

Agents Associated With Canine Infectious Respiratory Disease Complex (Infectious Tracheobronchitis, "Kennel Cough")

Viruses

Canine adenovirus 2
Canine influenza viruses (H3N8, H3N2)
Canine parainfluenza virus
Canine herpesvirus—type1
Canine respiratory coronavirus
Canine pneumovirus

Bacteria

Bordetella bronchiseptica
Streptococcus equi, subsp. *zooepidemicus*
Mycoplasma cynos
Other *Mycoplasma* spp.

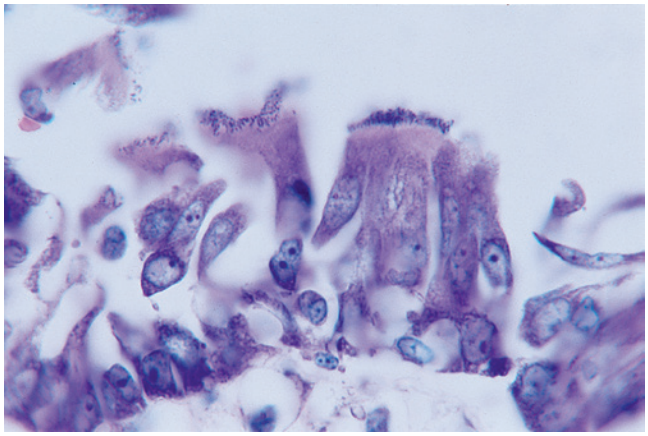


FIG 21.1
Photomicrograph of a tracheal biopsy specimen from a dog infected with *Bordetella bronchiseptica*. The organisms are small basophilic rods that are visible along the ciliated border of the epithelial cells. (Giemsa stain courtesy D. Malarkey.)

Be aware that, although rare, *B. bronchiseptica* has been documented to cause infection in people. A discussion regarding the potential exposure of a dog with CIRDC to immunocompromised individuals is warranted.

Clinical Features

Affected dogs are first seen because of the sudden onset of a severe productive or nonproductive cough, which is often exacerbated by exercise, excitement, or pressure of the collar on the neck. Palpating the trachea easily induces the cough. Gagging, retching, or nasal discharge can also occur. A recent history (i.e., within 2 weeks) of boarding, hospitalization, or exposure to a puppy or dog that has similar signs is common. Puppies recently obtained from pet stores, kennels, or shelters have often been exposed to the pathogens.

BOX 21.2

Client Education for Canine Infectious Respiratory Disease Complex (CIRDC)

CIRDC is like colds and flu in people. The following information is often well understood by the general public regarding colds and flu and correlates well with CIRDC.

- More than one type of organism is responsible
  - Being infected with, or vaccinated for, one organism does not prevent being infected with another
- Some people never get sick
- Some people get sick frequently
- More people get sick if they are frequently exposed to children or the general public
- Most people recover without any specific treatment
- Some people develop pneumonia and some people die, usually as a result of:
  - Particularly virulent organisms
  - Underlying respiratory disease (such as bronchitis or asthma)
  - Immune compromise or debilitation
  - Being very old or very young
- Vaccines are not completely effective
- Antibiotics are not usually necessary and are ineffective against viruses

Most dogs with CIRDC are considered to have "uncomplicated," self-limiting disease and do not show signs of systemic illness. Therefore dogs showing respiratory distress, weight loss, persistent anorexia, or signs of involvement of other organ systems, such as diarrhea, chorioretinitis, or seizures, may have some other, more serious disease, such as canine distemper or a mycotic infection. Secondary bacterial pneumonia can develop particularly in puppies, immunocompromised dogs, and dogs that have preexisting lung abnormalities such as chronic bronchitis. Dogs with chronic airway disease or tracheal collapse can experience an acute, severe exacerbation of their chronic problems, and extended management may be necessary to resolve the signs associated with infection in these animals. *B. bronchiseptica* infection has been associated with canine chronic bronchitis.

Diagnosis

Uncomplicated cases of CIRDC are diagnosed on the basis of presenting signs. However, differential diagnoses should also include the early presentation of a more serious disease. Diagnostic testing is indicated for dogs with systemic, progressive, or unresolving signs. Tests to be considered include thoracic radiographs, a complete blood count (CBC), tracheal wash fluid analysis, polymerase chain reaction (PCR) testing, paired serology, or other tests for the respiratory pathogens listed in Box 21.1. Tracheal wash fluid cytology shows acute inflammation, and bacterial culture of the fluid can be useful for identifying any bacteria involved in the

disease and for obtaining antibiotic sensitivity information to guide antibiotic selection.

Testing for specific pathogens by serology or PCR rarely provides information that will redirect treatment of an individual dog but may be helpful in managing outbreaks. Consultation with the diagnostic laboratory is recommended for optimizing results. The timing and recommended site of specimen collection varies with the infection of greatest concern. Serology for canine influenza viruses is the most sensitive method to detect infection but will be falsely negative before seroconversion. Influenza viruses are most readily identified by PCR from nasal swabs. The H3N8 strain is only shed early in the course of disease, whereas the H3N2 strain has been identified for as long as 26 days (Newbury et al., 2016). Testing by PCR for other CIRDC organisms is generally performed on pharyngeal swabs, although testing of bronchial brushings or airway washings would minimize false positive results from the carrier state. Positive PCR results can be obtained for up to 28 days in dogs that have been vaccinated with intranasal *B. bronchiseptica*, canine parainfluenza virus (PIV), and canine adenovirus 2 (CAV2) (Ruch-Galle et al., 2016). A negative PCR result for any of the CIRDC organisms does not rule out the possibility of their involvement.

Treatment

Uncomplicated CIRDC is a self-limiting disease. Rest for at least 7 days, specifically avoiding exercise and excitement, is indicated to minimize the continual irritation of the airways caused by excessive coughing. Cough suppressants are valuable for the same reason but should not be given if the cough is overtly productive or if exudate is suspected to be accumulating in the lungs on the basis of auscultation or thoracic radiograph findings. Because CIRDC is a tracheobronchitis, dogs with CIRDC will have exudate and excess mucus in their airways whether apparent externally or not. Therefore cough suppressants should be used judiciously to treat frequent or severe cough, to allow for restful sleep, and to prevent exhaustion.

A variety of cough suppressants can be used in dogs (Table 21.1). Dextromethorphan is available in over-the-counter preparations; however, it has questionable efficacy in dogs. Cold remedies with additional ingredients such as antihistamines and decongestants should be avoided. Pediatric liquid preparations are palatable for most dogs, and the alcohol contained in them may have a mild tranquilizing effect. Narcotic cough suppressants are more likely to be effective. Butorphanol is available as a veterinary labeled product (Torbutrol, Zoetis, Parsippany, NJ). Hydrocodone bitartrate is a potent alternative for dogs with refractory cough.

In theory, antibiotics are not indicated for most dogs with CIRDC for two reasons: (1) The disease is usually self-limiting and tends to resolve spontaneously, regardless of any specific treatment that is implemented, and (2) no antibiotic protocol has been proven to eliminate *Bordetella* or *Mycoplasma* organisms from the airways. The Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Disease (ISCAID) recommends that antimicrobial treatment be considered within the first 10 days of signs ONLY if fever, lethargy, or inappetence is present together with mucopurulent discharges (Lappin et al., 2017). In practice, however, antibiotics are often prescribed, and their use is justified because of the potential presence of these organisms. Doxycycline (5 mg/kg q12h or 10 mg/kg q24h, followed by a bolus of water) is effective against *Mycoplasma* spp. and many *Bordetella* isolates. Although the ability of doxycycline to reach therapeutic concentration within the airways has been questioned because it is highly protein bound in the dog, the presence of inflammatory cells may increase locally available concentrations of the drug and account for its anecdotal success. Amoxicillin with clavulanate (11 mg/kg orally q8h) is effective, in vitro, against many *Bordetella* isolates. Fluoroquinolones provide the advantage of reaching high concentrations in the airway secretions, but their use is ideally reserved for more serious infections. Bacterial susceptibility data from tracheal wash fluid can be used to guide the selection of an appropriate antibiotic. Antibiotics are administered for 5 days beyond the time the clinical signs resolve, or for at least 10 days.

Glucocorticoids should not be used. No field studies have demonstrated any benefit of steroid therapy, either alone or in combination with antibiotics.

If clinical signs have not resolved within 2 weeks, further diagnostic evaluation is considered. As with colds and flu in people, signs may be prolonged in some instances but careful monitoring is in order. See Chapter 22 for the management of bacterial pneumonia.

TABLE 21.1

Common Cough Suppressants for Use in Dogs*

AGENT	DOSAGE
Dextromethorphan†	1-2 mg/kg PO q6-8h
Butorphanol	0.5 mg/kg PO q6-12h
Hydrocodone bitartrate	0.25-0.5 mg/kg PO q6-12h

PO, By mouth.
*Centrally acting cough suppressants are rarely, if ever, indicated for use in cats and can result in adverse reactions. The preceding dosages are for dogs only.
†Efficacy is questionable in dogs.

Prognosis

The prognosis for recovery from uncomplicated CIRDC is excellent.

Prevention

CIRDC can be prevented by minimizing an animal's exposure to organisms and by providing vaccination programs. Excellent nutrition, routine deworming, and avoidance of stress improve the dog's ability to respond appropriately to infection without showing serious signs. Studies in shelters

and rehoming facilities have shown that the major variable associated with development of cough in newly arrived dogs is time in the facility.

Organisms can be shed by infected dogs before the onset of clinical signs. After the onset of signs, canine influenza virus (H3N2) was isolated from an infected dog after 26 days, although most dogs were negative by PCR of nasal swabs after 20 days (Newbury et al., 2016). Therefore a minimum isolation period of at least 21 days for dogs with signs of CIRDC is prudent. *Bordetella* may persist in the airways of dogs for up to 3 months after infection, but it has been assumed that shedding is minimal once clinical signs have completely resolved.

To minimize exposure to CIRDC organisms, dogs are kept isolated from puppies or dogs that have been recently boarded. Careful sanitation should be practiced in kenneling facilities. Caretakers should be instructed in the disinfection of cages, bowls, and runs, and everyone working with the dogs must wash their hands after handling each animal. Dogs should not be allowed to have face-to-face contact. Adequate air exchange and humidity control are necessary in rooms housing several dogs. Recommended goals are at least 10 to 15 air exchanges per hour and less than 50% humidity. An isolation area is essential for the housing of dogs with clinical signs of infectious tracheobronchitis. Facilities experiencing chronic problems should be referred to a shelter medicine specialist (www.sheltervet.org).

In the veterinary setting, reception staff should be trained to recognize historic signs that could be associated with CIRDC. Dogs with such signs should not be allowed into the waiting room but rather taken directly (ideally through a different entrance away from any other dogs) into an examination room. Protective clothing should be worn as some organisms can survive on clothing. Careful disinfection practices should be followed.

Injectable and intranasal vaccines are available for three of the major pathogens involved in CIRDC (i.e., *B. bronchiseptica*, PIV, and CAV2). An oral vaccine is available for *B. bronchiseptica*. Injectable modified-live virus vaccines are available against CAV2 and PIV. Killed, injectable vaccines are available for both identified strains of canine influenza virus (H3N8 and H3N2), including in combination as a bivalent vaccine.

Modified-live CAV2 and PIV are conveniently included in most combination distemper vaccines and are considered core vaccines. Because maternal antibodies interfere with the response to vaccines, puppies must be vaccinated with the combination distemper vaccines every 2 to 4 weeks, beginning at 6 to 8 weeks of age and through 14 to 16 weeks of age. At least two vaccines must be given initially. For most healthy dogs, a booster is recommended after 1 year, followed by subsequent vaccinations every 3 years (see Chapter 93).

Dogs at high risk for disease, such as those in kennels where the disease is endemic, those that participate in group dog sports or activities, or those that are frequently boarded, may benefit from annual vaccination against *B. bronchiseptica* and canine influenza. These vaccines do not prevent infection but aim to decrease clinical signs should infection occur. They may also reduce the duration of shedding of organisms after infection. A study by Ellis et al. (2001) indicated that both intranasal and parenteral *Bordetella* vaccines afford similar protection based on antibody titers, clinical signs, upper airway cultures, and histopathologic examination of tissues after exposure to organisms. The greatest benefit was achieved by administering both forms of vaccine sequentially at 2-week intervals (two doses of parenteral vaccine and then a dose of intranasal vaccine), but such an aggressive schedule is not routinely recommended. Also in experimental settings, protection against challenge after intranasal vaccination against *B. bronchiseptica* and PIV began by 72 hours (but not earlier) after vaccination and persisted for at least 13 months (Gore, 2005; Jacobs et al., 2005). Again in an experimental setting, intranasal vaccination against *B. bronchiseptica* provided superior protection compared with oral vaccination (Ellis et al., 2016). Intranasal *Bordetella* vaccines occasionally cause clinical signs, predominantly cough. The signs are generally self-limiting but are disturbing to most owners.

Canine influenza vaccines are killed products, and a booster vaccination is required 2 to 4 weeks after initial vaccination to achieve protection. Annual vaccination is recommended thereafter for dogs at risk.

CANINE CHRONIC BRONCHITIS

Etiology

Canine chronic bronchitis is a disease syndrome defined clinically as cough that occurs on most days of 2 or more consecutive months in the past year in the absence of other active disease. Histologic changes in the airways are those of long-term inflammation and include fibrosis, epithelial hyperplasia, glandular hypertrophy, and inflammatory infiltrates. Some of these changes are irreversible. Excessive mucus is present within the airways, and small airway obstruction occurs. In people, chronic bronchitis is strongly associated with smoking. It is presumed that canine chronic bronchitis is a consequence of a long-standing inflammatory process initiated by infection, allergy, or inhaled irritants or toxins. A continuing cycle of inflammation likely occurs as mucosal damage, mucus hypersecretion, and airway obstruction impair normal mucociliary clearance, and inflammatory mediators amplify the response to irritants and organisms.

Clinical Features

Chronic bronchitis occurs most often in middle-aged or older, small-breed dogs. Breeds commonly affected include Terriers, Poodles, and Cocker Spaniels. Small-breed dogs are also predisposed to the development of tracheobronchomalacia and mitral insufficiency with left atrial enlargement. These causes for cough must be differentiated, and their contribution to the development of the current clinical features determined, for appropriate management to be implemented.

Dogs with chronic bronchitis are evaluated because of loud, harsh cough. Mucus hypersecretion is a component of the disease, but the cough may sound productive or nonproductive. The disease has usually progressed slowly over months to years, although clients typically report the initial onset as acute. There should be no systemic signs of illness such as anorexia or weight loss. As the disease progresses, exercise intolerance becomes evident; then incessant coughing or overt respiratory distress is seen.

Potential complications of chronic bronchitis include bacterial or mycoplasmal infection, tracheobronchomalacia (discussed later in this chapter), pulmonary hypertension (see Chapter 22), and bronchiectasis. *Bronchiectasis* is the term for permanent dilation of the airways (Fig. 21.2; see also Fig. 20.4). Bronchiectasis can be present secondary to other causes of chronic airway inflammation or airway obstruction, and in association with certain congenital disorders such as ciliary dyskinesia (i.e., immotile cilia syndrome). Bronchiectasis caused by traction on the airways, rather than bronchial disease, can be seen with idiopathic pulmonary fibrosis. Generally, all the major airways are dilated in dogs with bronchiectasis, but occasionally the condition is localized. Recurrent bacterial infection and overt bacterial pneumonia are common complications in dogs with bronchiectasis.

Dogs with chronic bronchitis are often brought to a veterinarian because of a sudden exacerbation of signs. The change in signs may result from transient worsening of the chronic bronchitis, perhaps after a period of unusual excitement, stress, or exposure to irritants or allergens; from a secondary complication, such as bacterial infection; or from the development of a concurrent disease, such as left atrial enlargement or heart failure (Box 21.3). In addition to providing a routine complete history, the client should be carefully questioned about the character of the cough and the progression of signs. Detailed information should be obtained regarding the following: environmental conditions, particularly exposure to smoke, other potential irritants and toxins, or allergens; exposure to infectious agents, such as boarding or exposure to puppies; and all previous and current medications and responses to treatment.

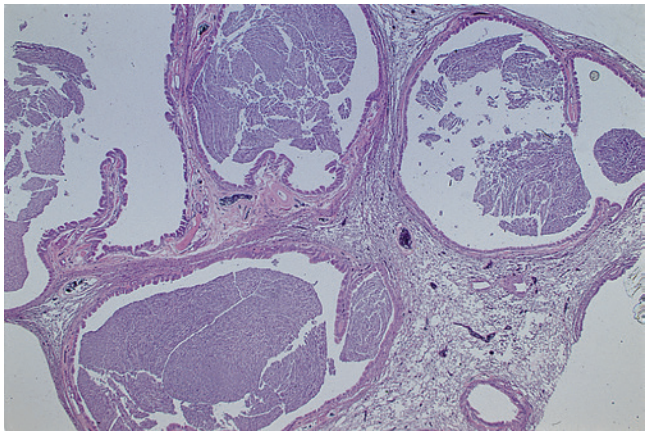


FIG 21.2
Photomicrograph of a lung biopsy specimen from a dog with severe bronchiectasis. The airways are filled with exudate and are greatly dilated (hematoxylin and eosin [H&E] stain).

On physical examination, increased breath sounds, crackles, or occasionally wheezes are auscultated in animals with chronic bronchitis. End-expiratory clicks caused by mainstem bronchial or intrathoracic tracheal collapse may be heard in animals with advanced disease. A prominent or split second heart sound occurs in animals with secondary pulmonary hypertension. Dogs with respiratory distress (end-stage disease) characteristically show marked expiratory efforts because of narrowing and collapse of the intrathoracic large airways. The presence of a fever or other systemic signs is suggestive of other disease, such as bacterial pneumonia.

Diagnosis

Canine chronic bronchitis is defined as a cough that occurs on most days of 2 or more consecutive months in the past year *in the absence of other active disease*. Therefore chronic bronchitis is diagnosed on the basis of not only clinical signs but also the elimination of other diseases from the list of differential diagnoses (see Box 21.3). The possibility of secondary or concurrent disease complicates this simple definition.

BOX 21.3

Diagnostic Considerations for Dogs With Signs Consistent With Canine Chronic Bronchitis

Other Active Disease (Rather Than Canine Chronic Bronchitis)

Bacterial infection
Mycoplasmal infection
Left atrial enlargement
Pulmonary parasites
Heartworm disease
Allergic bronchitis
Neoplasia
Foreign body
Chronic aspiration
Gastroesophageal reflux*

Potential Complications of Canine Chronic Bronchitis

Tracheobronchomalacia
Pulmonary hypertension
Bacterial infection
Mycoplasmal infection
Bronchiectasis

Most Common Concurrent Cardiopulmonary Diseases

Tracheobronchomalacia
Left atrial enlargement
Heart failure

*Gastroesophageal reflux is a common cause of chronic cough in people. Documentation in dogs and cats is limited.

A bronchial pattern with increased interstitial markings is typically seen on thoracic radiographs, but changes are often mild and difficult to distinguish from clinically insignificant changes associated with aging, and radiographs may be completely unremarkable. Thoracic radiographs are most useful for identifying *other* causes of cough or secondary diseases.

Tracheal wash or bronchoalveolar lavage (BAL) fluid should be collected at the time of the initial presentation and after a persistent exacerbation of signs. Tracheal wash will usually provide a sufficient specimen in diffuse airway disease. Neutrophilic or mixed inflammation and increased amounts of mucus are usually present. The finding of degenerative neutrophils indicates the possibility of a bacterial infection. Airway eosinophilia is suggestive of a hypersensitivity reaction, as can occur with allergy, parasitism, or heartworm disease. Slides should be carefully examined for organisms. Bacterial cultures are performed and the results interpreted as discussed in Chapter 20. Although the role of *Mycoplasma* infection in these cases is not well understood, *Mycoplasma* cultures or PCR are also considered.

Bronchoscopy, with specimen collection, is performed in selected cases, primarily to help rule out other diseases. The maximal benefit of bronchoscopy is obtained early in the course of disease, before severe permanent damage has occurred and while the risk of the procedure is minimal. Gross abnormalities visualized by bronchoscopy include an increased amount of mucus, roughened mucosa, and hyperemia (Video 21.1). Major airways may collapse during expiration as a result of weakened walls (Fig. 21.3), and polypoid mucosal proliferation may be present. Bronchial dilation may be visualized in animals with bronchiectasis.

Further diagnostic procedures are indicated to rule out other potential causes of chronic cough, and selection of these depends on the presenting signs and results of the previously discussed diagnostic tests. Diagnostic tests to be considered include heartworm tests, fecal examinations for pulmonary parasites (flotation, Baermann, and sediment examinations), echocardiography, and systemic evaluation (i.e., CBC, serum biochemical panel, urinalysis). Echocardiography may reveal evidence of secondary pulmonary hypertension, including right heart enlargement (i.e., cor pulmonale).

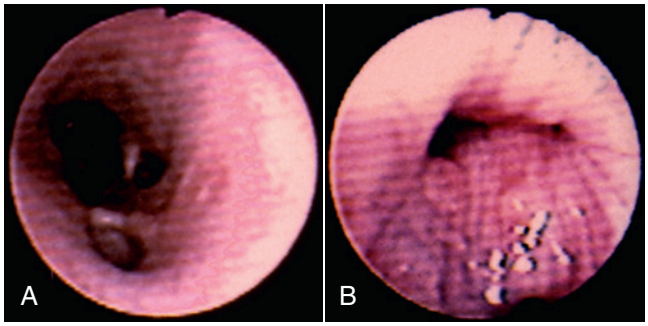


FIG 21.3
Bronchoscopic view of the right caudal bronchus of a dog with chronic bronchitis and severe bronchomalacia. The airways appear normal during inspiration **(A)** but completely collapse during expiration, obliterating the lumen of the airway **(B).**

Ciliary dyskinesia, in which ciliary motion is abnormal, is uncommon but should be considered in young dogs with bronchiectasis or recurrent bacterial infection. Abnormalities exist in all ciliated tissues, and situs inversus (i.e., lateral transposition of the abdominal and thoracic organs, such that left-sided structures are found on the right and vice versa) is seen in 50% of such dogs. Dextrocardia that occurs in association with chronic bronchitis is extremely suggestive of this disease. Sperm motility can be evaluated in intact male dogs. The finding of normal sperm motility rules out a diagnosis of ciliary dyskinesia. The disease is diagnosed on the basis of the rate at which radioisotopes deposited at the carina are cleared and the findings from electron microscopic examination of bronchial biopsy, nasal biopsy, or sperm specimens.

Treatment

Chronic bronchitis is managed symptomatically, with specific treatment possible only for concurrent or complicating diseases that are identified. Each dog with chronic bronchitis is presented at a different stage of the disease, with or without concurrent or secondary cardiopulmonary disease (see Box 21.3). Hence each dog must be managed individually. Ideally, medications are initiated one at a time to allow assessment of the most effective combination. It will likely be necessary to modify treatment over time.

GENERAL MANAGEMENT

Exacerbating factors, either possible or proven, are avoided. Potential allergens are considered in dogs with eosinophilic inflammation and trial elimination pursued (see the section on allergic bronchitis). Exposure to irritants such as smoke (from tobacco or fireplace) and perfumed products should be avoided in all dogs. Motivated clients can take steps to improve the air quality in their home through carpet, furniture, and drapery cleaning; cleaning of the furnace and frequent replacement of air filters; and the use of an air cleaner. The American Lung Association has a useful Web site with nonproprietary recommendations for improving indoor air quality (www.lung.org). Excitement or stress can cause an acute worsening of signs in some animals, and short-term tranquilization with acepromazine or sedation with phenobarbital can be helpful in relieving the signs for short periods. Anxiolytic drugs, such as trazadone, may be beneficial if long-term control is needed.

It is normal for flora from the oropharynx to be aspirated into the airways. Routine dental prophylaxis and teeth brushing will help maintain a healthy oral flora and may decrease any contributions of normal aspiration to ongoing airway inflammation in patients with reduced mucociliary clearance.

Airway hydration should be maintained to facilitate mucociliary clearance. Adequate airway hydration is best

achieved by maintaining systemic hydration. Therefore diuretic therapy is not recommended in these patients. For severely affected dogs, placing the animal in a steamy bathroom or in a room with a vaporizer daily may provide symptomatic relief, although the moisture does not penetrate very deeply into the airways. Nebulization of saline will allow moisture to go more deeply into the lungs. This technique is discussed further in the section on bacterial pneumonia in Chapter 22.

Patients that are overweight and/or unfit may benefit from weight loss (see Chapter 51) and exercise. Exercise should be tailored to the dog's current fitness level and degree of pulmonary dysfunction to keep from causing excessive respiratory efforts or even death. Observing the dog during specific exercise, such as a short walk, while in the client's presence may be necessary to make initial recommendations. Instructing clients in measurement of respiratory rate, observation of mucous membrane color, and signs of increased respiratory effort will improve their ability to assess the dog's status during exercise.

DRUG THERAPIES

Medications to control clinical signs include bronchodilators, glucocorticoids, and cough suppressants.

Theophylline, a methylxanthine bronchodilator, has been used for years for the treatment of chronic bronchitis in people and dogs (Box 21.4). This drug became unpopular with physicians when newer bronchodilators with fewer side effects became available. However, research in people suggests that theophylline is effective in treating the underlying inflammation of chronic bronchitis, even at concentrations below those resulting in bronchodilation (hence, reducing side effects), and that the antiinflammatory effects may be synergistic with those of glucocorticoids. Theophylline may also improve mucociliary clearance, decrease fatigue of respiratory muscles, and inhibit the release of mast cell mediators of inflammation. The potential beneficial effects of theophylline beyond bronchodilation may be of particular importance in dogs because their airways are not as reactive (i.e., likely to bronchospasm) as those of cats and people. However, theophylline alone is rarely sufficient to control the clinical signs of chronic bronchitis except in mild cases

Another advantage associated with theophylline is that plasma concentrations of drug can be easily measured by commercial diagnostic laboratories. A disadvantage of theophylline is that other drugs, such as fluoroquinolones, can delay its clearance, causing signs of theophylline toxicity if the dosage is not reduced by one third to one half, or the dosage interval doubled. Potential adverse effects include gastrointestinal signs, cardiac arrhythmias, nervousness, and seizures. Serious adverse effects are extremely rare at therapeutic concentrations.

Variability in sustained plasma concentrations has been noted for different theophylline products. At the time of this writing, only immediate-acting products are commercially available. If beneficial effects are not seen at the initial dosage selected, if the patient is predisposed to adverse effects, or if adverse effects occur, plasma theophylline concentrations should be measured. Therapeutic peak concentration for bronchodilation, based on data from people, ranges from 10 to 20 µg/mL, whereas antiinflammatory effects may occur at 5 to 10 µg/mL (Barnes, 2003). To confirm that plasma concentrations are being maintained in this range, blood is collected immediately before the next scheduled dose.

Sympathomimetic drugs are preferred by some clinicians as bronchodilators (see Box 21.4). Terbutaline and albuterol are selective for β2-adrenergic receptors, lessening their cardiac effects. Potential adverse effects include nervousness, tremors, hypotension, and tachycardia. Clinical use of bronchodilators delivered by MDI, such as albuterol and ipratropium (a parasympatholytic), has not been investigated for dogs with chronic bronchitis.

Glucocorticoids are generally the most effective treatment for controlling the signs of chronic bronchitis and may slow the development of permanent airway damage by decreasing inflammation. They may be particularly helpful in dogs with eosinophilic airway inflammation. Potential negative effects include increased susceptibility to infection in dogs already impaired by decreased airway clearance; a tendency toward obesity, hepatomegaly, and muscle weakness that may adversely affect ventilation; and pulmonary thromboembolism. Therefore short-acting products are used, the dose is tapered to the lowest effective one, and the drug is discontinued if no beneficial effect is seen.

Prednisone is initially given at a dose of 0.5 to 1 mg/kg orally q12h, with a positive response expected within 1 week. The initial dosage is continued until the cough has resolved or its intensity and frequency have reached a plateau. The subsequent taper should be slow, until the least effective dose is reached (ideally 0.5 mg/kg orally q48h or less of prednisone). Dogs with highly motivated owners, and dogs that



BOX 21.4

Common Bronchodilators for Use in Cats and Dogs

Methylxanthines

Aminophylline
- Cat: 5 mg/kg PO q12h
- Dog: 11 mg/kg PO q8h

Theophylline base (immediate release)
- Cat: 4 mg/kg PO q12h
- Dog: 9 mg/kg PO q8h

Sympathomimetics

Terbutaline
- Cat: ⅛–¼ of 2.5 mg tablet/cat PO q12h; or 0.01 mg/kg SC; can repeat once
- Dog: 1.25-5 mg/dog PO q8-12h

Albuterol
- Cat and dog: 20-50 µg/kg PO q8-12h (0.02-0.05 mg/kg), beginning with lower dose

PO, By mouth; *SC*, subcutaneously.

require relatively high dosages of prednisone, have unacceptable adverse effects, or have conditions for which glucocorticoids are relatively contraindicated (e.g., diabetes mellitus) may benefit from local treatment with metered dose inhalers (MDIs). This route of administration is discussed in greater detail later in this chapter, in the section on feline bronchitis.

Cough suppressants are used cautiously because cough is an important mechanism for clearing airway secretions. In some dogs, however, the cough is incessant and exhausting, or ineffective, because of marked tracheobronchomalacia. Cough suppressants can provide significant relief for such animals and may even facilitate ventilation and decrease anxiety. Although the doses given in Table 21.1 are the ones that provide prolonged effectiveness, less frequent administration (i.e., only during times of the day when coughing is most severe) may preserve some beneficial effect of cough. For dogs with severe cough, hydrocodone may provide the greatest relief.

Maropitant may be considered as a cough suppressant in dogs that cannot tolerate even low dosages of narcotic antitussives. Although there was no benefit in reducing airway inflammation, Grobman and Reinero (2016) reported a decrease in cough as described by owners of dogs with bronchitis. Maximal effect may not be seen before 1 to 2 weeks of treatment.

MANAGEMENT OF COMPLICATIONS

Antibiotics are often prescribed for dogs with chronic bronchitis. If possible, confirmation of infection and antibiotic sensitivity information should be obtained by culture of an airway specimen (e.g., tracheal wash fluid). Because cough in dogs with chronic bronchitis often waxes and wanes in severity, it is difficult to make a diagnosis of infection on the basis of the patient's response to therapy. Furthermore, organisms involved in bronchial infections generally originate from the oropharynx. They are frequently gram-negative with unpredictable antibiotic sensitivity patterns. The role of *Mycoplasma* organisms in canine chronic bronchitis is not well understood. They may be an incidental finding, or they may be pathogenic. Ideally, antibiotic selection is based on results of culture. Antibiotics that are generally effective against *Mycoplasma* include doxycycline, azithromycin, chloramphenicol, and fluoroquinolones.

In addition to the susceptibility of identified organisms, the ability of candidate antibiotics to penetrate the airway secretions to the site of infection should be considered when selecting an antibiotic. Antibiotics that are likely to reach concentrations effective against susceptible organisms include fluoroquinolones, azithromycin, chloramphenicol, and possibly amoxicillin with clavulanate. β-Lactam antibiotics do not generally reach therapeutic concentrations in airway secretions of healthy (not inflamed) subjects. If used for bronchial infection, the high end of the dosage range should be used.

Doxycycline is often recommended because *Mycoplasma* and many *Bordetella* isolates are susceptible to this drug. It may confer an additional benefit of mild antiinflammatory properties. The ability of doxycycline to reach therapeutic concentration within the airways is questionable because in the dog it is highly protein bound, but the presence of inflammatory cells may increase locally available concentrations of the drug. It is preferable to reserve fluoroquinolones for cases of serious infection.

If an antibiotic is effective, a positive response is generally seen within 1 week. Treatment is then continued for at least 1 week beyond the time when the clinical signs stabilize because complete resolution is unlikely in these animals. Antibiotic treatment usually is necessary for 3 to 4 weeks. Even longer treatment may be necessary in some cases, particularly if bronchiectasis or overt pneumonia is present. The use of antibiotics for the treatment of respiratory tract infection is also discussed in the section on CIRDC in this chapter and in the section on bacterial pneumonia in Chapter 22.

Tracheobronchomalacia is discussed later in this chapter, and pulmonary hypertension is discussed in Chapter 22.

Prognosis

Canine chronic bronchitis cannot be completely cured. The prognosis for the control of signs and for a satisfactory quality of life in animals is good if owners are conscientious about performing the medical management aspects of care and are willing to adjust treatment over time and treat secondary problems as they occur.

FELINE BRONCHITIS (IDIOPATHIC)

Etiology

Cats with respiratory disease of many origins present with signs of bronchitis or asthma. Cat airways are much more reactive and prone to bronchoconstriction than those of dogs. The common presenting signs of bronchitis (i.e., cough, wheezing, and/or respiratory distress) can occur in cats with diseases as varied as lung parasites, heartworm disease, allergic bronchitis, bacterial or viral bronchitis, toxoplasmosis, idiopathic pulmonary fibrosis, carcinoma, and aspiration pneumonia (Table 21.2). Veterinarians often assume that cats with presenting signs of bronchitis or asthma have idiopathic disease because in most cats an underlying cause cannot be found. However, as with canine chronic bronchitis, a diagnosis of idiopathic feline bronchitis can be made only by ruling out other active disease. **Care should be taken when using the terms *feline bronchitis* or *feline asthma* to distinguish between a presentation consistent with bronchitis in a broad sense and a clinical diagnosis of idiopathic disease.** Cats with idiopathic bronchitis often have some degree of airway eosinophilia, typical of an allergic reaction. This author prefers to reserve the diagnosis of allergic bronchitis for patients who respond dramatically to the elimination of a suspected allergen (see the section on allergic bronchitis later in this chapter).

A wide variety of pathologic processes can affect individual cats with idiopathic bronchitis. Clinically, the range in

TABLE 21.2

Differential Diagnoses (Etiologic) for Cats With Presenting Signs of Bronchitis

DIAGNOSIS	DISTINGUISHING FEATURES COMPARED WITH IDIOPATHIC FELINE BRONCHITIS
Allergic bronchitis	Dramatic clinical response to elimination of suspected allergen(s) from environment or diet.
Pulmonary parasites *(Aelurostrongylus abstrusus, Capillaria aerophila, Paragonimus kellicotti)*	Thoracic radiographs may have a nodular pattern; larvae *(Aelurostrongylus)* or eggs identified in tracheal wash or BAL fluid or in the feces. See Chapter 20 for appropriate procedures for fecal testing.
Heartworm disease	Pulmonary artery enlargement may be present on thoracic radiographs; positive heartworm antigen test or identification of adult worm(s) on echocardiography (see Chapter 10).
Bacterial bronchitis	Intracellular bacteria in tracheal wash or BAL fluid and significant growth on culture (see Chapter 20).
Mycoplasmal bronchitis	Positive PCR test or growth of *Mycoplasma* on specific culture of tracheal wash or BAL fluid (presence may indicate primary infection or secondary infection, or may be incidental).
Idiopathic pulmonary fibrosis	Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis. CT findings may be supportive. Diagnosis requires lung biopsy (see Chapter 22).
Carcinoma	Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis. Cytologic or histologic identification of malignant cells in tracheal wash or BAL fluid, lung aspirates, or lung biopsy. CT findings may be supportive. Histologic confirmation is ideal.
Toxoplasmosis	Systemic signs usually present (fever, anorexia, depression). Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis, possibly with a nodular pattern. Diagnosis is confirmed by identification of organisms (tachyzoites) in tracheal wash or BAL fluid. Rising serum antibody titers or elevated IgM concentrations are supportive of the diagnosis (see Chapter 98).
Aspiration pneumonia	Unusual in cats. History supportive of a predisposing event or condition. Radiographs typically show an alveolar pattern, worse in the dependent (cranial and middle) lung lobes. Neutrophilic inflammation, usually with bacteria, in tracheal wash fluid.
Idiopathic feline bronchitis	Elimination of other diseases from the differential diagnoses.

BAL, Bronchoalveolar lavage; *CT,* computed tomography; *PCR,* polymerase chain reaction.

severity of signs and responses to therapy shows this diversity. Different combinations of factors that result in small airway obstruction—a consistent feature of feline bronchial disease—are present in each animal (Box 21.5). Some of these factors (e.g., bronchospasm, inflammation) are reversible, and others (e.g., fibrosis, emphysema) are permanent. The classification proposed by Moise et al. (1989), which was formulated on the basis of similar pathologic processes that occur in people, is recommended as a way to better define bronchial disease in individual cats for the purpose of treatment recommendations and prognostication (Box 21.6). A cat can have more than one type of bronchitis. Although it is not always possible to absolutely determine the type or types of bronchial disease present without performing sophisticated pulmonary function testing, routine clinical data (i.e., history and physical examination findings, thoracic radiographs, analysis of airway specimens,

BOX 21.5

Factors That Can Contribute to Small Airway Obstruction in Cats With Bronchial Disease

Bronchoconstriction
Bronchial smooth muscle hypertrophy
Increased mucus production
Decreased mucus clearance
Inflammatory exudate in airway lumens
Inflammatory infiltrate in airway walls
Epithelial hyperplasia
Glandular hypertrophy
Fibrosis
Emphysema

BOX 21.6

Classification of Feline Bronchial Disease

Bronchial Asthma

Predominant feature: reversible airway obstruction primarily resulting from bronchoconstriction
Other common features: hypertrophy of smooth muscle, increased mucus production, eosinophilic inflammation

Acute Bronchitis

Predominant feature: reversible airway inflammation of short duration (<1-3 months)
Other common features: increased mucus production, neutrophilic or macrophagic inflammation

Chronic Bronchitis

Predominant feature: chronic airway inflammation (>2-3 months) resulting in irreversible damage (e.g., fibrosis)
Other common features: increased mucus production; neutrophilic, eosinophilic, or mixed inflammation; isolation of bacteria or *Mycoplasma* organisms causing infection or as nonpathogenic inhabitants; concurrent bronchial asthma

Emphysema

Predominant feature: destruction of bronchiolar and alveolar walls resulting in enlarged peripheral air spaces
Other common features: cavitary lesions (bullae); result of or concurrent with chronic bronchitis

Adapted from Moise NS et al.: Bronchopulmonary disease. In Sherding RG, ed.: *The cat: diseases and clinical management,* New York, 1989, Churchill Livingstone.

progression of signs) can be used to classify the disease in most cats.

Clinical Features

Idiopathic bronchitis can develop in cats of any age, although it most commonly develops in young adult and middle-aged animals. The major clinical feature is cough or episodic respiratory distress or both. Some clients will confuse cough in cats with attempts to vomit a hairball. Cats that never produce a hairball are likely coughing. Owners may report audible wheezing during an episode. The signs are often slowly progressive. Weight loss, anorexia, depression, and other systemic signs are not present. If systemic signs are identified, another diagnosis should be aggressively pursued.

Owners should be carefully questioned regarding an association with exposure to potential allergens or irritants. Irritants in the environment can cause worsening of signs of bronchitis regardless of the underlying cause. Environmental considerations include exposure to new litter (usually perfumed), cigarette or fireplace smoke, carpet cleaners, and household items containing perfumes such as deodorant or hair spray. Clients should also be questioned about whether there has been any recent remodeling or any other change in the cat's environment. Seasonal exacerbations are suggestive of potential allergen exposure.

Physical examination abnormalities result from small airway obstruction. Cats that are in distress show tachypnea. Typically the increased respiratory efforts are more pronounced during expiration, and auscultation reveals expiratory wheezes. Crackles are occasionally present. In some patients in distress, hyperinflation of the lungs due to air trapping may result in increased inspiratory efforts and decreased lung sounds. Physical examination findings may be unremarkable between episodes.

Diagnosis

The diagnosis of idiopathic feline bronchitis is made on the basis of typical historical, physical examination, and thoracic radiographic findings and the elimination of other possible differential diagnoses (see Table 21.2). A thorough search for other diagnoses is highly recommended, even though a specific diagnosis is not commonly found, because identifying a cause for the clinical signs may enable specific treatment and even cure of an individual cat. Factors to consider when developing a diagnostic plan include the clinical condition of the cat and the client's tolerance for expense and risk. Cats that are in respiratory distress or are otherwise in critical condition should not undergo any stressful testing until their condition has stabilized. Sufficiently stable cats that have any indication of a diagnosis other than idiopathic disease on the basis of presenting signs and thoracic radiographs or any subsequent test results require a thorough evaluation. Certain tests are completely safe, such as fecal testing for pulmonary parasites, and their inclusion in the diagnostic plan is based largely on financial considerations. In most cats with signs of bronchitis, collection of tracheal wash fluid for cytology and culture and tests for pulmonary parasitism and heartworm disease are recommended.

A CBC is often performed as a routine screening test. Cats with idiopathic bronchitis are often thought to have peripheral eosinophilia. However, this finding is neither specific nor sensitive and cannot be used to rule out or definitively diagnose feline bronchitis.

The presence of a bronchial pattern on thoracic radiographs is supportive of a diagnosis of bronchitis (see Fig. 20.3). Increased reticular interstitial markings and patchy alveolar opacities may also be present. The lungs may be seen to be overinflated as a result of trapping of air, and occasionally collapse (i.e., atelectasis) of the right middle lung lobe is seen (see Fig. 20.9). However, radiographs are insensitive for the detection of bronchial disease and may be normal in cats with bronchitis. Radiographs are also scrutinized for signs of specific diseases (see Table 21.2).

Tracheal wash or BAL fluid cytologic findings are generally representative of airway inflammation and consist of increased numbers of inflammatory cells and an increased amount of mucus. Inflammation can be eosinophilic, neutrophilic, or mixed. Although not a specific finding, eosinophilic inflammation is suggestive of a hypersensitivity response to allergens or parasites. Neutrophils should

be examined for signs of degeneration, suggestive of bacterial infection. Slides should be carefully scrutinized for the presence of organisms, particularly bacteria and parasitic larvae or ova. Fluid should be cultured for bacteria, although it is important to note that the growth of organisms may or may not indicate the existence of true infection (see Chapter 20). Cultures or PCR for *Mycoplasma* spp. may also prove helpful.

Testing for heartworm disease is described in Chapter 10. Multiple fecal examinations using special concentrating techniques are performed to identify pulmonary parasites, particularly in young cats and cats with airway eosinophilia (see Chapter 20). Other tests may be indicated for individual cats.

Treatment

EMERGENCY STABILIZATION

The condition of cats in acute respiratory distress should be stabilized before diagnostic tests are performed. Successful treatment includes administration of a bronchodilator, rapid-acting glucocorticoids, and oxygen supplementation. Terbutaline can be administered subcutaneously—a route that avoids additional patient stress (see Box 21.4). Dexamethasone sodium phosphate (0.1 to 0.5 mg/kg) is administered intravenously. If intravenous administration is too stressful, it can be given subcutaneously or intramuscularly. After the drugs are administered, the cat is placed in a cool, stress-free, oxygen-enriched environment. If additional bronchodilation is desired, albuterol can be administered by nebulization or MDI. Administration of drugs by MDI is described later in this section. (See Chapter 25 for further discussion of cats with respiratory distress.)

ENVIRONMENT

The potential influence of the environment on clinical signs should be investigated. Allergic bronchitis is diagnosed through the elimination of potential allergens from the environment (see the section on allergic bronchitis). However, even cats with idiopathic bronchitis can benefit from improvement in indoor air quality through the reduction of irritants or unidentified allergens. Potential sources of allergens or irritants are determined through careful owner questioning as described in the section on clinical features. Smoke can often aggravate signs through its local irritating effects. The effect of litter perfumes can be evaluated by replacing the litter with sandbox sand or plain clay litter. Indoor cats may show improvement in response to measures taken to decrease the level of dusts, molds, and mildew in the home. Such measures include carpet, furniture, and drapery cleaning; cleaning of the furnace and frequent replacement of air filters; and the use of an air cleaner. The American Lung Association has a useful Web site with nonproprietary recommendations for improving indoor air quality (www.lung.org). Any beneficial response to an environmental change is usually seen within 1 to 2 weeks.

GLUCOCORTICOIDS

Therapy with glucocorticoids, with or without bronchodilators, is necessary for most cats with idiopathic bronchitis. Results can be dramatic. However, drug therapy can interfere with environmental testing; therefore the ability of the animal to tolerate a delay in the start of drug therapy must be assessed on an animal-by-animal basis. Glucocorticoids can relieve the clinical signs in most cats and may protect the airways from the detrimental effects of chronic inflammation. Short-acting products such as prednisolone are recommended because the dose can be tapered to the lowest effective amount. A dose of 0.5 to 1 mg/kg is administered orally q12h initially, with the dose doubled if signs are not controlled within 1 week. Once the signs are well controlled, the dose is tapered. A reasonable goal is to administer 0.5 mg/kg or less every other day. Although not ideal, outdoor cats that cannot be treated frequently can be administered depot steroid products, such as methylprednisolone acetate (10 mg/cat intramuscularly may be effective for up to 4 weeks).

Glucocorticoids, such as fluticasone propionate (Flovent, GSK), can also be administered locally to the airways by MDI, as is routine for treating asthma in people. Advantages include minimal systemic side effects and relative ease of administration in some cats compared with pilling. Theoretical concerns about the oronasal deposition of the potent glucocorticoid in cats, compared with people, include the high incidence of periodontal disease and latent herpesvirus infections and the inability to effectively rinse the mouth with water after use. Local dermatitis can be caused by mites, dermatophytes, or bacteria. However, veterinarians have been using glucocorticoid MDIs to treat idiopathic feline bronchitis for many years without frequent, obvious adverse effects.

This author prefers to obtain a clinical remission of signs using an orally administered drug first, except in cats with relative contraindications for systemic glucocorticoid therapy, such as diabetes mellitus. Cats that require a relatively low dose of oral glucocorticoids to control clinical signs, that have no noticeable adverse effects, and that can be pilled without difficulty are often well maintained with oral therapy. Otherwise, once signs are in remission, treatment by MDI is initiated and the dosage of oral prednisolone gradually reduced.

A spacer must be used for effective administration of drugs by MDI to cats or dogs, and the airflow generated by the cat must be sufficient to activate the spacer valve. Spacers with masks specifically designed for use in cats or dogs are available (AeroKat and AeroDawg, Trudell Medical International, London, Ontario, Canada). This design includes a plastic tab that moves with each breath, making it easier for the client to determine whether the cat is inhaling the drug. The cat is allowed to rest comfortably on a table or in the client's lap. The client places his or her arms on either side of the cat or gently steadies the cat's neck and head to provide restraint (Fig. 21.4). The MDI, attached to the spacer, is actuated (i.e., pressed) twice. The mask is placed immediately on



FIG 21.4
Administering drugs by metered dose inhaler (MDI) to a cat. The mask and chamber apparatus is the Aerokat (Trudell Medical International, London, Ontario, Canada).

the cat's face, with the mouth and nose covered completely, and is held in place while the cat takes 7 to 10 breaths, inhaling the drug into its airways. Excellent videotaped examples of clients treating their cats are readily available by web search.

The following treatment schedule has been recommended (Padrid, 2000): cats with mild daily symptoms should receive 220 µg of fluticasone propionate by MDI twice daily and albuterol by MDI as needed. The maximal effect of fluticasone is not expected until after 7 to 10 days of treatment. Cats with moderate daily symptoms should receive treatments with MDI as described for mild symptoms; in addition, prednisolone is administered orally for 10 days (1 mg/kg q12h for 5 days, then q24h for 5 days). For cats with severe symptoms, dexamethasone is administered once (0.5-1 mg/kg, intravenously), albuterol is administered by MDI every 30 minutes for up to 4 hours, and oxygen is administered. Once stabilized, these cats are prescribed 220 µg of fluticasone propionate by MDI every 12 hours and albuterol by MDI every 6 hours as needed. Oral prednisolone is administered as needed.

Studies using cats with experimentally induced allergic bronchitis have demonstrated beneficial effects with a lower dosage of 44 µg/puff (Cohn et al., 2010). This form of bronchitis may be less complicated than that seen in clinical patients, so I prefer to begin treatment with higher concentrations and then taper to the least effective dose. Fluticasone is also available at 110 µg/puff, which is a reasonable compromise for clinically stable cats.

Disturbing findings were reported from a study by Cocayne et al. (2011), indicating that 7 of 10 cats with naturally occurring bronchitis that had resolution of clinical signs during treatment with oral prednisolone had detectable airway inflammation based on BAL cytology. The long-term clinical significance of the persistent inflammation is not yet known, but this matter deserves further study.

BRONCHODILATORS

Cats that require relatively large quantities of glucocorticoids to control clinical signs, that react unfavorably to glucocorticoid therapy, or that suffer from periodic exacerbations of signs can benefit from bronchodilator therapy. Recommended doses of these drugs are listed in Box 21.4.

This author prefers to use theophylline because it is inexpensive and often is effective with once-daily administration; moreover, the plasma concentrations can be easily measured for monitoring of difficult cases. Additional properties of theophylline, potential drug interactions, and adverse effects are described in the previous section on canine chronic bronchitis.

The pharmacokinetics of theophylline products are different in cats than in dogs, resulting in different dosages (see Box 21.4). Variability in sustained plasma concentrations in both species has been found for different manufacturers of theophylline products, and long-acting products are not currently available. If beneficial effects are not seen, if the patient is predisposed to adverse effects, or if adverse effects occur, plasma theophylline concentrations should be measured. Therapeutic peak concentrations, based on data from human subjects, are 10 to 20 µg/mL. Plasma for determination of these concentrations should be collected immediately before the next scheduled dose.

Sympathomimetic drugs can also be effective bronchodilators. Terbutaline is selective for β2-adrenergic receptors, lessening its cardiac effects. Potential adverse effects include nervousness, tremors, hypotension, and tachycardia. It can be administered subcutaneously for the treatment of respiratory emergencies; it can also be administered orally. Note that the recommended oral dose for cats (one eighth to one fourth of a 2.5-mg tablet; see Box 21.4) is lower than the commonly cited dose of 1.25 mg/cat. The subcutaneous dose is lower still: 0.01 mg/kg, repeated once in 5 to 10 minutes if necessary.

Bronchodilators can be administered to cats by MDI for the immediate treatment of acute respiratory distress (asthma attack). Cats with idiopathic bronchitis are routinely prescribed an albuterol MDI, a spacer, and a mask (see the section on glucocorticoids for details) to be kept at home for emergencies.

OTHER POTENTIAL TREATMENTS

A therapeutic trial with an antibiotic effective against *Mycoplasma* is considered because of the difficulty in documenting infection with this organism. Doxycycline (5 mg/kg orally q12h or 10 mg/kg q24h) is administered for 14 days as a therapeutic trial. For cats that are difficult to medicate, azithromycin (5-10 mg/kg orally q12h for 1 day, then every 3 days) can be tried. If a *Mycoplasma* is isolated from airway specimens or if a therapeutic response is seen, prolonged treatment for months may be required to eliminate infection. Further study is needed. Remember that administration of doxycycline should always be followed by a bolus of water to minimize the incidence of esophageal stricture. In addition to antibacterial effects, evidence is

mounting that in people these drugs have antiinflammatory properties.

Much interest has been shown by clients and veterinarians in the use of oral leukotriene inhibitors in cats (e.g., Accolate, Singulair, Zyflo). However, the clinician should be aware that in people, leukotriene inhibitors are *less* effective than glucocorticoids in the management of asthma. Their main advantages for people lie in decreased side effects, compared with glucocorticoids, and ease of administration. To date, toxicity studies have not been performed on these drugs in cats. Furthermore, several preliminary studies suggest that leukotriene inhibition in cats would not be expected to have efficacy comparable with that in people. Therefore routine use of leukotriene inhibitors in cats is not currently advocated.

FAILURE TO RESPOND

The clinician should ask himself or herself the questions listed in Box 21.7 if cats fail to respond to glucocorticoid and bronchodilator therapy, or if exacerbation of signs occurs during long-term treatment.

Prognosis

The prognosis for the control of clinical signs of idiopathic feline bronchitis is good for most cats, particularly if extensive permanent damage has not yet occurred. Complete cure is unlikely, and most cats require continued medication. Cats that have severe, acute asthmatic attacks are at risk for sudden death. Cats with persistent, untreated airway inflammation can develop the permanent changes of chronic bronchitis and emphysema.



BOX 21.7

Considerations for Cats With Bronchitis That Fail to Respond to Glucocorticoid and Bronchodilator Therapy

Is the Cat Receiving Prescribed Medication?

Measure plasma theophylline concentrations.
Initiate trial therapy with repositol glucocorticoids.

Was an Underlying Disease Missed on Initial Evaluation?

Repeat diagnostic evaluation, including complete history for potential allergens, thoracic radiographs, tracheal wash fluid analysis, heartworm tests, and fecal examinations for parasites. In addition, perform complete blood count, serum biochemical analysis, and urinalysis.
Initiate trial therapy with anti-*Mycoplasma* drug.
Initiate trial environmental manipulations to minimize potential allergen and irritant exposure.

Has a Complicating Disease Developed?

Repeat diagnostic evaluation as described in the preceding sections.

TRACHEOBRONCHOMALACIA (COLLAPSING TRACHEA)

Etiology

The normal trachea is seen to be circular on cross section (see Figs. 21.7, *B*, and 20.27, *A*). An open lumen is maintained during all phases of quiet respiration by the cartilaginous tracheal rings, which are connected by fibroelastic annular ligaments to maintain flexibility, thereby allowing movement of the neck without compromising the airway. The cartilaginous rings are incomplete dorsally. The dorsal tracheal membrane, consisting of the longitudinal tracheal muscle and connective tissue, completes the rings. The term *tracheal collapse* refers to narrowing of the tracheal lumen resulting from weakening of the cartilaginous rings, redundancy of the dorsal tracheal membrane, or both.

This common description of tracheal collapse represents an oversimplification of the disease, which has several clinical pictures. Collapse can be the result of a congenital abnormality of small-breed dogs. In many dogs, a congenital predisposition is exacerbated by subsequent inflammatory disease or other exacerbating factors. Collapse can also occur in dogs of breeds *not* known to be congenitally predisposed, as a consequence of chronic airway inflammation. Further, the bronchi can be involved along with the trachea or alone, as the bronchial lumen is normally supported by rafts of cartilage within its walls. In human medicine the term *tracheobronchomalacia* (TBM) is used, and TBM is classified further as primary (congenital) or secondary (acquired). This terminology more accurately describes the range of disease observed in dogs and should be adopted by the veterinary profession.

That TBM can have a congenital basis in dogs is supported by its high prevalence in small-breed dogs. Also, several studies have demonstrated ultrastructural differences in the tracheal cartilage of toy breed dogs with collapsed tracheas, compared with those with normal tracheas. Signs may not develop until later in life in many of these dogs. Presumably, the onset of signs is initiated by an "acute on chronic" event. An exacerbating problem develops in an affected dog, which results in increased respiratory efforts, airway inflammation, and/or cough. Exacerbating problems could include upper airway obstruction, canine infectious respiratory disease complex (CIRDC), heart enlargement or failure, or parasitic disease, perhaps with contributions from obesity, exposure to tobacco smoke, or poor oral health. Changes in intrathoracic pressures and airway pressures during increased respiratory efforts or cough contribute to narrowing of the trachea and stretching of the dorsal ligament. With severe collapse, fluttering or physical trauma to the mucosa may further stimulate cough. Inflammation also contributes to an ongoing cycle of cough and collapse. Collagenases and proteases released by inflammatory cells may weaken the structure of the airways. Damage to the tracheal epithelium and changes in mucus composition and secretion impair airway clearance. Previously tolerable irritants and organisms may perpetuate inflammation and cough.

If the described exacerbating factors are sufficiently severe or chronic, even dogs without congenitally weak cartilages may develop TBM. Of course it is possible that these dogs, too, have congenital cartilage abnormalities, imbalances in their proinflammatory and antiinflammatory mediators, or other predisposing factors that as yet are not understood.

The clinical consequences of TBM include chronic, progressive cough that can ultimately lead to large airway obstruction. In some cases the signs of extrathoracic large airway obstruction predominate in the absence of cough. Most of these dogs develop increased inspiratory efforts with activity or stress, inspiratory stertor, and, eventually, episodes of hypoxemia. Because the chronic progressive cough of TBM is similar to that of chronic airway inflammation (e.g., idiopathic chronic bronchitis, eosinophilic bronchopneumopathy, bacterial bronchitis, parasitic disease), and because TBM can be a consequence of (or coincidental with) these conditions, a thorough and careful diagnostic evaluation is essential.

The prevalence of TBM in dogs is not known. Studies often originate from referral institutions and may overrepresent dogs with poorly responsive signs. In a report of bronchoscopies performed on 58 dogs, half had some form of airway collapse (Johnson et al., 2010). Bronchial collapse was reported in 35 of 40 (87.5%) brachycephalic dogs undergoing bronchoscopy (Delorenzi et al., 2009). We reported findings from 115 dogs with chronic cough, of which 59 (51%) had tracheobronchomalacia (Hawkins et al., 2010). In addition, 31 of 32 (97%) toy-breed dogs had TBM among their diagnoses.

Tracheal collapse is rare in cats and most often occurs secondary to a tracheal obstruction, such as from a tumor, foreign body, or traumatic injury.

Clinical Features

Tracheobronchomalacia can be primary or secondary and can affect the trachea and/or bronchi. More important, from a clinical perspective, is that collapse may occur predominantly in either the extrathoracic (cervical trachea and/or thoracic inlet) or intrathoracic (intrathoracic trachea and/or bronchial) airways. Dogs with predominantly extrathoracic tracheal collapse can present with signs of upper airway obstruction, including respiratory distress most pronounced on inspiration and audible stertorous sounds. If respiratory distress occurs in dogs with intrathoracic airway collapse, it tends to be more pronounced on expiration and is usually associated with an audible, loud wheeze/cough (Video 21.2).

It is possible that a relationship exists whereby extrathoracic airway collapse is more often associated with primary (congenital) TBM, and intrathoracic airway collapse is more often associated with secondary (occurring in a predisposed or nonpredisposed breed) TBM. This conjecture is partially supported by a study of tidal breathing flow-volume loops in toy and small-breed dogs with tracheal collapse and no evidence of other respiratory disease, in which abnormalities were seen predominantly in the inspiratory limb (Pardali et al., 2010). In a study of 18 dogs with bronchomalacia, but no tracheal collapse, inflammation was identified on BAL and bronchial biopsy, and the presenting cough was described as mild and wheezing (Adamama-Moraitou et al., 2012).

Overall, although any signalment is possible, TBM occurs most commonly in middle-aged toy and miniature dogs. Signs may occur acutely but then may slowly progress over months to years. The primary clinical feature in most dogs is a nonproductive cough, described as a "goose honk." The cough is worse during excitement or exercise, or when the collar exerts pressure on the neck. Eventually (usually after years of chronic cough), respiratory distress caused by obstruction to airflow may be brought on by excitement, exercise, or overheating. Systemic signs such as weight loss, anorexia, and depression are not expected.

As discussed, some dogs are presented primarily for signs of upper airway obstruction without cough, also exacerbated during excitement, exercise, or hot weather. Stertorous sounds may be heard during periods of increased respiratory efforts.

Tracheal collapse in cats is rare and usually secondary to another obstructive disease. Careful questioning regarding possible trauma and exposure to foreign bodies is indicated.

On physical examination a cough can usually be elicited by palpation of the trachea, particularly in those dogs presented with cough as the predominant sign. An end-expiratory snap or click may be heard during auscultation as a result of complete intrathoracic collapse. Patients with exercise intolerance or respiratory distress will demonstrate increased inspiratory efforts and stertorous sounds from collapse of the extrathoracic trachea, and an audible expiratory wheeze/cough from collapse of the intrathoracic trachea. It may be helpful to exercise dogs whose signs are moderate or intermittent to identify characteristic breathing patterns or sounds.

History and physical examination should also emphasize a search for exacerbating or complicating disease. The frequent association with canine chronic bronchitis has been mentioned. Other possibilities include cardiac disease causing left atrial enlargement from mitral valve dysplasia or pulmonary edema; airway inflammation caused by bacterial infection, allergic bronchitis, exposure to smoke (e.g., from cigarettes or fireplaces), or recent intubation; upper airway obstruction caused by elongated soft palate, stenotic nares, or laryngeal paralysis or collapse; and systemic disorders such as obesity or hyperadrenocorticism.

Diagnosis

Tracheobronchomalacia is most often diagnosed on the basis of clinical signs in conjunction with findings from cervical and thoracic radiography. Radiographs of the neck to evaluate the size of the lumen of the extrathoracic trachea are taken during inspiration (Fig. 21.5), when narrowing caused by tracheal collapse is more evident because of negative airway pressure. Conversely, the size of the lumen of the intrathoracic trachea is evaluated on thoracic radiographs taken during expiration, when increased intrathoracic pressures make collapse more apparent (Fig. 21.6). Radiographs

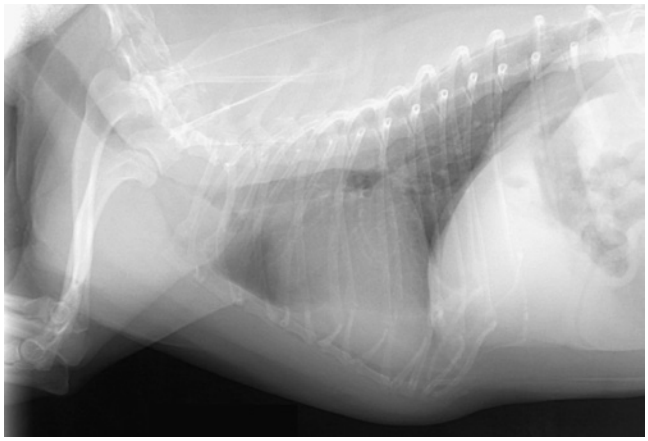


FIG 21.5
Lateral radiograph of the thorax and neck of a dog with collapsing trachea taken during inspiration. The extrathoracic airway stripe is severely narrowed cranial to the thoracic inlet.

of the thorax should also be taken during inspiration to detect concurrent bronchial or parenchymal abnormalities. (See Chapter 20 for further discussion of radiography.) It should be noted that the common radiographic finding of a redundant dorsal tracheal membrane can be a result of overlying soft tissue (most likely esophagus) rather than from TBM (Bylicki et al., 2015).

Fluoroscopic evaluation provides a "motion picture" view of large airway dynamics, making changes in luminal diameter easier to identify than by routine radiography. The sensitivity of fluoroscopy in detecting airway collapse is enhanced if the patient can be induced to cough during the evaluation by pressure applied to the trachea. Some degree of collapse is probably normal during cough, and in people a diagnosis of tracheobronchomalacia is generally made if luminal diameter decreases by more than 70% during forced exhalation. This criterion was recently increased from 50% because studies in people have shown that a strong cough can result in near total collapse in some apparently healthy individuals.

Bronchoscopy is also useful in the diagnosis of airway collapse (Fig. 21.7; see also Fig. 21.3). The bronchi of smaller dogs may be difficult to evaluate by radiography or fluoroscopy but are easily examined bronchoscopically. Bronchoscopy and the collection of airway specimens (such as by BAL and bronchial brushings) are useful for identifying exacerbating or concurrent conditions.

Bronchoscopy is performed with the patient under general anesthesia, which interferes with the ability to induce cough. However, allowing the patient to reach a light plane of anesthesia while the airways are manipulated will often cause more forceful respirations that increase the likelihood of identifying airway collapse.

Additional tests are performed to identify exacerbating or concurrent conditions. Tracheal wash fluid is analyzed by cytology and culture if bronchoscopy with specimen collection is not done. Other considerations include upper airway

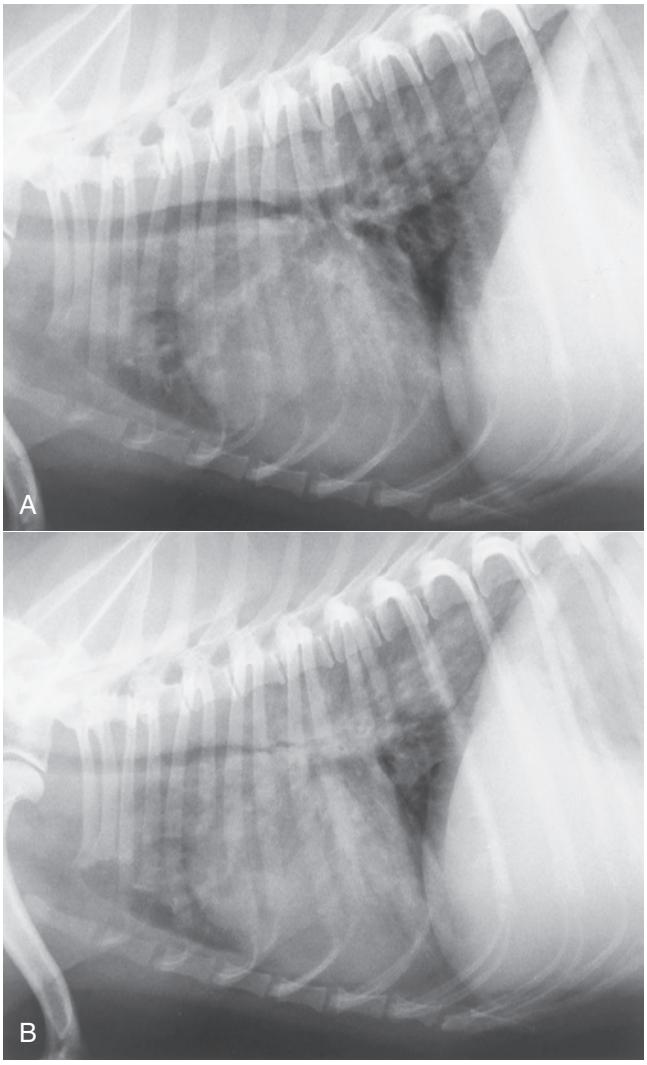


FIG 21.6
Lateral radiographs of a dog with tracheobronchomalacia. During inspiration **(A)** the trachea and mainstem bronchi are nearly normal. During expiration **(B)** the intrathoracic trachea and mainstem bronchi are markedly narrowed. Evaluation of the pulmonary parenchyma should not be attempted using films exposed during expiration.

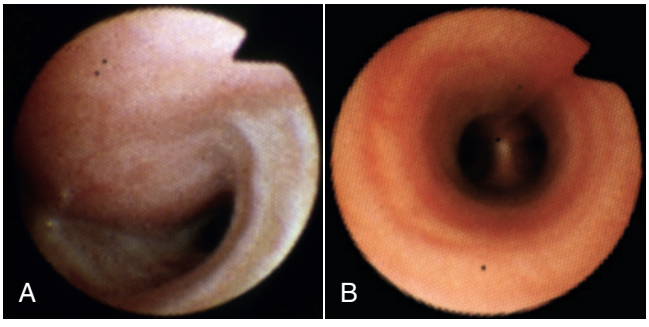


FIG 21.7
Bronchoscopic images from a dog with tracheal collapse **(A).** The dorsal tracheal membrane is much wider than that of a normal dog **(B).** The airway lumen is greatly compromised.

examination, cardiac evaluation, and screening for systemic disease.

Treatment

Medical therapy is adequate treatment for most animals. In a study of 100 dogs by White et al. (1994), medical therapy resulted in resolution of signs for at least 1 year in 71% of cases. Dogs that are overweight are placed on a weight-reducing diet. Harnesses should be used instead of collars, and owners should be counseled to keep their dogs from becoming overheated (e.g., they should not be left in a car). Excessive excitement should be avoided. Sedatives such as phenobarbital are prescribed for some animals for short-term use, and these can be administered before known stressful events. In some patients, anxiolytic drugs such as trazadone may be beneficial for prolonged management.

Cough suppressants are used to control signs and to disrupt the potential cycle of perpetuating cough (see Table 21.1). The dose and frequency of administration of cough suppressants are adjusted as needed. Initially, high, frequent dosing may be needed to break the cycle of coughing. Subsequently, it is often possible to decrease the frequency of administration and the dose. For refractory cases, the addition of maropitant or gabapentin is an option. The cough suppressant effect of maropitant may not be apparent for 1-2 weeks (Grobman and Reinero, 2016). Gabapentin has been used to aid in the control refractory chronic cough in people through mechanisms similar to interfering with neuropathic pain (Ryan, 2015).

Antiinflammatory doses of *glucocorticoids* can be given for a short period during exacerbation of signs (prednisone, 0.5-1 mg/kg orally q12h until signs have subsided, then tapered and discontinued over 3-4 weeks). Long-term use is ideally avoided to prevent potential detrimental side effects such as obesity but is often necessary to control signs, particularly in patients with chronic bronchitis. Inhaled corticosteroids can be tried if a positive therapeutic response is seen to minimize systemic side effects.

Bronchodilators may be beneficial in dogs with concurrent chronic bronchitis. Beneficial effects are likely attributable to antiinflammatory effects, enhancement of steroid activity, or improved mucociliary clearance rather than from bronchodilation. The use of glucocorticoids and bronchodilators for treatment of inflammatory airway disease is discussed in more detail in the sections on canine chronic bronchitis and feline bronchitis.

Dogs with signs referable to mitral insufficiency are managed for this disease (see Chapter 6). Dogs with abnormalities causing upper airway obstruction are treated with corrective surgical procedures.

Antibiotics are not indicated for the routine management of TBM. Dogs in which tracheal wash or BAL fluid analysis has revealed evidence of infection should be treated with appropriate antibiotics (selected on the basis of the results of sensitivity testing). Because most antibiotics do not reach high concentrations in the airways, relatively high doses of antibiotics should be administered for several weeks, as described for canine chronic bronchitis. Any other potentially related problems identified during the diagnostic evaluation are addressed.

A novel approach to treating TBM as reported by Adamama-Moraitou et al. (2012) uses *stanozolol* to improve tracheal wall strength, but this treatment has not been widely adopted. Possible mechanisms include enhanced protein or collagen synthesis, increased chondroitin sulfate content, increased lean body mass, and decreased inflammation. Dogs with tracheal collapse, but not bronchitis, were treated with 0.3 mg/kg stanozolol divided twice daily for 2 months orally, then tapered for 15 days. Dogs in the stanozolol group had improved clinical signs by some measures after 30 days, and improvement in grade of collapse was seen on tracheoscopy at 75 days.

Management of dogs in acute distress with signs of either extrathoracic airway obstruction or intrathoracic large airway obstruction is discussed in Chapter 25.

Tracheal stenting should be considered for dogs with TBM that cannot effectively ventilate due to airway obstruction despite aggressive medical management. Stenting can also be attempted in dogs with refractory cough, but the outcome for this use is often unsatisfactory. The introduction of intraluminal tracheal stents has greatly reduced the morbidity and improved the success of surgical intervention. The most commonly used stents are self-expanding and made of nickel-titanium alloys (Fig. 21.8). In experienced hands, these stents are simple to place during a short period of anesthesia under fluoroscopic or bronchoscopic guidance. Minimal morbidity is associated with stent placement, and response is immediate and often dramatic. However, clinical signs may not completely resolve, collapse of airways beyond the trachea and concurrent conditions are not directly addressed (nearly always resulting in the continued need for medical management), and complications such as infection, ingrowth of tissue, and stent fracture can occur. In particular, cough is usually significantly worse in the weeks

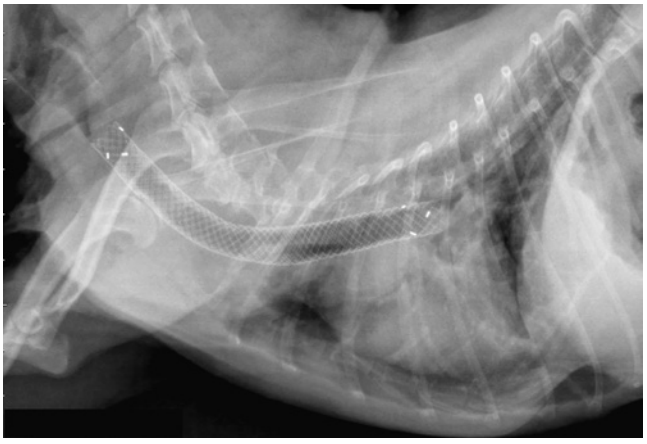


FIG 21.8
Lateral radiograph of the dog with tracheal collapse (shown in Fig. 21.6) after placement of an intraluminal stent. The stent has a mesh-like structure and extends nearly the entire length of the trachea.

immediately after stent placement and must be controlled to minimize trauma to the stent. Initially, cough results from direct damage to the tracheal endothelium by the stent. In addition, ongoing cough from airway inflammation may be exacerbated by areas of mucus accumulation where the stent does not lie perfectly against the epithelium and chronic infections. Results after intraluminal stent placement are sufficiently encouraging that motivated clients with a dog that is failing medical management of tracheal collapse, particularly related to ventilation, should be referred to someone experienced in stent placement for consideration of this option.

Extraluminal stenting can also be performed with the use of plastic rings. This procedure provides the benefit of great durability over many years. The procedure is technically more difficult than intraluminal stenting, perioperative morbidity is high as a result of damage to laryngeal nerves or other cervical structures, and only the cervical trachea is readily accessible. However, good success has been reported, even in dogs with intrathoracic collapse (Becker et al., 2012). This procedure may be worth considering, particularly in very young dogs that otherwise might be expected to outlive an intraluminal stent.

Prognosis

In most dogs clinical signs can be controlled with conscientiously performed medical management, with diagnostic evaluations performed during episodes of persistent exacerbation of signs. Animals in which severe signs develop despite appropriate medical care have a guarded prognosis, and motivated clients should be referred for possible stent placement. The following survival data was provided in a study of 27 dogs after intraluminal stent placement: median survival was 502 days; 78% of dogs survived 6 months; 60% of dogs survived 1 year; and 26% of dogs survive at least 2 years (Rosenheck et.al., 2017). Ongoing medical management is required, and the rate of serious complications from stents has been reported to be approximately 40% (Rosenheck et al., 2017; Tinga et al., 2015).

ALLERGIC BRONCHITIS

Allergic bronchitis is a hypersensitivity response of the airways to an allergen or allergens. The offending allergens are presumably inhaled, although food allergens could also be involved. A definitive diagnosis requires identification of allergen(s) and resolution of signs after elimination of the allergen(s) or successful hyposensitization. It is well documented that purposeful exposure of cats to inhaled allergens can produced feline bronchitis, but large controlled clinical studies describing allergic bronchitis in dogs or cats are lacking and are complicated by the challenges of ruling out other potential etiologies of bronchitis and differentiating allergic bronchitis from idiopathic chronic bronchitis (Trzil and Reinero, 2014).

A study by Prost (2004) presented as an abstract found that 15 of 20 cats had positive intradermal skin tests to aeroallergens. For cats that reacted to storage mites or cockroach antigen, discontinuation of any dry food was recommended (i.e., only canned food was provided). Remission of signs occurred in three cats given only this treatment. Immunotherapy (desensitization) appeared to reduce or eliminate signs in some of the other cats. As a preliminary study, other treatments were also given to the study cats, and a control population was not described.

It is likely that some patients with allergic bronchitis are misdiagnosed because of difficulty in identifying specific allergens. In dogs, long-standing allergic bronchitis may result in the permanent changes recognized as canine chronic bronchitis. In cats, failure to identify specific allergen(s) results in a diagnosis of idiopathic feline bronchitis.

Allergic bronchitis in dogs may result in acute or chronic cough. Rarely, respiratory distress and wheezing occur. Physical examination and radiographic findings reflect the presence of bronchial disease, as described in the section on canine chronic bronchitis. Eosinophilic inflammation is expected in tracheal wash or BAL fluid. Heartworm tests and fecal examinations for pulmonary parasites are performed to eliminate parasitism as the cause of eosinophilic inflammation. In dogs younger than 2 years of age, bronchoscopic evaluation for *O. osleri* also should be considered (see the following section).

Allergic bronchitis in cats has the same presentation and results of diagnostic testing as described for idiopathic feline bronchitis, with eosinophilia expected in airway specimens.

Management of allergic bronchitis is initially focused on identifying and eliminating potential allergens from the environment (see the section on feline bronchitis). Diet trials with novel protein and carbohydrate sources also can be considered. According to the preliminary study previously described, a change in diet to canned food may be beneficial in some cases. Such experimentation with environment and diet is possible only in patients with clinical signs that are sufficiently mild to delay the administration of glucocorticoids and bronchodilators, as described in the sections on canine chronic bronchitis and feline bronchitis (idiopathic). Elimination trials can still be pursued once clinical signs are controlled with medications, but confirmation of a beneficial effect will require discontinuation of the medication and, for a definitive diagnosis to be made, reintroduction of the allergen. The latter may not be necessary or practical in all cases.

Specific immunotherapy for cats with artificially induced allergic bronchitis has been reported. Hyposensitization regimens for cats and dogs with naturally occurring allergic bronchitis hold promise, but criteria for patient selection and expected success rate have not been established.

OSLERUS OSLERI

Etiology

Oslerus osleri is an uncommon parasite of young dogs, usually those younger than 2 years of age. Adult worms live at the carina and mainstem bronchi and cause a local,

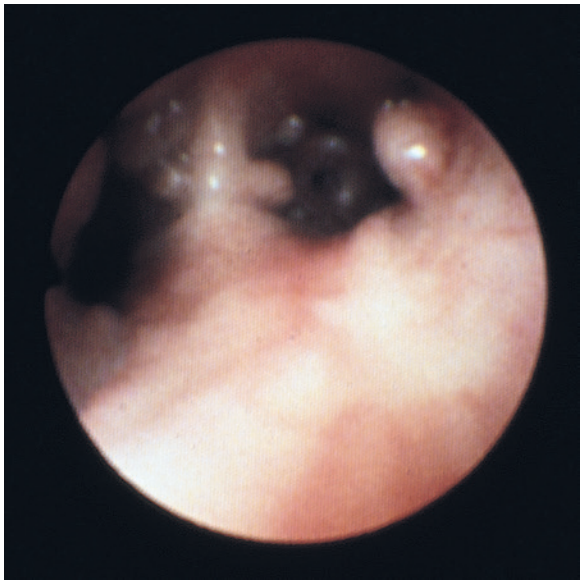


FIG 21.9
Bronchoscopic view of multiple nodules at the carina of a dog infected with *Oslerus osleri*.

nodular inflammatory reaction with fibrosis. First-stage larvae are coughed up and swallowed. The main cause of infection in dogs appears to be intimate contact with their dam as puppies.

Clinical Features

Young affected dogs have an acute, loud, nonproductive cough and occasionally exhibit wheezing. The dogs appear otherwise healthy, making the initial presentation indistinguishable from that of canine infectious respiratory disease complex (CIRDC). However, the cough persists, and eventually airway obstruction occurs as a result of the formation of reactive nodules.

Diagnosis

Nodules at the carina occasionally can be recognized radiographically. Cytologic examination of tracheal wash fluid in some dogs reveals the characteristic ova or larvae, providing the basis for a definitive diagnosis (see Table 20.1). Rarely, larvae are found in fecal specimens with the use of zinc sulfate (specific gravity [s.g.], 1.18) flotation (preferred) or the Baermann technique.

The most sensitive diagnostic method, bronchoscopy, enables the nodules to be readily seen (Fig. 21.9). Brushings of the nodules are obtained and are immediately evaluated cytologically for detection of the larvae. Material can be examined directly in saline solution or stained with new methylene blue. If a definitive diagnosis is not obtained by analysis of the brushings, biopsy specimens are obtained.

Treatment

Treatment with ivermectin (400 µg/kg orally or subcutaneously) is recommended for appropriate breeds of dogs. The same dose is administered again every 3 weeks for four treatments. It cannot be administered to Collies or related breeds. An alternative treatment is fenbendazole (50 mg/kg q24h for 7-14 days).

Prognosis

The prognosis for dogs treated with ivermectin is good; the drug appears to be successful in eliminating infection in the limited number of dogs that have been treated. Follow-up of individual patients is indicated to ensure successful elimination.

Suggested Readings

Adamama-Moraitou KK, et al. Conservative management of canine tracheal collapse with stanozolol: a double blinded, placebo control clinical trial. *Int J Immunopathol Pharmacol*. 2011;24:111.

Adamama-Moraitou KK, et al. Canine bronchomalacia: a clinicopathological study of 18 cases diagnosed by endoscopy. *Vet J*. 2012;191:261.

American Animal Hospital Association (AAHA) Canine Vaccination Taskforce. AAHA canine vaccination guidelines. *J Am Anim Hosp Assoc*. 2011;47(1):2011.

Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med*. 2003;167:813.

Becker WM, et al. Survival after surgery for tracheal collapse and the effect of intrathoracic collapse on survival. *Vet Surg*. 2012;4:501.

Bylicki BJL, et al. Comparison of the radiographic and tracheoscopic appearance of the dorsal tracheal membrane in large and small breed dogs. *Vet Radiol Ultrasound*. 2015;56:602.

Castleman WL, et al. Canine H3N8 influenza virus infection in dogs and mice. *Vet Pathol*. 2010;47:507.

Cocayne CG, et al. Subclinical airway inflammation despite high-dose oral corticosteroid therapy in cats with lower airway disease. *J Feline Med Surg*. 2011;13:558.

Cohn LA, et al. Effects of fluticasone propionate dosage in an experimental model of feline asthma. *J Fel Med Surg*. 2010;12:91.

Crawford PC, et al. Transmission of equine influenza virus to dogs. *Science*. 2005;310:482.

DeLorenzi D, et al. Bronchial abnormalities found in a consecutive series of 40 brachycephalic dogs. *J Am Vet Med Assoc*. 2009;235:835.

Ellis JA, et al. Effect of vaccination on experimental infection with *Bordetella bronchiseptica* in dogs. *J Am Vet Med Assoc*. 2001;218:367.

Ellis JA, et al. Comparative efficacy of intranasal and oral vaccines against Bordetella bronchiseptica in dogs. *Vet J*. 2016;212:71.

Ellis JA. How well do vaccines for Bordetella bronchiseptica work in dogs? A critical review of the literature 1977-2014. *Vet J*. 2015;204:5.

Foster S, Martin P. Lower respiratory tract infections in cats: reaching beyond empirical therapy. *J Fel Med Surg*. 2011;13:313.

Gore T. Intranasal kennel cough vaccine protecting dogs from experimental *Bordetella bronchiseptica* challenge within 72 hours. *Vet Rec*. 2005;156:482.

Grobman M, Reinero C. Investigation of neurokinin-1 receptor antagonism as a novel treatment for chronic bronchitis in dogs. *J Vet Intern Med*. 2016;30:847.

Hawkins EC, et al. Demographic and historical findings, including exposure to environmental tobacco smoke, in dogs with chronic cough. *J Vet Intern Med*. 2010;24:825.

Jacobs AAC, et al. Protection of dogs for 13 months against *Bordetella bronchiseptica* and canine parainfluenza virus with a modified live vaccine. *Vet Rec*. 2005;157:19.

Johnson LR, et al. Tracheal collapse and bronchomalacia in dogs: 58 cases (7/2001-1/2008). *J Vet Intern Med*. 2010;24:298.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Moise NS, et al. Bronchopulmonary disease. In: Sherding RG, ed. *The cat: diseases and clinical management*. New York: Churchill Livingstone; 1989.

Newbury S, et al. Prolonged intermittent virus shedding during an outbreak of canine influenza A H3N2 virus infection in dogs in three Chicago area shelters: 16 cases (March to May 2015). *J Am Vet Med Assoc*. 2016;248:1022.

Padrid P. Feline asthma: diagnosis and treatment. *Vet Clin North Am Small Anim Pract*. 2000;30:1279.

Pardali D, et al. Tidal breathing flow-volume loop analysis for the diagnosis and staging of tracheal collapse in dogs. *J Vet Intern Med*. 2010;24:832.

Prost C. Treatment of allergic feline asthma with allergen avoidance and specific immunotherapy. *Vet Dermatol*. 2004;13(suppl 1):55. Abstract.

Reinero CR. Advances in the understanding of pathogenesis, and diagnostics and therapeutics for feline allergic asthma. *Vet J*. 2011;190:28.

Rosenheck S, et al. Effect of variations in stent placement on outcome of endoluminal stenting for canine tracheal collapse. *J Am Anim Hosp Assoc*. 2017;53:150.

Ruch-Gallie R, et al. Adenovirus 2, *Bordetella bronchiseptica*, and parainfluenza molecular diagnostic assay results in puppies after vaccination with modified live vaccines. *J Vet Intern Med*. 2016;30:164.

Ryan NM. A review on the efficacy and safety of gabapentin in the treatment of chronic cough. *Expert Opin Pharmacother*. 2015;16:135.

Rycroft AN, et al. Serologic evidence of *Mycoplasma cynos* infection in canine infectious respiratory disease. *Vet Microbiol*. 2007;120:358.

Speakman AJ, et al. Antibiotic susceptibility of canine *Bordetella bronchiseptica* isolates. *Vet Microbiol*. 2000;71:193.

Tinga S, et al. Comparison of outcome after use of extra-luminal rings and intra-luminal stents for treatment of tracheal collapse in dogs. *Vet Surg*. 2015;44:858.

Trzil JE, Reinero CR. Update on feline asthma. *Vet Clin North Am Small Anim Pract*. 2014;44:91.

White RAS, et al. Tracheal collapse in the dog: is there really a role for surgery? A survey of 100 cases. *J Small Anim Pract*. 1994;35:191.

Yao C, et al. Filaroides osleri (Oslerus osleri): two case reports and a review of canid infections in North America. *Vet Parasitol*. 2011;179:123.

CHAPTER 22

Disorders of the Pulmonary Parenchyma and Vasculature



VIRAL PNEUMONIAS

Most respiratory viruses cause self-limiting signs of tracheobronchitis in dogs (see Canine Infectious Respiratory Disease Complex, CIRDC, in Chapter 21) or upper respiratory infection in cats (see Feline Upper Respiratory Infection in Chapter 15). In dogs, *Bordetella bronchiseptica*, canine influenza viruses, and canine distemper virus can directly result in pneumonia. *B. bronchiseptica* and canine influenza are discussed primarily with CIRDC in Chapter 21; canine distemper is discussed in Chapter 94. Secondary bacterial infections can complicate infections with these, or other, CIRDC organisms. Treatment is supportive for viral infection. The diagnostic approach and management of bacterial pneumonia is discussed in the next section.

In cats, calicivirus can cause pneumonia, but this manifestation of infection is rare. The dry form of feline infectious peritonitis can affect the lungs, but cats are generally seen because of signs of involvement of other organs. Feline infectious peritonitis is discussed in Chapter 94.

BACTERIAL PNEUMONIA

Etiology

A wide variety of bacteria can infect the lungs. Common bacterial isolates from dogs and cats with pulmonary infection include *B. bronchiseptica, Streptococcus* spp., *Staphylococcus* spp., *Escherichia coli, Pasteurella* spp., *Klebsiella* spp., *Proteus* spp., and *Pseudomonas* spp. Anaerobic organisms can be part of mixed infections, particularly in animals with aspiration pneumonia or with lung lobe consolidation. *Mycoplasma* spp. has been isolated from dogs and cats with pneumonia, but its exact role is not known. *Mycoplasma cynos,* in particular, may be pathogenic in dogs.

Bacteria can colonize the airways, alveoli, or interstitium. The term *pneumonia* means inflammation of the lung, but the term is not specific for bacterial disease. Infection that clinically appears to be limited to the airways and peribronchial tissues is called *bacterial bronchitis.* If all three regions are involved, the disease is called either *bacterial bronchopneumonia* or *bacterial pneumonia.* Many cases of bacterial pneumonia result from entry of bacteria of the oral cavity and pharynx into the lungs via the airways, which causes a bronchopneumonia involving primarily the gravity-dependent cranial and ventral lung lobes (see Fig. 20.5). Bacteria that enter the lung through the hematogenous route usually cause pneumonia that assumes a caudal or diffuse pattern and marked interstitial involvement. Bacterial pneumonia of hematogenous origin was documented in more than half of cats with bacterial pneumonia on the basis of postmortem examination findings (MacDonald et al., 2003).

Bacterial pneumonia is a common lung disease, particularly in dogs. Community-acquired infectious pneumonia has been described in puppies (Radhakrishnan et al., 2007), most often caused by *B. bronchiseptica* (49% of cases). Coinfection with complicated infectious respiratory disease complex (CIRDC) viruses was identified in 8 of 20 household dogs with bacterial pneumonia (7 with canine parainfluenza virus and 1 with canine respiratory corona virus) (Viitanen et al., 2015). However, consideration should also be given to predisposing abnormalities. *A predisposing abnormality often exists in adult dogs whose bacterial pneumonia is not associated with CIRDC.* Abnormalities to consider in all patients include aspiration of ingested material or gastric contents caused by cleft palate, megaesophagus, or other conditions associated with aspiration pneumonia (discussed separately in a later section); decreased clearance from the lungs of normally inhaled debris, particularly in animals with chronic bronchitis, ciliary dyskinesia, or bronchiectasis; immunosuppression resulting from drugs, malnutrition, stress, or endocrinopathies; inhalation or migration of foreign bodies; and, rarely, neoplasia or fungal or parasitic infection. Immunosuppression from infection with feline leukemia virus or immunodeficiency virus is also a consideration for cats.

Clinical Features

Dogs and cats with bacterial pneumonia are evaluated because of respiratory signs, systemic signs, or both. Respiratory signs can include cough (which is often, but not always, productive), bilateral mucopurulent nasal discharge, exercise

intolerance, and respiratory distress. Cough is less common in cats with pneumonia. Systemic signs may include lethargy, anorexia, fever, and weight loss. The animal may have a history of chronic airway disease or regurgitation. Cats, particularly kittens, from stressful housing situations (e.g., overcrowding) appear predisposed to develop pneumonia as a result of *Bordetella* infection. Dogs with CIRDC may have a recent history of harsh cough and a history consistent with exposure, as described in Chapter 21. Other potential predisposing factors, as listed in the preceding section, are pursued through careful history taking.

Fever may be noted on physical examination but is identified in only about half of patients. Crackles and occasionally expiratory wheezes may be auscultated, with abnormal lung sounds often prominent over the cranioventral lung fields in patients with infection of airway origin.

Diagnosis

Bacterial pneumonia is diagnosed on the basis of the complete blood count (CBC), thoracic radiographic findings, and results from tracheal wash fluid cytologic analysis and bacterial culture. A CBC showing neutrophilic leukocytosis with a left shift, neutropenia with a degenerative left shift, or moderate to marked neutrophil toxicity is supportive of bacterial pneumonia. However, a normal or stress leukogram is as likely to be found.

Abnormal patterns on thoracic radiographs vary with the underlying disease. The typical abnormality is an alveolar pattern, possibly with consolidation, which is most severe in the dependent lung lobes (see Fig. 20.5). Increased bronchial and interstitial markings are often present. Infection secondary to foreign bodies can be localized to any region of the lung. An interstitial pattern alone may be present in animals with early or mild disease or in those with infection of hematogenous origin. A bronchial pattern alone may be present in animals with a primarily bronchial infection. Radiographs are also evaluated for the presence of megaesophagus and other extrapulmonary disease.

Ideally, pulmonary specimens are evaluated cytologically and microbiologically (bacterial and, ideally, *Mycoplasma* cultures or polymerase chain reaction (PCR)) to establish a definitive diagnosis and provide guidance in antibiotic selection. To maximize the diagnostic yield, specimens should be collected before antibiotic therapy is initiated. A tracheal wash specimen is generally sufficient. Septic neutrophilic inflammation is typically found in animals with bacterial pneumonia, and growth of organisms on bacterial culture is expected. Examination of a gram-stained preparation will provide early guidance in antibiotic selection pending results of culture and will assist in the identification of anaerobes or other organisms that may not be easily grown in culture (e.g., *Mycobacteria,* filamentous organisms).

A conscientious effort is made to identify any underlying problems. In some animals, such as those with megaesophagus, the initiating cause is obvious. Further diagnostic tests are indicated in other animals, depending on the results of the clinicopathologic evaluation. These may include bronchoscopy to search for airway abnormalities or foreign bodies, conjunctival scrapings to look for distemper virus, serologic or PCR tests to detect specific viral or fungal organisms, and hormonal assays to determine whether the animal has hyperadrenocorticism. Ciliary dyskinesia is discussed briefly in Chapter 21. Diagnostic evaluation for aspiration pneumonia is discussed in the section dedicated to aspiration pneumonia.

Treatment

Antibiotics

Treatment for bacterial pneumonia consists of antibiotics and supportive care, with follow-up evaluation (Box 22.1). The antibiotic sensitivity of involved organisms is difficult to predict. Gram-negative infection and infection with multiple organisms are common. Antibiotics are initially selected on the basis of severity of clinical signs and cytologic characteristics (i.e., morphology and gram-staining) of organisms found in pulmonary specimens. Antibiotic selection is subsequently modified, as needed, according to clinical response and sensitivity data from bacterial cultures of pulmonary specimens.

The extent to which an antibiotic can penetrate into the airway secretions does not need to be a major consideration in patients with bacterial pneumonia. Antibiotics generally achieve concentrations within the pulmonary parenchyma

BOX 22.1

Therapeutic Considerations for Bacterial Pneumonia

Antibiotics

Ideally, selected on basis of results from Gram staining and culture and sensitivity testing of pulmonary specimens. See text for specific guidelines.

Airway Hydration

Maintenance of systemic hydration
Saline nebulization

Physiotherapy

Turning of recumbent animals every 1 to 2 hours
Mild exercise of animals in stable condition
Coupage

Bronchodilators

As needed, particularly in cats

Oxygen Supplementation

As needed

AVOID

Diuretics
Cough suppressants
Corticosteroids

equal to those in plasma. Nebulization of antibiotics is rarely indicated.

Based on recommendations of the Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases (ISCAID), dogs and cats with mild pneumonia suspected based on history to be from infection with *B. bronchiseptica* or *Mycoplasma spp* can be treated with doxycycline (5 mg/kg q12h PO or 10 mg/kg q24h; followed by a bolus of water). However, broader coverage is indicated in these patients if systemic signs of disease such as fever, dehydration, lethargy, or respiratory compromise is present (Lappin et al., 2017).

For other animals with mild or moderate clinical signs, oral antibiotics that can be initiated include amoxicillin-clavulanate (dogs, 11 mg/kg q8h; cats, 12.5 mg/kg q8h), cephalexin (22-25 mg/kg q12h), and trimethoprim-sulfonamide (15 mg/kg q12h). Fluoroquinolones are reserved for animals with resistant gram-negative infections.

Animals with severe clinical signs or possible sepsis should be treated initially with broad-spectrum intravenous antibiotics that provide coverage for gram-negative and gram-positive aerobes and anaerobes. A fluoroquinolone in combination with ampicillin with sulbactam (20 mg/kg of ampicillin q6-8h) is commonly used. This combination has the advantages of availability of oral formulations for continuation of therapy after hospitalization, and the flexibility of de-escalation if clinical response and culture results support doing so. Alternatively, meropenem (8.5 mg/kg SC q12h or 24 mg/kg IV q12h in dogs; 10 mg/kg IV, IM, SC q12h in cats) or the combination of an aminoglycoside (e.g., amikacin, 15 mg/kg IV q24h in dogs and 10 mg/kg IV q24h in cats) and ampicillin with sulbactam can be used. If *Toxoplasma* infection is among the differential diagnoses, usually in cats, clindamycin (10-15 mg/kg PO, SC q12h in cats) can substituted for the ampicillin with sulbactam in combination with a fluoroquinolone (see Chapter 98).

Antibiotic treatment should be continued for at least 1 week after clinical signs have resolved. Guidelines for patient monitoring are provided later in this section.

Airway Hydration

Drying of secretions results in increased viscosity and decreased ciliary function, which interfere with the normal clearance mechanisms of the lung. Thus the water content of airway secretions must be maintained and airways must be hydrated in animals with pneumonia. Animals with any evidence of dehydration should receive fluid therapy. Diuretics can cause dehydration, and their use is relatively contraindicated in such animals.

Additional moisture for the airways can be provided through humidification or nebulization. Such therapy is particularly recommended for animals with areas of consolidation or with suspected decreased airway clearance, such as those with bronchiectasis. *Humidification* refers to the saturation of air with water vapor. Depending on the temperature, the volume of water that remains as vapor is limited. Moisture reaches only the nasal cavity and the proximal trachea. Vaporization is not effective in hydrating deeper regions of the lungs. However, the more proximal effect can still provide some relief, particularly in animals with nasal discharge. Humidification is convenient and can be achieved simply by placing the animal in a steamy bathroom or in a small room with an inexpensive vaporizer, which is readily available at pharmacies.

Nebulization is necessary to provide moisture deeper into the airways. Nebulizers generate small, variably sized droplets, with a diameter ranging from 0.5 to 5 µm, as is required to reach the deeper airways. Several types of nebulizers are available. Disposable jet nebulizers are readily available and inexpensive, and they can be attached to bottled oxygen or to an air compressor (Fig. 22.1). Effective, inexpensive portable compressors are commercially available if needed for home use. The nebulizing solution is delivered to the animal through a face mask. The particles can be seen as a mist. Excellent information on the use and cleaning of nebulizing equipment in the home can be found on the Web sites of many large human hospitals where patient information is provided for the management of cystic fibrosis or bronchial asthma.

Sterile saline solution is used as a nebulizing solution because it has mucolytic properties and is relatively nonirritating. Premedication with bronchodilators has been suggested as a way to reduce bronchospasms, although the use of saline alone in dogs does not usually cause problems. It is recommended that nebulization be performed two to six times daily for 10 to 30 minutes each time. Nebulization should be followed immediately by physiotherapy to promote the expectoration of exudate that may have increased in volume with rehydration. Nebulizers and tubing should be replaced after no more than 24 hours of use in

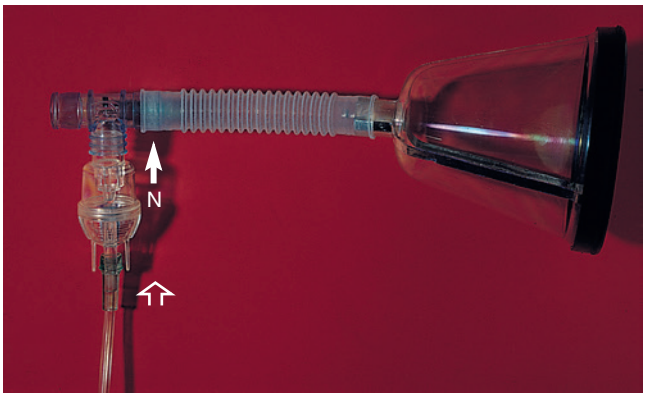


FIG 22.1
Disposable jet nebulizers are readily available and inexpensive. Sterile saline solution is placed in the nebulizer *(N)*. Oxygen enters the bottom of the nebulizer *(open arrow)*, and nebulized air exits the top *(closed arrow)*. Nebulized air is delivered to the animal with a face mask, as shown here, or it can be delivered into an enclosed cage.

actively infected patients, and face masks should be cleaned and disinfected.

Physiotherapy

Animals that are in a sufficiently stable condition and can tolerate the oxygen demands should be mildly exercised. Activity causes animals to take deeper breaths and to cough, which promotes airway clearance. Animals that are recumbent are turned every 2 hours. Lying in one position impairs airway clearance, and lung consolidation can occur if one side remains dependent for prolonged periods.

Physiotherapy is indicated after nebulization to promote coughing and facilitate the clearance of exudate from the lungs. Mild exercise is used when possible. Otherwise, coupage is performed. To perform coupage, the clinician strikes the animal's chest over the lung fields with cupped hands. The action should be forceful but not painful and should be continued for 5 to 10 minutes if tolerated by the patient. Coupage may also be beneficial for animals with lung consolidation that are not receiving nebulization.

Bronchodilators

In cats, bronchospasm can occur secondary to inflammation. Bronchodilators are used in cats that show increased respiratory efforts, particularly if expiratory wheezes are auscultated. Bronchospasm is uncommon in dogs, but bronchodilators (particularly theophylline) may have other potentially advantageous effects. If bronchodilators are administered, patient status should be monitored closely because bronchodilators may worsen ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching, thereby exacerbating hypoxemia. They are discontinued if clinical signs worsen or do not improve. Bronchodilators are discussed in the sections on Canine Chronic Bronchitis and Feline Bronchitis (Idiopathic) in Chapter 21.

Other Treatment

Expectorants are of questionable value in dogs and cats. *Acetylcysteine* is a mucolytic agent that some clinicians believe is beneficial for the treatment of dogs with severe bronchopneumonia when administered intravenously. It is quite possible that the antioxidant effects of this drug, rather than its mucolytic property, account for any benefit that may be seen. Acetylcysteine should not be administered by nebulization because of its irritant effects on the respiratory mucosa. *Glucocorticoids* are relatively contraindicated in animals with bacterial pneumonia. *Oxygen therapy* (see Chapter 25) is provided if clinical signs, arterial blood gas measurements, or pulse oximetry measurements indicate the need for it.

Monitoring

Dogs and cats with bacterial pneumonia should be closely monitored for signs of deteriorating pulmonary function. Respiratory rate and effort and mucous membrane color are monitored at least twice daily. Thoracic radiographs and the CBC are evaluated every 24 to 72 hours. If the animal's condition does not improve within 72 hours, it may be necessary to alter treatment or perform additional tests. Animals that show improvement are sent home and are reevaluated every 10 to 14 days. Once clinical and radiographic signs have resolved, antibiotic treatment is continued for an additional week.

A more objective way to determine adequate duration of therapy may be possible through the monitoring of C-reactive protein (CRP). Eighteen dogs with bacterial pneumonia that were treated for 5 to 7 days beyond the normalization of CRP had a shorter total duration of antibiotic therapy (median 21 days) compared with dogs treated for 3 to 6 weeks in total or 1 to 2 weeks beyond the resolution of alveolar densities on radiographs (median 35 days) without an increase in relapses (Viitanen et al., 2017).

Evidence of infection on initial radiographs can obscure that of focal disease processes such as neoplasia or foreign bodies, and focal opacities may not be apparent while an animal is receiving antibiotics. Therefore radiographs should be reevaluated approximately 1 week after antibiotic therapy has been discontinued in animals with recurrent infection or suspected localized disease. Persistence of localized disease after long-term antibiotic therapy is an indication for computed tomography and bronchoscopy, thoracoscopy, or thoracotomy.

Prognosis

Bacterial pneumonia responds readily to appropriate therapy. The prognosis is more guarded in animals with underlying problems that predispose them to infection, and the likelihood of eliminating these problems must be taken into consideration.

Pulmonary abscess formation is an uncommon complication of bacterial pneumonia. Abscesses are seen as focal lesions on radiographs, and entire lobes may be involved. Horizontal-beam radiographs can be useful in determining whether lesions are filled with fluid. Ultrasonography can also be helpful in characterizing areas of consolidation. Abscesses resolve in response to prolonged medical therapy in some animals, but if improvement is not observed or radiographic evidence of disease reappears after discontinuation of therapy, surgical excision (i.e., lobectomy) is indicated.

TOXOPLASMOSIS

The lungs are a common site of involvement in cats with toxoplasmosis. Thoracic radiographs typically show fluffy alveolar and interstitial opacities throughout the lungs in such animals. Less often, a nodular interstitial, diffuse interstitial, or bronchial pattern, lung lobe consolidation, or pleural effusion is seen. Organisms are rarely recovered from the lungs by tracheal wash. Bronchoalveolar lavage is more likely to retrieve organisms (see Fig. 20.17). Toxoplasmosis is a multisystemic disease and is discussed in detail in Chapter 98.

FUNGAL PNEUMONIA

Common mycotic diseases that can involve the lungs are blastomycosis, histoplasmosis, and coccidioidomycosis. In most cases, organisms enter the body through the respiratory tract. The infection may be successfully eliminated without the animal showing clinical signs, or the animal may show only transient respiratory signs. The infection may also progress to cause disease involving the lungs alone or may spread systemically to various target organs. Cryptococcal organisms also enter the body through the respiratory tract and can infect the lungs, particularly in cats. However, the presenting signs in cats are generally those of nasal infection. Pulmonary signs are most often the primary presenting complaint in dogs with blastomycosis and in cats with histoplasmosis.

Pulmonary mycoses are considered in the differential diagnoses of dogs or cats with progressive signs of lower respiratory tract disease, especially if they occur in conjunction with weight loss, fever, lymphadenopathy, chorioretinitis, or other evidence of multisystemic involvement. Thoracic radiographs typically show a diffuse, nodular, interstitial pattern of the lungs (see Fig. 20.6). The nodules are often miliary. The presence of this pattern in dogs with suspicious clinical signs supports a diagnosis of mycotic infection, although similar radiographic patterns can be seen with neoplasia; parasitic lung disease; infection with atypical bacteria such as *Mycobacterium, Actinomyces* or *Nocardia*; and eosinophilic lung disease. Other potential radiographic abnormalities include alveolar and bronchointerstitial patterns and consolidated regions of lung. Hilar lymphadenopathy can occur, most commonly in animals with histoplasmosis. The lesions caused by histoplasmosis can also be calcified.

Organisms can be retrieved by tracheal wash in some cases. However, because of the interstitial nature of these diseases, bronchoalveolar lavage or lung aspiration may be necessary (see Figs. 20.15 and 20.16). Fungal culture is probably more sensitive than cytologic analysis alone. An inability to find organisms in pulmonary specimens does not rule out the diagnosis of mycotic disease, however. A complete discussion of systemic mycoses is provided in Chapter 97.

PULMONARY PARASITES

Several parasites can cause lung disease. Certain intestinal parasites, especially *Toxocara canis,* can cause transient pneumonia in young animals, usually those younger than a few months of age, as the larvae migrate through the lungs. Infection with *Dirofilaria immitis* can result in severe pulmonary disease through inflammation and thrombosis (see Chapter 10). *Oslerus osleri* resides at the carina and mainstem bronchi of dogs and is discussed in Chapter 21. The other primary lung parasites that are most commonly diagnosed are *Capillaria (Eucoleus) aerophila* and *Paragonimus kellicotti* in dogs and cats, *Aelurostrongylus abstrusus* in cats, and *Crenosoma vulpis* in dogs.

Infection occurs as a result of ingestion of infective forms, often within intermediate or paratenic hosts, that subsequently migrate to the lungs. An eosinophilic inflammatory response often occurs within the lungs, causing clinical signs in some, but not all, infected animals. The definitive diagnosis is made by identification of the characteristic eggs or larvae in respiratory or fecal specimens (see Chapter 20).

CAPILLARIA (EUCOLEUS) AEROPHILA

Capillaria aerophila, also known as *Eucoleus aerophila,* is a small nematode. Adult worms are located primarily beneath the epithelial surfaces of the large airways. Clinical signs develop in very few animals with *Capillaria* infection, and the disease is most often identified through the fortuitous identification of characteristic eggs during routine fecal examination.

The rare animal that displays signs shows signs of allergic bronchitis. Thoracic radiographic findings are generally normal, although a bronchial or bronchointerstitial pattern may be seen. Tracheal wash fluid can show eosinophilic inflammation. *Capillaria* is diagnosed by the finding of characteristic eggs in tracheal wash fluid or fecal flotation material (see Fig. 20.12, *C*).

The treatment of choice for dogs and cats is fenbendazole (50 mg/kg PO q24h for 14 days). Levamisole (8 mg/kg PO for 10-20 days) has also been used successfully in dogs. Ivermectin has been suggested for treatment, but a consistently effective dosage has not been established. The prognosis in animals with the disease is excellent.

PARAGONIMUS KELLICOTTI

Paragonimus kellicotti is a small fluke. Both snails and crayfish are necessary intermediate hosts, thus limiting the disease to animals that have been in the region of the Great Lakes, in the Midwest, or in the southern United States. Pairs of adults are walled off by fibrous tissue, usually in the caudal lung lobes, with connection to an airway to allow for the passage of eggs. A local granulomatous reaction may occur around the adults, or a generalized inflammatory response to the eggs may be noted.

Infection is more common in cats than in dogs. Some dogs and cats have no clinical signs. When clinical signs are present, they may be the same as those seen in animals with allergic bronchitis. Alternatively, signs of spontaneous pneumothorax can result from the rupture of cysts.

The classic radiographic abnormality is single or multiple solid or cavitary mass lesions, most commonly present in the right caudal lobe (see Fig. 20.10). Other abnormal patterns seen on thoracic radiographs can be bronchial, interstitial (reticular or nodular), or alveolar in nature, depending on the severity of the inflammatory response (see Fig. 20.11).

Infection is diagnosed definitively through identification of the ova in fecal specimens (using the sedimentation technique described in Chapter 20), tracheal wash fluid, or bronchoalveolar lavage fluid (see Fig. 20.12, *D*). Multiple fecal

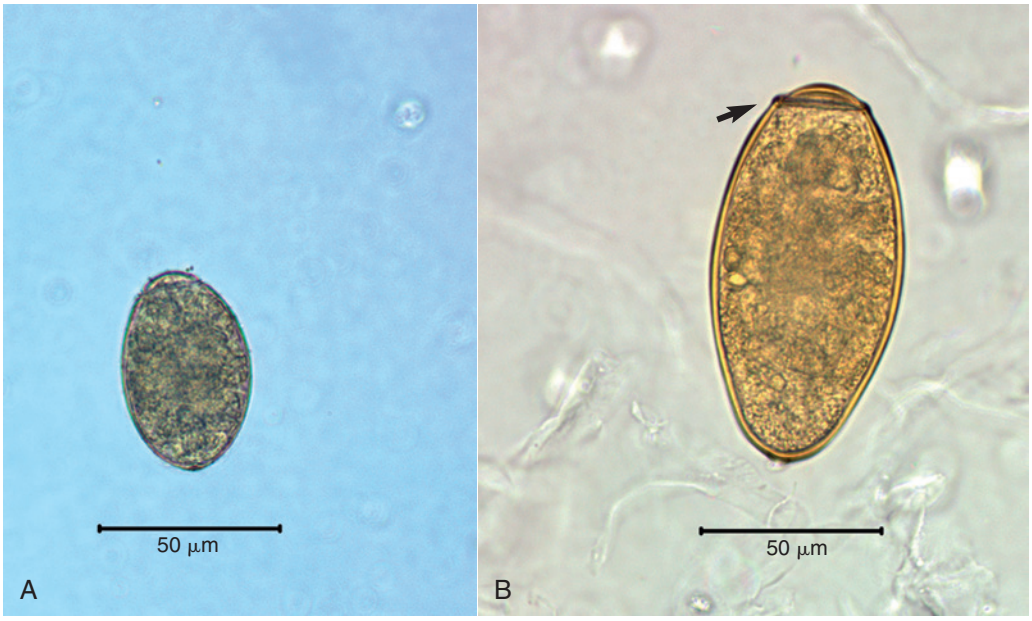


FIG 22.2
The operculated ova from *Spirometra* tapeworms **(A)** can be misdiagnosed as *Paragonimus* ova **(B).** The *Spirometra* ova are smaller and paler than the yellow-brown *Paragonimus* ova. Most notably, *Paragonimus* ova have a distinctly visible shoulder *(arrow)* at the operculated end. (Courtesy James R. Flowers.)

specimens should be examined in suspected cases because the eggs are not always present. A presumptive diagnosis is necessary in some cases. Note that ova from the tapeworm *Spirometra* spp. can be mistakenly identified as ova from *Paragonimus* (Fig. 22.2).

Fenbendazole is used to treat paragonimiasis at the same dosage as that recommended for the treatment of capillariasis. Alternatively, praziquantel can be used at a dosage of 23 mg/kg orally every 8 hours for 3 days.

Thoracocentesis should be used to stabilize the condition of animals with pneumothorax. If air continues to accumulate within the pleural space, however, it may be necessary to place a chest tube and perform suction until the leak has been sealed (see Chapter 24). Surgical intervention is rarely required.

Thoracic radiographs and periodic fecal examinations should be used to monitor the response to treatment. Treatment may have to be repeated in some cases. The prognosis is excellent.

AELUROSTRONGYLUS ABSTRUSUS

Aelurostrongylus abstrusus is a small worm that infects the small airways and pulmonary parenchyma of cats. Snails or slugs serve as intermediate hosts. Most cats with infection have no clinical signs. Those cats that do are usually young. Clinical signs are those of bronchitis. Abnormalities seen on radiographs may also reflect bronchitis, although a diffuse miliary or nodular interstitial pattern is present in some cats. Pulmonary arterial enlargement can occur, making this disease a differential diagnosis in cats with possible heartworm disease. Eosinophilic inflammation may be apparent in peripheral blood and airway specimens.

A definitive diagnosis is made through identification of larvae, which may be present in fecal specimens prepared using the Baermann technique (see Fig. 20.12, *A*) or in airway specimens obtained by tracheal washing or bronchoalveolar lavage. Fecal Baermann examination is most sensitive for the detection of organisms, although multiple fecal specimens should be examined in suspected cases because organisms are shed intermittently. Airway specimens are often negative for organisms, despite infection, and stained squash preparations of mucus are recommended to increase sensitivity (Lacorcia et al., 2009).

Cats should be treated with fenbendazole at the same dosage as that used for the treatment of capillariasis. In one study, the dosage of 50 mg/kg orally every 24 hours for 15 days was effective in eliminating infection in all four cats treated (Grandi et al., 2005). In contrast with a previous report, ivermectin (0.4 mg/kg, administered subcutaneously) was not effective in one cat. Thoracic radiographs and periodic fecal examinations are used to monitor the response to treatment. Treatment may have to be repeated in some cases.

Antiinflammatory therapy with glucocorticoids alone often causes the clinical signs to resolve. However, eliminating the underlying parasitic disease is a preferable treatment goal, and glucocorticoid therapy may interfere with the effectiveness of antiparasitic drugs. Bronchodilators may provide symptomatic relief and presumably do so without interference with antiparasitic drug action. The prognosis in animals with the infection is excellent.

CRENOSOMA VULPIS

Crenosoma vulpis is a lungworm of foxes that can also infect dogs. Dogs living in Atlantic Canada and parts of Europe are most commonly diagnosed with this disease, and the diagnosis remains rare in the United States. However, it is possible that with increased residential development into fox habitats, the frequency of cases in this country will increase. The worm resides in the airways (i.e., trachea, bronchi, bronchioles). Snails or slugs serve as intermediate hosts. The clinical signs are those of allergic or chronic bronchitis. Thoracic radiographs may have a bronchointerstitial or patchy alveolar pattern or occasionally a nodular pattern. Infection is diagnosed definitively through identification of the larvae in fecal specimens (using the Baermann technique), tracheal wash fluid, or bronchoalveolar lavage fluid (see Fig. 20.12, *B*). Multiple fecal specimens should be examined in suspected cases because the larvae are not always present. A single oral dose of milbemycin oxime (0.5 mg/kg) was effective in resolving clinical signs and eliminating larvae from feces collected 4 to 6 weeks after treatment in 32 dogs (Conboy, 2004). This treatment may not be effective against immature larvae. As with other pulmonary parasites, the response to treatment is monitored with thoracic radiographs and periodic fecal examinations.

ASPIRATION PNEUMONIA

Etiology

A small amount of fluid and bacteria is aspirated from the oropharynx into the airways of healthy animals, but normal airway clearance mechanisms prevent infection. Organisms from the oropharynx are thought to be the source of bacteria in many animals with bacterial pneumonia, specifically bacterial bronchopneumonia (see earlier section). In people, such infection is termed *aspiration pneumonia.* In veterinary medicine, the term *aspiration pneumonia* is generally used to refer to the inflammatory lung disease that occurs as a result of the inhalation of overt amounts of solid or liquid material into the lungs. The materials that are usually aspirated are stomach contents or food. Normal laryngeal and pharyngeal function prevents aspiration in healthy animals, although occasionally an excited puppy or a dog running through tall grass aspirates a foreign body. Otherwise, the presence of aspiration pneumonia in an animal of any age indicates an underlying predisposing abnormality (Box 22.2).

Aspiration pneumonia is a common complication of animals with regurgitation. Megaesophagus and esophageal dysmotility are the most common causes of regurgitation (see Chapter 29). Other causes of regurgitation (e.g., reflux esophagitis, esophageal obstruction) are less common. Another cause of aspiration pneumonia is localized or systemic neurologic or muscular disease affecting the normal swallowing reflexes of the larynx or pharynx. These reflexes can also be depressed in dogs or cats with abnormal levels of consciousness or in those that are anesthetized. Laryngeal paralysis has been associated with concurrent esophageal dysfunction (see Chapter 18), and aspiration pneumonia is a complication of therapeutic laryngoplasty. Aspiration pneumonia can also occur in animals with abnormal pharyngeal anatomy resulting from mass lesions, brachycephalic airway syndrome, or cleft palate. Bronchoesophageal fistulae are a rare cause of aspiration pneumonia.

Aggressive force-feeding, especially in mentally depressed animals, and improper placement of stomach tubes into the trachea are iatrogenic causes of aspiration pneumonia. Mineral oil administered to prevent hairballs can be a cause of aspiration pneumonia in cats because the pharynx poorly handles the tasteless and odorless oil.

Damage to the lung resulting from aspiration may stem from chemical damage, obstruction of the airways, infection, and the resulting inflammatory response to each of these factors. Gastric acid causes severe chemical injury to the lower airways. Tissue necrosis, hemorrhage, edema, and bronchoconstriction ensue, and a marked acute inflammatory response is initiated. Hypoxemia resulting from decreased alveolar ventilation and compliance can be fatal.

BOX 22.2

Underlying Causes of Aspiration Pneumonia in Dogs and Cats*

- Esophageal Disorders
  - Megaesophagus, Chapter 29
  - Reflux esophagitis, Chapter 29
  - Esophageal dysmotility, Chapter 29
  - Esophageal obstruction, Chapter 29
  - Myasthenia gravis (localized), Chapter 66
  - Bronchoesophageal fistulae
- Localized Oropharyngeal Abnormalities
  - Laryngeal paralysis, Chapter 18
  - Cleft palate
  - Cricopharyngeal motor dysfunction, Chapter 29
  - Laryngoplasty, Chapter 17
  - Brachycephalic airway syndrome, Chapter 17
- Systemic Neuromuscular Disorders
  - Myasthenia gravis, Chapter 66
  - Polyneuropathy, Chapter 66
  - Polymyopathy, Chapter 67
- Decreased Mentation
  - General anesthesia
  - Sedation
  - Post ictus, Chapter 62
  - Head trauma
  - Severe metabolic disease
- Iatrogenic†
  - Force-feeding
  - Stomach tubes, Chapter 28
- Vomiting (in Combination with Other Predisposing Factors), Chapter 28

*Discussions of these abnormalities can be found at the given chapters.

†Overzealous feeding, incorrect tube placement, or loss of lower esophageal sphincter competence because of presence of tube.

Severe respiratory distress can result from physical obstruction of the airways by the aspirated material. In most cases only small airways are obstructed, but rarely a large piece of food will obstruct a major airway. Obstruction is subsequently exacerbated by reflex bronchoconstriction and inflammation. Inhaled solid material initiates an inflammatory reaction that includes an abundance of macrophages. This response can become organized, resulting in the formation of granulomas.

Bacterial infection may result from the aspiration of contaminated material, such as ingesta that remained in the esophagus. Acidic gastric contents are probably sterile, although in people the contents are considered contaminated if antacids have been taken, if an intestinal obstruction is present, or if periodontal disease is present. Note that many veterinary patients have periodontal disease. Regardless of the sterility of the aspirated material, the resultant damage to the lungs by gastric acid predisposes the animal to the development of a secondary infection.

The inhalation of mineral oil elicits a chronic inflammatory response. Clinical signs in this setting are often mild, but in rare instances they may be severe. Radiographic abnormalities persist and can be erroneously interpreted as representing neoplastic lesions.

Clinical Features

Dogs and cats with aspiration pneumonia are frequently presented for acute, severe respiratory signs. Systemic signs such as anorexia and depression are common, and these patients may even present in shock. Vomiting, regurgitation, or eating may have preceded the onset of distress. Other patients are seen because of chronic intermittent or progressive signs of coughing or increased respiratory efforts. Occasionally, patients show only signs of depression or the predisposing disease. A thorough history is obtained, with all organ systems carefully reviewed. Owners are specifically questioned about eating behavior (prehension and swallowing), regurgitation (particularly after eating or drinking), voice change, force-feeding, and medication administration.

Fever may be present, but it is an inconsistent finding. Crackles are often auscultated, particularly over dependent lung lobes. Wheezes are heard in some cases. Once a patient is in stable condition, a thorough neuromuscular examination is performed. The ability of the patient to prehend and swallow food and water should also be observed.

Diagnosis

Aspiration pneumonia is usually diagnosed on the basis of suggestive radiographic findings in conjunction with evidence of a predisposing condition. Thoracic radiographs typically show diffuse, increased interstitial opacities with alveolar flooding (air bronchograms) and consolidation of the dependent lung lobes (see Fig. 20.5). Radiographic abnormalities may not be apparent until 12 to 24 hours after aspiration, however. Occasionally, nodular interstitial patterns are seen in chronic cases. Large nodules can form around solids; miliary nodules often form in animals that have aspirated mineral oil. A marked, diffuse alveolar pattern can be seen in dogs that have severe secondary edema (see the section on pulmonary edema later in this chapter).

The peripheral blood count can reflect the pulmonary inflammatory process, but it is often normal. Neutrophils are examined for the presence of toxic changes suggestive of sepsis.

Tracheal wash is indicated for animals that can tolerate the procedure to identify complicating bacterial infection and obtain antibiotic sensitivity data. A marked inflammatory response characterized by a predominance of neutrophils is seen in cytologic specimens. Blood resulting from hemorrhage may be seen in specimens from animals in the acute period after aspiration. Bacteria may also be seen. Bacterial cultures should always be performed.

Bronchoscopy can be used to grossly examine the airways and detect and remove large solids. However, the likelihood of a large airway obstruction is very small, so bronchoscopy is performed only if clear signs of large airway obstruction are noted (see Chapter 25), or if the animal is not conscious and therefore does not require general anesthesia for the procedure.

Blood gas analysis can be helpful in differentiating hypoventilation from ventilation/perfusion abnormalities (see Chapter 20), although a combination of abnormalities is found in most animals with aspiration pneumonia. Animals with evidence of profound hypoventilation may have a large airway obstruction or muscle weakness secondary to an underlying neuromuscular disorder such as myasthenia gravis. Blood gas analysis also assists in the therapeutic management of these animals and can be used effectively to monitor the response to therapy.

Diagnostic evaluation is indicated to identify potential underlying diseases (see Box 22.2). This may include a thorough oral and pharyngeal examination, contrast-enhanced radiographic studies to evaluate the esophagus, or specific neuromuscular tests.

Treatment

Suctioning of the airways is helpful only for animals that aspirate in the hospital while already anesthetized or unconscious, when it can be performed immediately after aspiration. If a bronchoscope is immediately available, suctioning can be performed through the biopsy channel, which affords visualized guidance. Alternatively, a sterile soft rubber tube attached to a suction pump can be passed blindly into the airways through an endotracheal tube. Excessive suction may result in lung lobe collapse. Therefore low-pressure, intermittent suction is used, followed by expansion of the lungs with several positive-pressure ventilations using an anesthetic or Ambu bag. Therapeutic airway lavage is contraindicated.

Animals in severe respiratory distress should be treated with fluid therapy, oxygen supplementation, bronchodilators, and possibly glucocorticoids. Fluids are administered intravenously at high rates to treat shock (see Chapter 28) and should be continued after initial stabilization of the

animal's condition to maintain systemic hydration, which is necessary to maximize the effectiveness of airway clearance mechanisms. However, overhydration must be avoided because of a tendency for pulmonary edema.

Oxygen supplementation (see Chapter 25) is initiated immediately in compromised animals. Positive-pressure ventilation is required for animals in severe respiratory distress that is unresponsive to oxygen therapy.

Bronchodilators can be administered to decrease bronchospasms and ventilatory muscle fatigue. They are most likely to be effective in cats. Bronchodilators can worsen $\dot{V}/\dot{Q}$ mismatching, exacerbating hypoxemia. They are discontinued if no improvement is seen, or if clinical signs appear to worsen after their administration.

The antiinflammatory effects of glucocorticoids can be beneficial, but glucocorticoids can interfere with normal host defense mechanisms in tissues that have already been severely compromised. This author reserves the use of glucocorticoids for patients that have severe respiratory compromise and a deteriorating clinical picture despite appropriate antibiotic therapy and supportive care. Low (antiinflammatory) doses of short-acting preparations are administered for up to 48 hours.

Animals with a large airway obstruction can benefit from bronchoscopy and foreign body removal. However, routine bronchoscopy is not indicated because of the risk associated with the general anesthesia needed during the procedure and the infrequency of large airway obstructions.

Antibiotics are administered immediately in animals that are presented in severe distress or with overt systemic signs of sepsis. Selected antibiotics should have a broad spectrum of activity and be administered intravenously. Such drugs include the combination of a fluoroquinolone or an aminoglycoside with ampicillin with sulbactam (see the earlier section on bacterial pneumonia).

A tracheal wash is ideally performed in stable patients before antibiotics are initiated, to document the presence of infection and to obtain antibiotic sensitivity data. This information is particularly valuable because prolonged treatment is often needed, and also because research in human medicine has amply demonstrated that resistant secondary infection can develop after aspiration in patients given antibiotics initially or on an empirical basis. As discussed for bacterial pneumonia, the high incidence of gram-negative and mixed infections makes assumptions regarding antibiotic sensitivity prone to error. Pending results of culture, it is reasonable to initiate treatment in stable patients with penicillin with a β-lactamase inhibitor (e.g., amoxicillin-clavulanate or ampicillin with sulbactam). Because infection can occur as a later complication in these patients, frequent monitoring with physical examination, CBC, and thoracic radiographs is necessary to detect any deterioration consistent with secondary infection. Tracheal wash is repeated if infection is suspected.

Further therapeutic and monitoring considerations are discussed in the section on bacterial pneumonia. Underlying diseases are treated to prevent recurrence.

Prognosis

Animals with mild signs of disease and a correctable underlying problem have an excellent prognosis. The prognosis is worse for animals with more severe disease or uncorrectable underlying problems.

EOSINOPHILIC LUNG DISEASE (EOSINOPHILIC BRONCHOPNEUMOPATHY)

Eosinophilic lung disease, or eosinophilic bronchopneumopathy, is a broad term that describes inflammatory lung disease in which the predominant infiltrating cell is the eosinophil. Eosinophilic inflammation can involve primarily the airways or the interstitium. Allergic bronchitis and idiopathic bronchitis are by far the most common eosinophilic lung diseases seen in cats and are discussed in Chapter 21. Interstitial infiltration, with or without concurrent bronchitis, was historically referred to as *pulmonary infiltrates with eosinophils* (PIE) and is typically seen in dogs. ***Eosinophilic pulmonary granulomatosis*** is a severe type of eosinophilic lung disease of dogs and characterized by the development of nodules and often hilar lymphadenopathy. It must be differentiated from mycotic infection and neoplasia. These names are descriptive only and likely encompass a variety of hypersensitivity disorders of the lung.

Because eosinophilic inflammation is a hypersensitivity response, an underlying antigen source is actively pursued in affected animals. Considerations include heartworms, pulmonary parasites, drugs, and inhaled allergens. Food allergy could play a role in these disorders, but this association has not been explored. Potential allergens are discussed further in the section on allergic bronchitis in Chapter 21. Bacteria, fungi, and neoplasia can also induce a hypersensitivity response, but this response often is not the predominant finding. In many cases no underlying disease can be found. Eosinophilic pulmonary granulomatosis is strongly associated with heartworm disease.

Clinical Features

Eosinophilic lung diseases are seen in young and older dogs. Affected dogs are evaluated because of progressive respiratory signs such as cough, increased respiratory efforts, and exercise intolerance. Systemic signs such as anorexia and weight loss are usually mild. Lung sounds are often normal, although crackles or expiratory wheezes are possible.

Diagnosis

The finding of peripheral eosinophilia is not present in all animals with the eosinophilic lung disease, nor is it a specific finding. A diffuse interstitial or bronchointerstitial pattern is seen on thoracic radiographs. Eosinophilic pulmonary granulomatosis results in the formation of nodules, usually with indistinct borders. These nodules can be quite large, and hilar lymphadenopathy may also be present. A patchy

alveolar opacity and consolidation of the lung lobes can occur as well.

Pulmonary specimens must be examined to establish a diagnosis. In some cases, particularly those with bronchial involvement, evidence of eosinophilic inflammation may be found in tracheal wash fluid. More aggressive techniques for collecting pulmonary specimens, such as bronchoalveolar lavage, lung aspiration, or lung biopsy, are required to identify the eosinophilic response in other cases. Other inflammatory cell populations are frequently present in lesser numbers in such specimens.

Potential antigen sources should be considered, and pulmonary specimens should be carefully examined for the presence of infectious agents and features of malignancy. Heartworm tests and fecal examinations for pulmonary parasites (including sedimentation, Baermann and flotation-concentrating techniques) are indicated in all cases.

Treatment

Any primary disease identified during the diagnostic evaluation of these animals is treated directly. Eliminating the source of the antigen that may be triggering the excessive immune response may result in a cure.

Antiinflammatory therapy with glucocorticoids is indicated for dogs in which an antigen source cannot be identified, and for dogs with heartworm disease if the eosinophilic inflammation is causing respiratory compromise (see Chapter 10). Dogs with eosinophilic granulomatosis often require more aggressive immunosuppressive therapy.

Dogs are typically treated with glucocorticoids, such as prednisone, at an initial dosage of 1 to 2 mg/kg orally every 12 hours. Clinical signs and thoracic radiographs are used to monitor the animal's response to therapy, and initially these should be assessed every 1 to 2 weeks. Once the clinical signs have completely resolved, the dosage of glucocorticoids is decreased to the lowest effective one. If signs have remained in remission for 3 months, discontinuation of therapy can be attempted. If signs are exacerbated by glucocorticoid therapy, immediate reevaluation to search for underlying infectious agents is indicated.

Inhaled steroids administered from a metered-dose inhaler using a spacer and mask may be effective in controlling signs, minimizing the systemic effects of oral steroids. This route of administration is most likely to be effective in patients with predominantly bronchial involvement or to maintain remission of signs after initial treatment with oral steroids. The use of inhaled steroids is described in detail with treatment for feline bronchitis (idiopathic) in Chapter 21.

Dogs with large nodular lesions (eosinophilic granulomatosis) should be treated with a combination of glucocorticoids and a cytotoxic agent. Prednisone is administered to these animals at a dosage of 1 mg/kg orally every 12 hours, in combination with cyclophosphamide at a dosage of 50 mg/m^2 orally every 48 hours. Clinical signs and thoracic radiographs are evaluated every 1 to 2 weeks until remission is achieved. CBCs are also done every 1 to 2 weeks to detect excessive bone marrow suppression resulting from the cyclophosphamide. Attempts to discontinue therapy can be made after several months of remission. It may be necessary to discontinue the cyclophosphamide earlier than this because long-term treatment is associated with sterile hemorrhagic cystitis. (See Chapter 77 for further discussion of the adverse effects of cyclophosphamide therapy.) The effectiveness of other immunosuppressive drugs, such as cyclosporine, has not been reported.

Prognosis

A wide spectrum of disease is seen in terms of both the severity of signs and the underlying causes. The prognosis is generally fair to good. However, the prognosis is guarded in dogs with severe eosinophilic pulmonary granulomatosis.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

The term *idiopathic interstitial pneumonia* generally denotes inflammatory infiltration and/or fibrosis of the lungs involving primarily the alveolar septa. Small airways, alveoli, and the pulmonary vasculature may also be affected. The alveolar septa include alveolar epithelium, epithelial basal lamina, capillary endothelial basal lamina, and capillary endothelium. Other cells include fibroblasts and alveolar macrophages. For a diagnosis of idiopathic disease, the known etiologies of interstitial lung disease must be ruled out as completely as possible. Causes of interstitial lung disease are numerous and include many infectious agents and some toxins and neoplasia.

Idiopathic pulmonary fibrosis is the best described idiopathic interstitial pneumonia in dogs and cats. Some of the eosinophilic lung diseases (not including allergic or idiopathic feline bronchitis) may also be part of this group of diseases. Other inflammatory lung diseases of the interstitium in which a cause cannot be identified are occasionally seen in dogs and cats. The lesions may represent a form of vasculitis, a component of systemic lupus erythematosus, immune complex disease, or some other hypersensitivity response. These diseases are rare, however, and are not well documented. A lung biopsy must be performed for a definitive diagnosis to be made. A clinical diagnosis is made only after extensive testing has been done to rule out more common causes of lung disease, particularly infectious agents and neoplasia, and after a prolonged positive response to immunosuppressive therapy.

IDIOPATHIC PULMONARY FIBROSIS

In people idiopathic pulmonary fibrosis is the clinical diagnosis that is defined by the histopathologic diagnosis of *usual interstitial pneumonia*. However, the histopathologic pattern of usual interstitial pneumonia can be seen as a result of other diseases; according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association consensus statement (Raghu et al., 2011), the diagnosis of idiopathic pulmonary

fibrosis also requires (1) the exclusion of other known causes of interstitial lung diseases including domestic and occupational environmental exposures, connective tissue disease, and drug toxicity; (2) characteristic pattern on high resolution computed tomography (HRCT) in patients without surgical lung biopsy abnormalities; and (3) specific combinations of HRCT and surgical lung biopsy lesions in patients with biopsy. In veterinary medicine, the latter criterion may be difficult to apply, but attention should be paid to the other criteria.

Characteristic lesions that result in the histopathologic pattern of usual interstitial pneumonia are as follows: fibrosis, areas of fibroblast proliferation, metaplasia of the alveolar epithelium, and mild to moderate inflammation. Honeycomb change may occur as a result of enlarged airspaces lined by abnormal alveolar epithelium. The lungs are heterogeneously affected, with areas of normal lung intermixed with abnormal regions. The abnormal regions are often subpleural. A defect in wound healing has been hypothesized as the cause.

Idiopathic pulmonary fibrosis has been described in cats on the basis of histologic lesions that are quite similar to those in people (Cohn et al., 2004; Williams et al., 2006; Fig. 22.3). Unlike the disease that affects people and cats, the disease in dogs has been associated with the primary lesion of collagen deposition in the alveolar septa with no fibroblastic foci (Norris et al., 2005).

Neoplasia can occur concurrently with idiopathic pulmonary fibrosis in people and was reported in 6 of 23 cats (Cohn et al., 2004). The lesions of pulmonary fibrosis can also be misinterpreted as carcinoma, and 4 of 23 cats considered to have pulmonary fibrosis were initially given a pathologic diagnosis of carcinoma.

Clinical Features

A breed predisposition is seen in dogs with pulmonary fibrosis. West Highland White Terriers are most frequently reported, with fewer cases documented among Staffordshire Bull Terriers, Jack Russell Terriers, Cairn Terriers, and Schipperkes. Both dogs and cats tend to be middle-aged or older at the time of presentation, although characteristic signs have been found in patients as young as 2 years of age.

Signs are most often slowly progressive over months. In cats the duration of signs may be shorter, with 6 of 23 cats having shown signs for only 2 days to 2 weeks (Cohn et al., 2004). Respiratory compromise is the most prominent clinical sign of pulmonary fibrosis, manifested as exercise intolerance and/or rapid, labored breathing. Cough often occurs, but if it is the predominant sign, higher consideration should be given to a diagnosis of bronchitis. Syncope may occur in dogs.

Crackles are the hallmark auscultatory finding in dogs and are noted in some cats. Wheezes are heard in approximately half of dogs and in some cats. The abnormal breathing pattern is typically tachypnea with relatively effortless expiration.

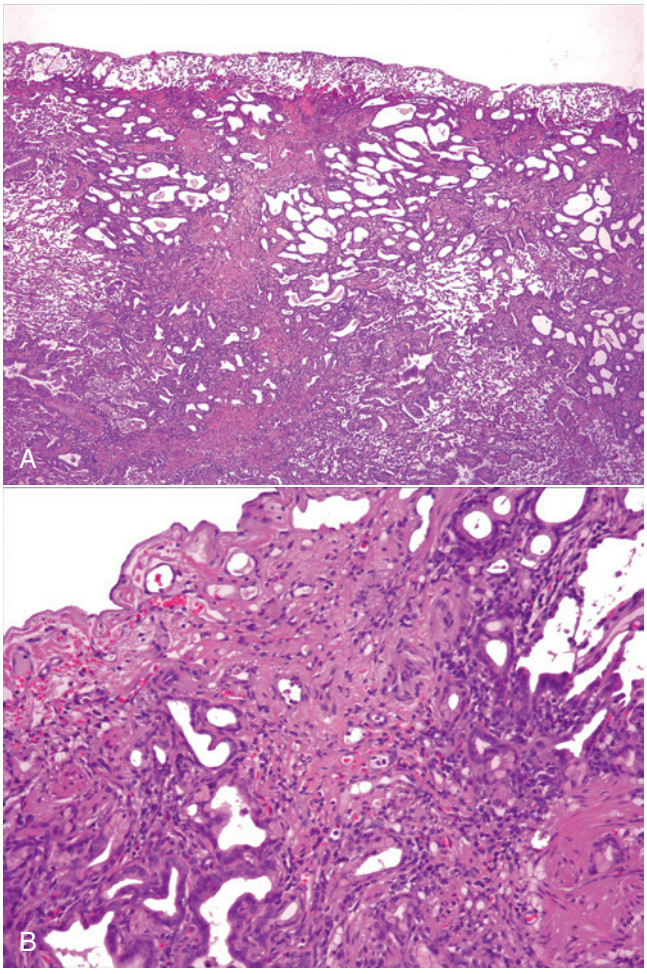


FIG 22.3
Photomicrographs of a lung biopsy from a cat with idiopathic pulmonary fibrosis. At lower power **(A),** distortion and obliteration of the normal pulmonary architecture are evident because of replacement of the parenchyma with disorganized bands of fibrous tissue and scattered mononuclear inflammatory cells. Few recognizable alveoli can be seen in this section. The alveolar septae are thickened, and metaplasia of the alveolar epithelium is present. At higher power **(B),** subpleural alveoli show marked distortion with clear septal fibrosis and type 2 epithelial hyperplasia. Although normal areas of the lung are not shown, the disease is characterized by heterogeneity of lesions within the lung. (Photomicrographs courtesy Stuart Hunter.)

Diagnosis

Thoracic radiographs of dogs with pulmonary fibrosis typically show a diffuse interstitial pattern. The abnormal densities generally must be moderate to severe to be distinguished from age-related change. A bronchial pattern is often noted concurrently, contributing to the overlap in signs between pulmonary fibrosis and chronic bronchitis. Evidence of pulmonary hypertension may be seen (see later in this chapter). Radiographs of cats with this disease may show diffuse or patchy infiltrate (Fig. 22.4). Patterns may be interstitial,



FIG 22.4
Lateral thoracic radiograph from a cat with idiopathic pulmonary fibrosis showing a diffuse interstitial pattern with patchy areas of alveolar disease in the caudal lung lobes. Pericardial and mediastinal fat is also seen. Radiographic abnormalities in cats with fibrosis are quite variable, including the range of interstitial, bronchial, alveolar, or mixed patterns.

bronchial, alveolar, or mixed but are often quite severe. Bronchiectasis, caused by traction on the airways, may be noted in either species with advanced disease.

Results of the CBC, serum biochemistry panel, and urinalysis are generally unremarkable. Polycythemia may be present secondary to chronic hypoxemia. Screening tests to identify other causes of interstitial lung disease include fecal examinations for parasites, heartworm tests, and appropriate infectious disease serology.

Airway specimens should be collected in sufficiently stable patients, primarily to assist in the identification of other causes of lung disease. Be aware that patients may be more compromised than they appear to be based on history and physical examination. Mild to moderate inflammation may be seen in patients with pulmonary fibrosis, but this is a nonspecific finding. Bronchoscopy may be useful in some patients for identifying other causes of lung disease, such as chronic bronchitis.

Typical lesions identified by computed tomography are often used in making a presumptive diagnosis of idiopathic pulmonary fibrosis in people. Similar lesions can be seen in some dogs with the disease (Johnson et al., 2005; Heikkila et al., 2011). Results of computed tomography in cats have not been reported.

Although not yet commercially available, measurement of serum endothlin-1 (ET-1) shows promise as a diagnostic test for idiopathic pulmonary fibrosis in dogs. In a study that included dogs with idiopathic pulmonary fibrosis, chronic bronchitis, or eosinophilic bronchopneumopathy, and healthy Beagle dogs, serum ET-1 concentrations greater than 1.8 pg/mL had a sensitivity of 100% and a specificity of 81% for the diagnosis of idiopathic pulmonary fibrosis (Krafft et al., 2011).

A definitive diagnosis of pulmonary fibrosis requires a lung biopsy obtained by thoracotomy or thoracoscopy. The expense and invasiveness of biopsy preclude its use in some patients. Furthermore, the lack of specific treatment recommendations for pulmonary fibrosis is a deterrent. However, biopsy should be considered in patients that are stable and whose owners have sufficient resources. The less invasive tests cannot completely rule out the existence of a different, directly treatable disease (e.g., atypical bacterial infection, fungal disease, parasitism).

Treatment

Idiopathic pulmonary fibrosis remains a relentless progressive disease even in people (Raghu and Richeldi, 2017). Historically, most individuals were treated with prednisone at low dosages and with azathioprine, as corticosteroids alone were not considered to be effective. Many other drugs, including colchicine, penicillamine, and *N*-acetylcysteine, have not been proven to be effective. A recent placebo-controlled, prospective study carried out by the Idiopathic Pulmonary Fibrosis Clinical Research Network (2012) found that risks of death and hospitalization were actually increased in patients receiving the combination of prednisone, azathioprine, and *N*-acetylcysteine.

Two drugs have been recently approved for the treatment of idiopathic pulmonary fibrosis in people. Nintedanib is an antifibrotic drug, and perfenidone has both antifibrotic and antiinflammatory properties. Their safety and efficacy in treating IPF in dogs or cats is not known. Further, these drugs are prescribed for patients with mild to moderate disease to slow progression of signs and delay the need for lung transplantation.

Most dogs and cats have been treated with corticosteroids and bronchodilators. Theophylline derivatives have the theoretical potential to provide some benefit through potentiation of steroid activity. It is likely that any beneficial effect from this combination is actually due to the presence of a steroid-responsive interstitial lung disease (i.e., not idiopathic pulmonary fibrosis) or control of concurrent bronchitis. Animals with signs of pulmonary hypertension are treated for this complication, as described later in this chapter. Omeprazole may be beneficial, particularly for patients receiving steroids. In people, gastroesophageal reflux is common with idiopathic pulmonary fibrosis, and microaspiration is speculated to play a role in the pathogenesis of the disease. Hypoxemia and corticosteroid administration can make patients more prone to adverse gastrointestinal effects (Heikkila-Laurila and Rajamaki, 2014).

Prognosis

The prognosis for idiopathic pulmonary fibrosis in dogs and cats is poor, with relentless progression of disease expected. Nevertheless, individual patients, particularly dogs, can survive for longer than a year. The mean survival time in dogs in one study was 18 months from the onset of signs, with survival up to 3 years (Corcoran et al., 1999). The prognosis in cats is poorer. Of 23 cats, 14 died or were euthanized

within weeks of onset of signs, and only 7 of 23 survived longer than 1 year (Cohn et al., 2004).

PULMONARY NEOPLASIA

Primary pulmonary tumors, metastatic neoplasia, and multicentric neoplasia can involve the lungs. Most primary pulmonary tumors are malignant. Carcinomas predominate and include adenocarcinoma, bronchoalveolar carcinoma, and squamous cell carcinoma. Sarcomas and benign tumors are much less common. Small cell carcinoma, or oat cell tumor, which occurs frequently in people, is rare in dogs and cats.

The lungs are a common site for the metastasis of malignant neoplasia from other sites in the body and even from primary pulmonary tumors. Neoplastic cells can be carried in the bloodstream and trapped in the lungs, where low blood flow and an extensive capillary network are present. Lymphatic spread or local invasion can also occur.

Multicentric tumors can involve the lungs. Such tumors include lymphoma, malignant histiocytosis, and mastocytoma.

Multiple tumors of different origins can occur in the same animal. In other words, the presence of a neoplasm in one site of the body does not necessarily imply that the same tumor is also present in the lungs.

Clinical Features

Neoplasms are most common in older animals but also occur in young adult animals. Tumors involving the lungs can produce a wide spectrum of clinical signs. These signs are usually chronic and slowly progressive, but peracute manifestations such as pneumothorax or hemorrhage can occur.

Most signs reflect respiratory tract involvement. Infiltration of the lung by the tumor can cause interference with oxygenation, leading to increased respiratory effort and exercise intolerance. Mass lesions can compress airways, provoking cough and obstructing ventilation. Erosion through vessels can result in pulmonary hemorrhage. Blood loss can be sudden, resulting in acute hypovolemia and anemia, in addition to respiratory compromise. Edema, nonseptic inflammation, or bacterial infection can occur secondary to the tumor. Erosion through the airways can result in pneumothorax. Pleural effusion of nearly any character can form. In rare cases, the caudal or cranial venae cavae are obstructed, resulting in the development of ascites or head and neck edema, respectively.

Nonspecific signs in dogs and cats with pulmonary neoplasms include weight loss, anorexia, depression, and fever. Gastrointestinal signs may be the primary complaint. Vomiting and regurgitation may be the presenting signs in cats in particular. Lameness may be the presenting sign in patients with hypertrophic osteopathy secondary to thoracic mass lesions and in cats with metastasis of carcinoma to their digits.

Some animals with lung neoplasia have no clinical signs at all, and the tumor is discovered as an incidental finding on thoracic radiographs or at postmortem examination. Animals with metastatic or multicentric lung neoplasia may have signs of tumor involvement in another organ.

Lung sounds may be normal, decreased, or increased. They are decreased over all lung fields in animals with pneumothorax or pleural effusion. Localized decreased or increased lung sounds can be heard over regions that are consolidated. In a few patients, crackles and wheezes can be auscultated. Evidence of other organ involvement or hypertrophic osteopathy may be noted.

Diagnosis

Neoplasia is definitively diagnosed through the histologic or cytologic identification of criteria of malignancy in populations of cells in pulmonary specimens (Fig. 22.5). Thoracic radiographs are commonly evaluated initially, and findings can support a tentative diagnosis of neoplasia. Radiographs can be used to identify the location of disease; this information helps the clinician select the most appropriate technique for specimen collection.

Good-quality radiographs, including both left and right lateral projections, should be evaluated. Primary pulmonary tumors can cause localized mass lesions (see Figs. 20.7 and 20.10) or the consolidation of an entire lobe (see Fig. 20.9, *A*). Tumor margins are often distinct but can be ill defined as a result of associated inflammation and edema. Cavitation may be evident. Metastatic or multicentric disease results in a diffuse reticular, nodular, or reticulonodular interstitial

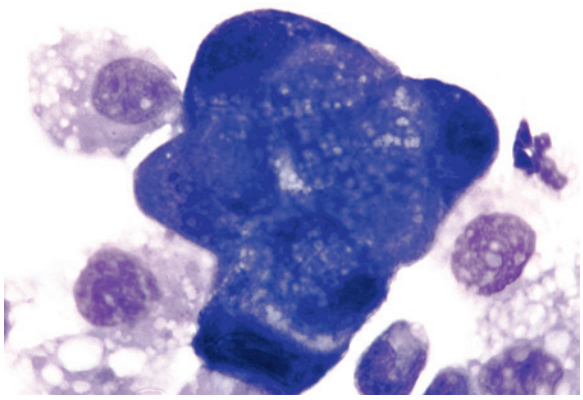


FIG 22.5
Bronchoalveolar lavage fluid from the dog whose lateral thoracic radiograph showing a severe, unstructured interstitial pattern is depicted in Fig. 20.8. Many clumps of deeply staining epithelial cells showing marked criteria of malignancy were seen. One such clump is shown here. A diagnosis of carcinoma was made. Note that a cytologic diagnosis of carcinoma should not be made if concurrent inflammation is noted. The surrounding lighter-staining cells are alveolar macrophages—the normal predominant cell type in bronchoalveolar lavage fluid.

pattern (see Fig. 20.8). In cats primary lung tumors often have a diffuse distribution by the time of presentation, and the radiographic pattern may be suggestive of bronchitis, edema, or pneumonia.

Pulmonary neoplasia is occasionally associated with hemorrhage, edema, inflammation, infection, or airway occlusion that can contribute to the formation of alveolar patterns and consolidation. Lymphadenopathy, pleural effusion, or pneumothorax can also be identified by radiography in some patients with neoplasia.

Non-neoplastic disease, including fungal infection, lung parasites, aspiration of mineral oil, eosinophilic granulomatosis, atypical bacterial infection, and inactive lesions from previous disease, can produce similar radiographic abnormalities. Pulmonary specimens must be evaluated to establish a diagnosis.

Tracheal wash fluid cytology rarely results in a definitive diagnosis. It is generally necessary to evaluate lung aspirates, bronchoalveolar lavage fluid, or lung biopsy specimens. Mass lesions located adjacent to the body wall are readily sampled by transthoracic lung aspiration. Accuracy and safety are improved with ultrasound guidance. Seeding of tumor as a result of aspiration of a pulmonary adenocarcinoma has been reported (Warren-Smith et al., 2011). This complication appears to be rare, but if the identified lesion will likely require surgical excision regardless of cause, the argument can be made to proceed directly to surgery.

It may be appropriate to delay the collection of pulmonary specimens in asymptomatic animals with multifocal disease or in animals with significant unrelated problems. Rather, radiographs are obtained again in 4 to 6 weeks to document the progression of lesions. Such delay is never recommended in dogs or cats with potentially resectable disease.

The confirmation of malignant neoplasia in other organs in conjunction with typical thoracic radiographic abnormalities is often adequate for a presumptive diagnosis of pulmonary metastases. Overinterpretation of subtle radiographic lesions should be avoided. Conversely, the absence of radiographic changes does not eliminate the possibility of metastatic disease.

Evaluation of the thorax by computed tomography should be considered in patients with known or suspected neoplasia. Computed tomography is much more sensitive than thoracic radiography in the detection of metastatic disease (see Chapter 20). In patients with localized disease for whom surgical excision is being planned, computed tomography provides more detailed anatomic information regarding the involvement of adjacent structures and is more accurate in identifying involvement of tracheobronchial lymph nodes, compared with radiography.

Treatment

Solitary pulmonary tumors are treated by surgical resection. To obtain clear margins, usually the entire lung lobe that is involved must be excised. Lymph node biopsy specimens, as well as biopsy specimens from any grossly abnormal lung, are obtained for histologic analysis.

In animals with a large mass lesion, respiratory signs may abate after excision, even if metastatic lesions are present throughout the lungs. If the lesions cannot be removed surgically, chemotherapy can be attempted (see Chapter 76). No protocol is uniformly effective for the treatment of primary lung tumors.

Metastatic neoplasms of the lungs are treated with chemotherapy. In most animals the initial protocol is determined by the expected sensitivity of the primary tumor. Unfortunately, metastatic neoplasms do not always have the same response to specific agents as the primary tumor.

Multicentric tumors are treated with standard chemotherapeutic protocols, regardless of whether the lungs are involved. Multicentric tumors are discussed in Chapter 78.

Prognosis

The prognosis for animals with benign neoplasms is excellent, but these tumors are uncommon. The prognosis for animals with malignant neoplasia is potentially related to several variables, which include tumor histology, the presence of regional lymph node involvement, and the presence of clinical signs. Survival times of several years are possible after surgical excision. Ogilvie et al. (1989) reported that, of 76 dogs with primary pulmonary adenocarcinoma, surgical excision resulted in remission (i.e., elimination of all macroscopic evidence of tumor) in 55 dogs. The median survival time of dogs that went into remission was 330 days, whereas the survival time in dogs that did not achieve remission was 28 days. At the completion of the study, 10 dogs remained alive. McNiel et al. (1997) found that the histologic score of the tumor, the presence of clinical signs, and regional lymph node metastases were significantly associated with the prognosis in 67 dogs with primary lung tumors. Median survival times for dogs with and without clinical signs were 240 and 545 days, respectively. Median survival times for dogs with and without lymph node involvement were 26 and 452 days, respectively. Median survival time for dogs with papillary carcinoma was 495 days, compared with 44 days for dogs with other histologic tumor types. Survival times ranged from 0 to 1437 days. A report of 21 cats with primary lung tumor described a median survival time of 115 days after surgery (Hahn et al., 1998). Cats with moderately differentiated tumors had a median survival time of 698 days (range, 13-1526 days), whereas cats with poorly differentiated tumors had a median survival time of 75 days (range, 13-634 days). The prognosis for animals with multicentric neoplasms is not known to depend on the presence or absence of pulmonary involvement.

PULMONARY HYPERTENSION

Etiology

Pulmonary hypertension is diagnosed when pulmonary systolic pressure exceeds 30 mm Hg. The diagnosis is most accurately made by direct pressure measurements obtained via cardiac catheterization—a procedure rarely performed in

dogs or cats. However, an estimation of pulmonary artery pressure can be made by Doppler echocardiography in patients with pulmonary or tricuspid valvular insufficiency (see Chapter 6). The widespread availability of this technology has increased awareness of the existence of pulmonary hypertension in veterinary medicine. Causes of pulmonary hypertension include obstruction to venous drainage as can occur with left-sided heart disease (see Chapter 6), increased pulmonary blood flow caused by congenital heart lesions (see Chapter 5), and increased pulmonary vascular resistance. When no underlying disease can be identified to explain the hypertension, a clinical diagnosis of primary (idiopathic) pulmonary hypertension is made.

Pulmonary vascular resistance can be increased as a result of pulmonary thromboembolism (PTE; see later) or heartworm disease (see Chapter 10). Vascular resistance can also be increased as a complication of chronic pulmonary parenchymal disease, such as canine chronic bronchitis (see Chapter 21) and idiopathic pulmonary fibrosis (see prior discussion). An overly simplistic explanation for increased vascular resistance as a complication of pulmonary disease is the adaptive response of the lung to improve the matching of ventilation and perfusion ($\dot{V}/\dot{Q}$) through hypoxic vasoconstriction. However, other factors are thought to contribute significantly to the development of hypertension associated with pulmonary disease, including endothelial dysfunction, vascular remodeling, and thrombosis in situ.

Clinical Features and Diagnosis

Pulmonary hypertension is diagnosed more commonly in dogs than in cats. Clinical signs include those of progressive hypoxemia and can be difficult to distinguish from any underlying cardiac or pulmonary disease. Signs include exercise intolerance, weakness, syncope, and respiratory distress. Physical examination may reveal a loud split second heart sound (see Chapter 6). Radiographic evidence of pulmonary hypertension may be present in severely affected patients and includes pulmonary artery enlargement and right-sided cardiomegaly. Radiographs are evaluated closely for underlying cardiopulmonary disease. The diagnosis of pulmonary hypertension is most often made through Doppler echocardiography. Use of this modality to estimate pulmonary artery pressure requires the presence of pulmonary or tricuspid regurgitation and a skilled echocardiographer.

Treatment

Pulmonary hypertension is best treated by identifying and aggressively managing any underlying disease process. In people, pulmonary hypertension associated with chronic bronchitis is usually mild and is not directly treated. Long-term oxygen therapy is often provided, but this treatment is rarely practical for veterinary patients.

Treatment targeted specifically to address the pulmonary hypertension itself is indicated for patients showing clinical signs of pulmonary hypertension when no underlying disease is identified, or when management of underlying disease fails to improve pulmonary arterial pressures or clinical signs. The drug most commonly used in dogs is sildenafil citrate (Viagra, Pfizer), a phosphodiesterase V inhibitor that causes vasodilation through a nitric oxide pathway. A dosage of 1 mg/kg orally every 8 hours was shown in a cross-over study of dogs with pulmonary hypertension to decrease systolic pulmonary arterial pressure and result in increased exercise capacity and quality of life compared with placebo (Brown et al., 2010). However, a retrospective study documented improvement in quality of life but not pressure measurements (Kellum and Stepien, 2007). A range of dosages has been reported from 0.5 to 3.0 mg/kg every 8 to 12 hours. Monitoring for both beneficial and adverse effects is important, with adjustments to dosage as indicated by response.

Pimobendan, a phosphodiesterase III inhibitor, results in decreased pulmonary artery pressure in dogs with pulmonary hypertension associated with chronic valvular heart disease (Atkinson et al., 2009). In a retrospective study, pimobendan was not shown to improve survival times in dogs with severe pulmonary hypertension due to lung disease when combined with sildenafil, compared with treatment with sildenafil alone (Murphy et al., 2017). Pimobendan is discussed further in Chapter 3.

Long-term anticoagulation with warfarin or heparin is often prescribed for people with primary pulmonary hypertension to prevent small thrombi formation. Its potential benefits for veterinary patients are not known.

Prognosis

The prognosis for pulmonary hypertension is presumably influenced by the severity of hypertension, the presence of clinical signs, and any underlying disease.

PULMONARY THROMBOEMBOLISM (PTE)

The extensive low-pressure vascular system of the lungs is a common site for emboli to lodge. It is the first vascular bed through which thrombi from the systemic venous network or the right ventricle pass. Respiratory signs can be profound and even fatal in dogs and cats. Hemorrhage, edema, and bronchoconstriction, in addition to decreased blood flow, can contribute to the respiratory compromise. The attendant increased vascular resistance secondary to physical obstruction by emboli and vasoconstriction results in pulmonary hypertension, which can ultimately lead to the development of right-sided heart failure.

Microthrombi are thought to play a role in pulmonary hypertension, as discussed in the previous section. However, most patients who present primarily with signs of thromboembolism have a predisposing disease in organs other than the lungs, and a search for the underlying cause of clot formation is therefore essential. Abnormalities predisposing to clot formation include venous stasis, turbulent blood flow, endothelial damage, and hypercoagulation. In addition to emboli originating from thrombi, emboli can consist of

bacteria, parasites (particularly heartworms), neoplasia, or fat. Conditions that have been associated with the development of pulmonary emboli, and the chapters where they are discussed, are listed in Box 22.3.

Clinical Features

In many instances, the predominant presenting sign of animals with PTE is peracute respiratory distress. Cardiovascular shock and sudden death can occur. As awareness of PTE has increased, the diagnosis is being made with greater frequency in patients with milder and more chronic signs of tachypnea or increased respiratory efforts. Historical or physical examination findings related to a potential underlying disease increase the index of suspicion for a diagnosis of PTE. A loud or split second heart sound may be heard on auscultation and is indicative of pulmonary hypertension. Crackles or wheezes are heard in occasional cases.

Diagnosis

Routine diagnostic methods do not provide information that can be used to make a definitive diagnosis of PTE. A high index of suspicion must be maintained because this disease is frequently overlooked. The diagnosis is suspected on the basis of clinical signs, thoracic radiography, arterial blood gas analysis, echocardiography, and clinicopathologic data. A definitive diagnosis requires contrast-enhanced computed tomography, pulmonary angiography, selective angiography, or nuclear perfusion scanning, but contrast-enhanced computed tomography is the routine modality for diagnosis.

PTE is suspected in dogs and cats with severe dyspnea of acute onset, particularly if minimal or no radiographic signs of respiratory disease are evident. In many cases of PTE, the lungs appear normal on thoracic radiographs in spite of severe lower respiratory tract signs. When radiographic lesions occur, the caudal lobes are most often involved. Blunted pulmonary arteries, in some cases ending with focal or wedge-shaped areas of interstitial or alveolar opacity resulting from extravasation of blood or edema, may be present. Areas of lung without a blood supply can appear hyperlucent. Diffuse interstitial and alveolar opacities and right-sided heart enlargement can occur. Pleural effusion is present in some cases and is usually mild. Echocardiography may show secondary changes (e.g., right ventricular enlargement, increased pulmonary artery pressures), underlying disease (e.g., heartworm disease, primary cardiac disease), or residual thrombi.

Arterial blood gas analysis can show mild or profound hypoxemia. Tachypnea leads to hypocapnia, except in severe cases, and the abnormal alveolar-arterial oxygen gradient (*A-a* gradient) supports the presence of a ventilation/perfusion disorder (see Chapter 20). A poor response to oxygen supplementation is supportive of a diagnosis of PTE.

Clinicopathologic evidence of a disease known to predispose animals to thromboemboli further heightens suspicion for this disorder. Unfortunately, routine measurements of clotting parameters (e.g., prothrombin time, partial thromboplastin time) are not helpful in making the diagnosis or even in identifying at-risk patients. *Thromboelastography* (TEG) is a diagnostic tool that results in a graph, indicating rate of clot development, clot strength, and subsequent dissolution. Interest has been growing for the use of this technique and related techniques in veterinary critical care settings. The test cannot be used as a diagnostic tool for PTE itself but may prove useful in identifying at-risk patients (those with measured hypercoagulability), directing treatment to affected arms of coagulation, and monitoring the effect of specific treatment on measured coagulability.

In people, measurement of circulating D-dimers (a degradation product of cross-linked fibrin) is used as an indicator of the likelihood of PTE. It is not considered a specific test, so its primary value has been in the elimination of PTE from the differential diagnoses. However, even a negative result can be misleading in certain disease states and in the presence of small subsegmental emboli.

Measurement of D-dimer concentrations is available for dogs through commercial laboratories. A study of 30 healthy dogs, 67 clinically ill dogs without evidence of thromboembolic disease, and 20 dogs with thromboembolic disease provides some guidance for interpretation of results (Nelson et al., 2003). A D-dimer concentration > 500 ng/mL was able to predict the diagnosis of thromboembolic disease with 100% sensitivity but with a specificity of only 70% (i.e., having 30% false-positive results). A D-dimer concentration > 1000 ng/mL decreased the sensitivity of the result to 94% but increased the specificity of the result to 80%. A D-dimer concentration > 2000 ng/mL decreased the sensitivity of the result to 36% but increased the specificity to 98.5%. Thus the degree of elevation in D-dimer concentration must be considered in conjunction with other clinical information.

Computed tomography pulmonary angiography is commonly used in people to confirm a diagnosis of PTE and is being used routinely for the diagnosis in veterinary

BOX 22.3

Abnormalities Potentially Associated With Pulmonary Thromboembolism*

Surgery
Severe trauma
Hyperadrenocorticism, Chapter 50
Immune-mediated hemolytic anemia, Chapter 82
Hyperlipidemia
Glomerulopathies
Dirofilariasis and adulticide therapy, Chapter 10
Cardiomyopathy, Chapters 7 and 8
Endocarditis, Chapter 6
Pancreatitis, Chapter 37
Disseminated intravascular coagulation, Chapter 87
Hyperviscosity syndromes
Neoplasia

*Discussions of these abnormalities can be found in the given chapters.

medicine. The diagnosis can never be ruled out on the basis of computed tomography because multiple small arteries, rather than one or more large vessels, may be obstructed. Further, changes may be apparent for only a few days after the event. One limitation of thoracic computed tomography in dogs and especially in cats is patient size. In addition, veterinary patients will not hold their breath. Patients must be anesthetized and positive-pressure ventilation applied during scanning for maximal resolution. A high-quality computed tomography scanner and an experienced radiologist are required for accurate interpretation.

Selective angiography is the historic gold standard for the diagnosis of PTE. Sudden pruning of pulmonary arteries or intravascular filling defects and extravasation of dye are characteristic findings. Nuclear scans can provide evidence of PTE with minimal risk to the animal. Unfortunately, this technology has limited availability.

Pulmonary specimens for histopathologic evaluation are rarely collected, except at necropsy. However, evidence of embolism is not always found at necropsy because clots may dissolve rapidly after death. Therefore such tissue should be collected and preserved immediately after death. The extensive vascular network makes it impossible to evaluate all possible sites of embolism, and the characteristic lesions may also be missed.

Treatment

All animals with suspected PTE should be given aggressive supportive care and treatment for any underlying, predisposing conditions. Oxygen therapy (see Chapter 25) is indicated for all patients. Fluids are administered as needed to support circulation, with care to avoid fluid overload. Theophylline may be beneficial in some patients (see Chapter 21). Sildenafil may be helpful for patients with evidence of pulmonary hypertension (see prior discussion of Pulmonary Hypertension in this chapter).

The use of fibrinolytic agents for the treatment of PTE in animals has not been well established. Animals with suspected hypercoagulability are likely to benefit from anticoagulant therapy. The goal of such therapy is to prevent the formation of additional thrombi. Anticoagulant therapy is administered only to animals in which the diagnosis is highly probable. Dogs with heartworm disease suffering from post-adulticide therapy reactions usually are not treated with anticoagulants (see Chapter 10). Potential surgical candidates should be treated with great caution. Clotting times must be monitored frequently to minimize the risk of severe hemorrhage.

Specific recommendations for the treatment and prevention of thromboembolic disease with anti-coagulant drugs are provided in Chapter 12. Because of the serious problems and limitations associated with anticoagulant therapy, eliminating the predisposing problem must be a major priority.

Prevention

No methods of preventing PTE in at-risk patients have been objectively studied in veterinary medicine. Treatments that have potential benefit include the long-term administration of low-molecular-weight heparin, aspirin, or clopidogrel. Aspirin for the prevention of PTE remains controversial because aspirin-induced alterations in local prostaglandin and leukotriene metabolism may be detrimental.

Prognosis

The prognosis depends on the severity of the respiratory signs, the response to supportive care, and the ability to eliminate the underlying process. In general, a guarded prognosis is warranted.

PULMONARY EDEMA

Etiology

The same general mechanisms that cause edema elsewhere in the body cause edema in the pulmonary parenchyma. Major mechanisms include decreased plasma oncotic pressure, vascular overload, lymphatic obstruction, and increased vascular permeability. The disorders that can produce these problems are listed in Box 22.4. Most cases of pulmonary edema resulting primarily from increased vascular permeability fall within the classification system of *acute lung injury* (ALI) and *acute respiratory distress syndrome* (ARDS). ALI is an excessive inflammatory response of the lung to a pulmonary or systemic insult. ARDS describes severe ALI based on degree of hypoxemia. The rapid leakage of high-protein edema fluid from damaged capillaries is a key feature of ALI. In some patients that survive the initial edema, epithelial cell proliferation and collagen deposition add to pulmonary dysfunction and can ultimately result in pulmonary fibrosis within a short time (e.g., weeks).

Regardless of cause, edema fluid initially accumulates in the interstitium. However, because the interstitium is a small compartment, the alveoli are soon involved. When profound fluid accumulation occurs, even the airways become filled. Respiratory function is further affected as a result of the atelectasis and decreased compliance caused by compression of the alveoli and decreased concentrations of surfactant. Airway resistance increases as a result of the luminal narrowing of small bronchioles. Hypoxemia results from ventilation/perfusion abnormalities.

Clinical Features

Animals with pulmonary edema are seen because of cough, tachypnea, respiratory distress, or signs of the inciting disease. Crackles are heard on auscultation, except in animals with mild or early disease. Blood-tinged froth may appear in the trachea, pharynx, or nares immediately preceding death from pulmonary edema. Respiratory signs can be peracute, as in ALI/ARDS, or subacute, as in hypoalbuminemia. However, a prolonged history of respiratory signs (e.g., months) is not consistent with a diagnosis of edema. The list of differential diagnoses in Box 22.4 can often be greatly narrowed by obtaining a thorough history and performing a thorough physical examination.

BOX 22.4

Possible Causes of Pulmonary Edema

Decreased Plasma Oncotic Pressure

Hypoalbuminemia
- Gastrointestinal loss
- Glomerulopathy
- Liver disease
- Iatrogenic overhydration
- Starvation

Vascular Overload

Cardiogenic
- Left-sided heart failure
- Left-to-right shunts

Overhydration

Lymphatic Obstruction (Rare)

Neoplasia

Increased Vascular Permeability

Inhaled agents
- Smoke inhalation
- Gastric acid aspiration
- Oxygen toxicity

Drugs or toxins
- Snake venom
- Cisplatin in cats
- Paraquat

Electrocution

Trauma
- Pulmonary contusions
- Multisystemic

Sepsis or systemic inflammatory response (SIRS)

Pancreatitis

Uremia

Disseminated intravascular coagulation

Inflammation (infectious or noninfectious)

Miscellaneous Causes

Thromboembolism

Upper airway obstruction

Near-drowning

Neurogenic edema
- Seizures
- Head trauma

Diagnosis

Pulmonary edema in most dogs and cats is based on typical radiographic changes in the lungs in conjunction with clinical evidence (from the history, physical examination, radiography, echocardiography, and serum biochemical analysis [particularly albumin concentration]) of a disease associated with pulmonary edema.

Early pulmonary edema assumes an interstitial pattern on radiographs, which progresses to become an alveolar pattern. In dogs edema caused by heart failure is generally more severe in the hilar region. In cats the increased opacities are more often patchy and unpredictable in their distribution. Edema resulting from increased vascular permeability tends to be most severe in the dorsocaudal lung regions.

Radiographs should be carefully examined for signs of heart disease, venous congestion, PTE, pleural effusion, and mass lesions. Echocardiography is helpful in identifying primary cardiac disease if the clinical signs and radiographic findings are ambiguous.

Decreased oncotic pressure can be identified by the serum albumin concentration. Concentrations less than 1 g/dL are usually required before decreased oncotic pressure is considered to be the sole cause of the pulmonary edema. Pulmonary edema resulting purely from hypoalbuminemia is probably rare. In many animals volume overload or vasculitis is a contributing factor. Plasma protein quantitation using a refractometer can indirectly assess albumin concentration in emergency situations.

Vascular permeability edema can result in the full range of compromise, from minimal clinical signs that spontaneously resolve to the frequently fatal, fulminant process of ARDS. A consensus group has determined definitions for ALI/ARDS in veterinary patients (Wilkins et al., 2007). At least four, and ideally five, of the following criteria must be met: acute onset (<72 hours) of tachypnea and labored breathing at rest; known risk factors; evidence of pulmonary capillary leak without increased pulmonary capillary pressure (e.g., bilateral diffuse pulmonary infiltrates on radiography or computed tomography, proteinaceous fluid retrieved from airways); evidence of insufficient gas exchange; and evidence of diffuse pulmonary inflammation based on tracheal wash or BAL fluid analysis. One measure of insufficient gas exchange is a low Pa_{O_2} (partial pressure of oxygen in the blood)/Fi_{O_2} (fraction of inspired oxygen) ratio without the mechanical ventilation technique of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). A ratio of < 300 mm Hg is consistent with ALI. A ratio of < 200 mm Hg is consistent with the more severe form, ARDS. Arterial blood gas analysis and pulse oximetry in dogs and cats with pulmonary edema of any origin are useful in selecting and monitoring therapy. Hypoxemia is present, usually in conjunction with hypocapnia and a widened *A-a* gradient.

Treatment

It is easier for the body to prevent edema fluid from forming than it is to mobilize existing fluid. The initial management of pulmonary edema should be aggressive. Once edema has resolved, the body's own compensatory mechanisms become more effective and the intensity of therapeutic interventions can often be decreased.

All animals with pulmonary edema are treated with cage rest and minimal stress. Dogs and cats with significant hypoxemia should receive oxygen therapy (see Chapter 25). Positive-pressure ventilation is required in severe cases. Methylxanthine bronchodilators (see Chapter 21) may also be beneficial in some patients. They are mild diuretics that also decrease bronchospasms and possibly respiratory

muscle fatigue. However, in some patients bronchodilators exacerbate $\dot{V}/\dot{Q}$ mismatching. The patient's response to bronchodilators should be carefully observed.

Furosemide is indicated for the treatment of most forms of edema but is not used in hypovolemic animals. Animals with hypovolemia actually require conservative fluid supplementation. If this is necessary to maintain vascular volume in animals with cardiac impairment or decreased oncotic pressure, then positive inotropic agents or plasma infusions, respectively, are necessary.

Edema caused by hypoalbuminemia is treated with plasma or colloid infusions. However, it is not necessary for the plasma protein concentrations to reach normal levels for edema to decrease. Furosemide can be administered to more quickly mobilize fluid from the lungs, but clinical dehydration and hypovolemia must be prevented. Diagnostic and therapeutic efforts are directed at the underlying disease.

Treatment of cardiogenic edema is discussed in Chapter 3.

Overhydration is treated by discontinuation of fluid therapy. Furosemide is administered if respiratory compromise is present. If excessive volumes of fluid were not administered inadvertently, causes of fluid intolerance, such as oliguric renal failure, heart failure, and increased vascular permeability, must be sought.

Edema caused by increased vascular permeability is difficult to treat. In some cases, pulmonary compromise is mild and edema transient. Routine supportive care with oxygen supplementation may be sufficient, but mechanical ventilation is often required. Any active underlying problem should be identified and corrected.

Patients with ALI/ARDS respond poorly to management. Ventilator therapy with PEEP is indicated, and even with such aggressive support the mortality rate is high. Furosemide is generally ineffective in treating edema caused by increased vascular permeability, but because of limitations in our diagnostic capabilities it is reasonable to include this drug in the initial management of these patients. Glucocorticoids are of no clear benefit in these patients, but they are frequently given to animals with moderate to severe signs. Many novel therapies for ARDS have been studied in people, although to date none has been shown to be consistently effective in improving outcome. Emphasis is on specific inhibitors of the inflammatory response.

Prognosis

The prognosis for an animal with pulmonary edema depends on the severity of the edema, the response to oxygen therapy, and the ability to eliminate or control the underlying problem. Aggressive management early in the course of edema formation improves the prognosis for an animal with any given disease. Animals with ARDS have a guarded to grave prognosis.

Suggested Readings

Atkinson KJ, et al. Evaluation of pimobendan and N-terminal pro-brain natriuretic peptide in the treatment of pulmonary hypertension secondary to degenerative mitral valve disease in dogs. *J Vet Intern Med*. 2009;23:1190.

Bidgood T, et al. Comparison of plasma and interstitial fluid concentrations of doxycycline and meropenem following constant rate intravenous infusion in dogs. *Am J Vet Res*. 2003;64:1040.

Bowman DD, Little SE. Canine pulmonary helminths: recommendations from the Companion Animal Parasite Council. *Today's Veterinary Practice*. 2014;4:67.

Brown AJ, et al. Clinical efficacy of sildenafil in treatment of pulmonary arterial hypertension in dogs. *J Vet Intern Med*. 2010;24:850.

Clercx C, Peeters D. Canine eosinophilic bronchopneumopathy. *Vet Clin North Am Small Anim Pract*. 2007;37:917.

Cohn LA, et al. Identification and characterization of an idiopathic pulmonary fibrosis-like condition in cats. *J Vet Intern Med*. 2004;18:632.

Conboy G. Natural infections of *Crenosoma vulpis* and *Angiostrongylus vasorum* in dogs in Atlantic Canada and their treatment with milbemycin oxime. *Vet Rec*. 2004;155:16.

Corcoran BM, et al. Chronic pulmonary disease in West Highland white terriers. *Vet Rec*. 1999;144:611.

Declue AE, Cohn LA. Acute respiratory distress syndrome in dogs and cats: a review of clinical findings and pathophysiology. *J Vet Emerg Crit Care (San Antonio)*. 2007;17:340.

DeMonye W, et al. Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. *Am J Respir Crit Care Med*. 2002;165:345.

Foster S, Martin P. Lower respiratory tract infections in cats: reaching beyond empirical therapy. *J Feline Med Surg*. 2011;13:313.

Goggs R, et al. Pulmonary thromboembolism (state-of-the-art-review). *J Vet Emerg Crit Care (San Antonio)*. 2009;19:30.

Grandi G, et al. *Aelurostrongylus abstrusus* (cat lungworm) infection in five cats from Italy. *Vet Parasitol*. 2005;25:177.

Hahn KA, et al. Primary lung tumors in cats: 86 cases (1979-1994). *J Am Vet Med Assoc*. 1997;211:1257.

Hahn KA, et al. Prognosis factors for survival in cats after removal of a primary lung tumor: 21 cases (1979-1994). *Vet Surg*. 1998;27:307.

Heikkila HP, et al. Clinical, bronchoscopic, histopathologic, diagnostic imaging, and arterial oxygenation findings in West Highland White Terriers with idiopathic pulmonary fibrosis. *J Vet Intern Med*. 2011;25:533.

Heikkila-Laurila HP, Rajamaki MM. Idiopathic pulmonary fibrosis in West Highland white terriers. *Vet Clin North Am Small Anim Pract*. 2014;44:129.

Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. *N Engl J Med*. 2012;366:1968.

Johnson VS, et al. Thoracic high-resolution computed tomographic findings in dogs with canine idiopathic pulmonary fibrosis. *J Small Anim Pract*. 2005;46:381.

Kellum HB, Stepien RL. Sildenafil citrate therapy in 22 dogs with pulmonary hypertension. *J Vet Intern Med*. 2007;21:1258.

Krafft E, et al. Serum and bronchoalveolar lavage fluid endothelin-1 concentrations as diagnostic biomarkers of canine idiopathic pulmonary fibrosis. *J Vet Intern Med*. 2011;2:5990.

Lacorcia L, et al. Comparison of bronchoalveolar lavage fluid examination and other diagnostic technique with the Baermann technique for detection of naturally occurring *Aelurostrongylus abstrusus* infection in cats. *J Am Vet Med Assoc*. 2009;235:43.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial

Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

MacDonald ES, et al. Clinicopathologic and radiographic features and etiologic agents in cats with histologically confirmed infectious pneumonia: 39 cases (1991-2000). *J Am Vet Med Assoc*. 2003;223:1142.

McMillan CJ, Taylor SM. Transtracheal aspiration in the diagnosis of pulmonary blastomycosis (17 cases: 2000-2005). *Can Vet J*. 2008;49:53.

McNiel EA, et al. Evaluation of prognostic factors for dogs with primary lung tumors: 67 cases (1985-1992). *J Am Vet Med Assoc*. 1997;211:1422.

Murphy LA, et al. Retrospective evaluation of pimobendan and sildenafil therapy for severe pulmonary hypertension due to lung disease and hypoxia in 28 dogs (2007-2013). *Vet Med Sci*. 2017;3(99).

Nelson OL, et al. The utility of plasma D-dimer to identify thromboembolic disease in dogs. *J Vet Intern Med*. 2003;17:830.

Norris AJ, et al. Interstitial lung disease in West Highland white terriers. *Vet Pathol*. 2005;42:35.

Ogilvie GK, et al. Prognostic factors for tumor remission and survival in dogs after surgery for primary lung tumor: 76 cases (1975-1985). *J Am Vet Med Assoc*. 1989;195:109.

Radhakrishnan A, et al. Community-acquired infectious pneumonia in puppies: 65 cases (1993-2002). *J Am Vet Med Assoc*. 2007;230:1493.

Raghu G, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183:788.

Raghu G, Richeldi L. Current approaches to the management of idiopathic pulmonary fibrosis. *Respir Med*. 2017;129:24.

Rheinwald M, et al. Antibiotic susceptibility of bacterial isolates from 502 dogs with respiratory signs. *Vet Rec*. 2015;176:357.

Schermerhorn T, et al. Pulmonary thromboembolism in cats. *J Vet Intern Med*. 2004;18:533.

Sherding RG. Respiratory parasites. In: Bonagura JD, et al., eds. *Kirk's current veterinary therapy XIV*. St Louis: Saunders Elsevier; 2009.

Tart KM, et al. Potential risks, prognostic indicators, and survival in dogs with presumptive aspiration pneumonia: 125 cases (2005-2008). *J Vet Emerg Crit Care (San Antonio)*. 2010;20:319.

Traversa D, et al. Efficacy and safety of imidacloprid 10%/moxidectin 1% spot-on formulation in the treatment of feline *Aelurostrongylus*. *Parasitol Res*. 2009;105:S55.

Viitanen SJ, et al. Co-infections with respiratory viruses in dogs with bacterial pneumonia. *J Vet Intern Med*. 2015;29:544.

Viitanen SJ, et al. The utility of acute-phase proteins in the assessment of treatment responses in dogs with bacterial pneumonia. *J Vet Intern Med*. 2017;31:124.

Warren-Smith CMR, et al. Pulmonary adenocarcinoma seeding along a fine needle aspiration tract in a dog. *Vet Rec*. 2011;169:181.

Wilkins PA, et al. Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: the Dorothy Russell Havemeyer Working Group on ALI and ARDS in veterinary medicine. *J Vet Emerg Crit Care (San Antonio)*. 2007;17:333.

Williams K, et al. Identification of spontaneous feline idiopathic pulmonary fibrosis. *Chest*. 2006;125:2278.

Yoon K-J, et al. Influenza virus in racing greyhounds. *Emerg Infect Dis*. 1974;11:2005.

CHAPTER 23

Clinical Manifestations and Diagnostic Tests of Pleural Cavity and Mediastinal Disease



CLINICAL SIGNS

Common abnormalities of the pleural cavity in the dog and cat include the accumulation of fluid (pleural effusion) or air (pneumothorax) in the pleural space. Mediastinal masses and the pneumomediastinum are also discussed in this chapter and the next. Respiratory signs caused by pleural disease result from interference with normal expansion of the lungs. Exercise intolerance is an early sign; overt respiratory distress ultimately occurs. Physical examination findings that assist in localizing the cause of respiratory compromise to the pleural space include increased respiratory rate and decreased lung sounds on auscultation (see Chapter 25). With increasing compromise, increased abdominal excursions during breathing may be seen. Breathing effort may be increased during inspiration relative to expiration, but this finding is not always obvious. Paradoxical breathing refers to a breathing pattern in which the abdominal walls are "sucked in" during inspiration. Paradoxical breathing has been associated with pleural diseases in dogs and cats presented for respiratory distress (LeBoedec et al., 2012). In cats with mediastinal masses, decreased compressibility of the anterior thorax may be palpable.

Pulmonary thromboembolism (PTE) can cause pleural effusion. The effusion is generally mild and may be an exudate or a modified transudate. PTE should be considered as a diagnosis, particularly in patients whose respiratory efforts seem in excess of the volume of effusion (see Chapter 22).

GENERAL DIAGNOSTIC APPROACH

The presence of pleural or mediastinal disease in a dog or cat is usually confirmed by thoracic radiography, thoracic ultrasonography, or thoracocentesis. In animals presented in respiratory distress with suspected pleural effusion or pneumothorax, thoracocentesis is performed immediately to stabilize the animal's condition before radiographs are taken. Although thoracocentesis is more invasive than radiography, the potential therapeutic benefit of the procedure far outweighs the small risk of complications. Animals in stable condition at presentation can be evaluated initially with thoracic radiographs or ultrasound to confirm the presence of air or fluid and the location of fluid before thoracocentesis is performed.

Ultrasonography is a valuable tool for the evaluation of patients with pleural effusion. If equipment is available on site, animals in critical condition can be examined with minimal stress to confirm the presence of fluid and direct needle placement for thoracocentesis. Ultrasonography is also useful in evaluating the thorax for the presence of mass lesions, hernias, and primary cardiac or pericardial disease. Because sound waves cannot pass through aerated lungs, any masses must be adjacent to the chest wall, heart, or diaphragm to be detected by ultrasound. The presence of pleural fluid facilitates ultrasonographic evaluation of the chest. If the patient is stable, it is preferable to evaluate the thorax ultrasonographically before the pleural fluid is removed.

Thoracic radiographs should be taken again after as much fluid or air as possible has been removed from the pleural space and the lungs have had time to reexpand. Full expansion of the lungs is required for accurate evaluation of the pulmonary parenchyma. The presence of fluid also obscures visibility of heart size and shape and mass lesions.

Cytologic analysis of pleural fluid obtained by thoracocentesis is indicated for the diagnostic evaluation of all animals with pleural effusion. Measurement of protein concentration and total nucleated cell count, as well as qualitative assessment of individual cells, is essential for accurate classification of the fluid, formulation of a diagnostic plan, and initiation of appropriate therapy (Table 23.1). The diagnostic approach to patients with pleural effusion based on cytologic findings is described further later. For patients with a mediastinal mass, fine-needle aspirates are obtained with ultrasound guidance for analysis.

TABLE 23.1

Diagnostic Approach in Dogs and Cats With Pleural Effusion Based on Fluid Type

FLUID TYPE	COMMON DISEASE	DIAGNOSTIC TESTS
Pure and modified transudates	Right-sided heart failure	Evaluate pulses, auscultation, ECG, thor rad, echo
	Pericardial disease	See right-sided heart failure
	Hypoalbuminemia (pure transudate)	Serum albumin concentrations
	Neoplasia	Thor rad and US, CT, thoracoscopy, thoracotomy
	Diaphragmatic hernia	Thor rad and US
Nonseptic exudates	Feline infectious peritonitis (FIP)	Pleural fluid cytology is generally sufficient. In questionable cases many tests are available, but none has shown good specificity for diagnosing FIP. Consider systemic evaluation, ophthalmoscopic examination, serum or fluid electrophoresis, coronavirus antibody titer, PCR of tissues or effusion (see Chapter 96)
	Neoplasia	See Neoplasia above
	Diaphragmatic hernia	See Diaphragmatic hernia above
	Lung lobe torsion	Thor rad and US, bronchoscopy, thoracotomy
Septic exudates	Pyothorax	Gram staining, aerobic and anaerobic cultures, serial thor rad
Chylous effusion	Chylothorax	See Box 24.1
Hemorrhagic effusion	Trauma	History
	Bleeding disorder	Systemic examination, coagulation tests (ACT, PT, PTT), platelet count
	Neoplasia	See Neoplasia above
	Lung lobe torsion	See Lung lobe torsion above

ACT, Activated clotting time; *CT,* computed tomography; *ECG,* electrocardiography; *echo,* echocardiography; *PCR,* polymerase chain reaction; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *thor rad,* thoracic radiography; *US,* ultrasonography.

Chest tube (thoracostomy tube) placement is indicated primarily for the treatment of patients with progressive pneumothorax or pyothorax. However, fluid obtained from chest tubes is used for therapeutic monitoring, and a description of chest tube placement and management appears at the end of this chapter.

Thoracic computed tomography (CT) is indicated in patients with pleural or mediastinal disease without a diagnosis after routine imaging and cytologic analysis of fluid or masses. Thoracoscopy and/or thoracotomy may be necessary to obtain a diagnosis in challenging cases.

DIAGNOSTIC APPROACH FOR PLEURAL EFFUSIONS BASED ON FLUID CYTOLOGY

Pleural fluid is classified as a transudate, a modified transudate, or an exudate on the basis of protein concentration and nucleated cell count. Further classification of fluid may be possible on the basis of other cytologic or biochemical features. Additional clinically useful fluid categories include septic exudate, chylous effusion, hemorrhagic effusion, and effusion caused by neoplasia. Although various types of fluid have a typical gross appearance (Fig. 23.1), reliance on gross appearance alone will lead in some cases to the misclassification of fluid and missed diagnoses through failure to identify organisms or abnormal or unexpected cell populations. In addition to the inflammatory cell types included in each cytologic category described in subsequent sections of this chapter, mesothelial cells are generally present and are often reactive.

TRANSUDATES AND MODIFIED TRANSUDATES

Pure transudates are fluids with low protein concentrations of less than 2.5 to 3 g/dL and low nucleated cell counts of less than 500 to 1000/μL. The primary cell types are mononuclear cells, composed of macrophages, lymphocytes, and mesothelial cells. Modified transudates have a slightly higher protein concentration of up to 3.5 g/dL and nucleated cell counts of up to 5000/μL. Primary cell types include neutrophils and mononuclear cells.

Transudates and modified transudates are formed as a result of increased hydrostatic pressure, decreased plasma oncotic pressure, or lymphatic obstruction. Increased hydrostatic pressure occurs in association with right-sided congestive heart failure or pericardial disease. Physical examination findings such as abnormal jugular pulses, gallop rhythms, arrhythmias, or murmurs support a diagnosis of heart disease. Heart sounds may be muffled in animals with pericardial effusion. Thoracic radiography (after fluid removal), electrocardiography, and echocardiography are indicated for cardiac evaluation (see Chapter 2).

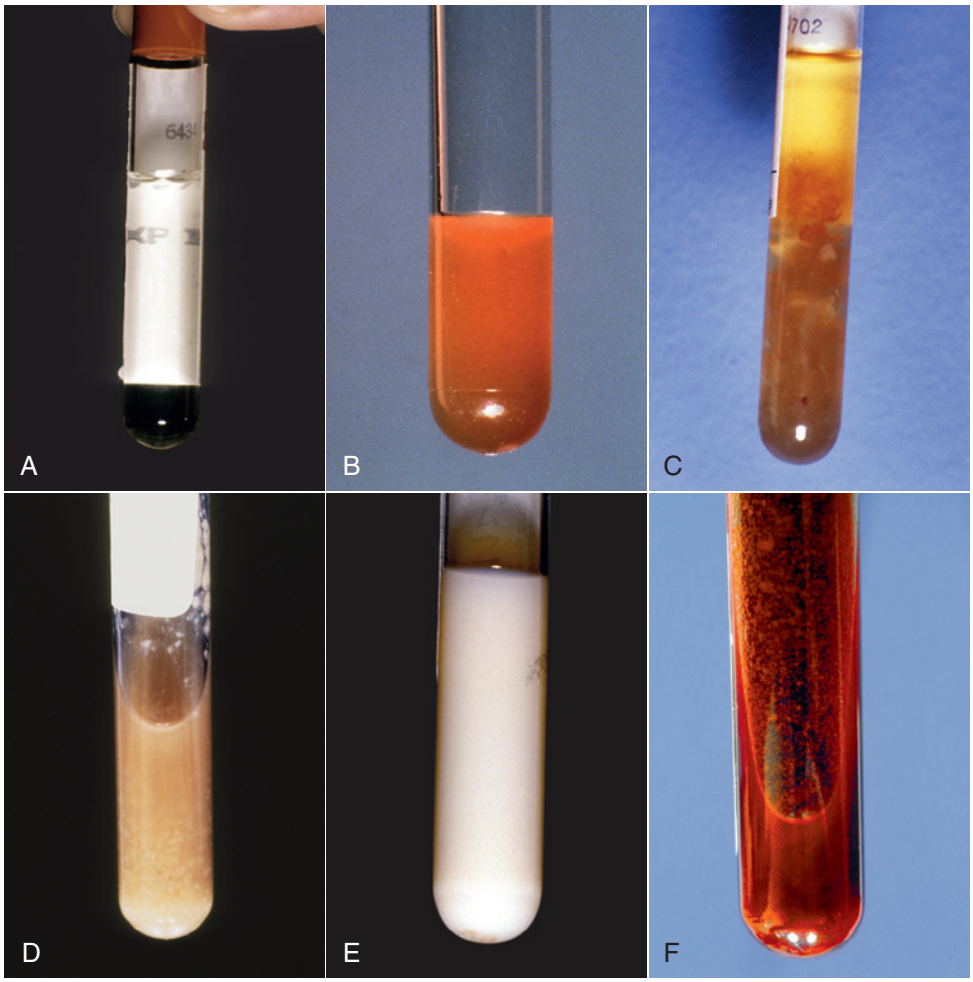


FIG 23.1
Characteristic gross appearance of the various types of pleural effusions. Note that cytologic analysis should always be performed to ensure accurate classification of fluid and to avoid missing diagnostic organisms or neoplastic cells. **(A)** Transudate. Fluid is nearly clear. **(B)** Modified transudate. Fluid is slightly opaque and, in this example, red-tinged. **(C)** Nonseptic exudate. Fluid is more opaque. The fluid shown is from a cat with feline infectious peritonitis (FIP). FIP fluid is characteristically straw-colored with grossly visible fibrin clots. **(D)** Septic exudate. Fluid has a purulent appearance, with cellular debris gravitating toward the bottom of the tube. **(E)** Chylous effusion. Fluid is milky white. **(F)** Hemorrhagic effusion. Hemorrhagic effusions are bright to dark red. In this case, cytologic examination revealed filamentous organisms, demonstrating the importance of cytologic analysis.

Decreased plasma oncotic pressure is a result of hypoalbuminemia. Effusions secondary to hypoalbuminemia alone are pure transudates that have very low protein concentrations. Subcutaneous edema may be detected in dependent areas of the body. Decreased production of albumin causes hypoalbuminemia in patients with liver disease, and increased loss of albumin causes it in patients with glomerulopathy or protein-losing enteropathy. The total plasma protein concentration shown by refractometry during initial evaluation of the dog or cat can serve as a rapid screening test for hypoalbuminemia. Serum biochemical analysis provides an exact measurement of the albumin concentration. In general, albumin concentrations must be lower than 1 g/dL before transudation caused only by hypoalbuminemia occurs. However, a combination of factors may contribute to effusions (e.g., vasculitis, hypoalbuminemia, and fluid overload).

Neoplasia and diaphragmatic hernias can cause lymphatic obstruction. Diaphragmatic hernias should be suspected in any animal with a history of trauma. The trauma may have been recent or may have occurred years ago. Although a modified transudate usually forms as a result of chronic diaphragmatic hernia, an exudative fluid can also be found. Diaphragmatic hernias are identified by radiography or ultrasonography. Occasionally, it is necessary to administer barium orally and perform an upper gastrointestinal series,

to intraperitoneally administer water-soluble iodinated contrast media and perform peritoneography, or perform CT, to confirm the presence of a diaphragmatic hernia.

Neoplasia must be considered as a differential diagnosis for patients with any type of effusion, although it is rare for a pure transudate to develop. (See the section on effusions caused by neoplasia.)

SEPTIC AND NONSEPTIC EXUDATES

Exudates have a high protein concentration (greater than 3 g/dL) compared with that in transudates. Nucleated cell counts are also high (greater than 5000/μL). Cell types in nonseptic exudates include neutrophils, macrophages, eosinophils, and lymphocytes. The macrophages and lymphocytes may be activated, and typically the neutrophils are nondegenerative. There is no evidence of organisms. Differential diagnoses in animals with nonseptic exudates include feline infectious peritonitis (FIP), neoplasia, chronic diaphragmatic hernia, lung lobe torsion, and resolving septic exudates. Prior treatment with antibiotics in animals with a septic effusion can alter the characteristics of the neutrophil population in the fluid, making them appear nondegenerative, and can decrease the number of organisms present in the fluid to an undetectable level. Therefore pleural fluid analysis should be performed before treatment is initiated so that bacterial infection is not overlooked.

Cats with FIP can present with fever or chorioretinitis in addition to respiratory signs (see Chapter 96). The pleural fluid protein concentration is often very high in such animals, approaching serum concentrations. It is common to see fibrin strands or clots in the fluid. Careful cytologic evaluation of the fluid is essential to differentiate FIP fluid from exudates caused by pyothorax or malignant lymphoma. Evaluation of animals for diaphragmatic hernia was described for transudates, and evaluation for neoplasia is discussed later in the section titled Effusion Caused by Neoplasia.

Spontaneous lung lobe torsions are most common in dogs with deep, narrow thoracic cavities. In addition to causing an effusion, torsions can be seen in dogs and cats secondary to pleural effusion. Underlying pulmonary disease resulting in lobe atelectasis can also contribute to the development of torsion. Torsion should be considered in animals with a preexisting effusion or pulmonary disease if their condition suddenly deteriorates. The effusion is often a nonseptic exudate, but it may be chylous or hemorrhagic. Signs of lung lobe torsion may be identified through thoracic radiography or ultrasonography (see Chapter 20). CT, bronchoscopy, or thoracotomy is required to verify the condition in some animals.

Septic exudates often have extremely high nucleated cell counts (e.g., 50,000 to more than 100,000/μL), and degenerate neutrophils are the predominant cells. Bacteria can often be observed within neutrophils and macrophages as well as extracellularly (see Fig. 24.1). The fluid may have a foul odor. Septic exudates are diagnostic for pyothorax, which can occur spontaneously, secondary to wounds that penetrate into the thoracic cavity through the chest wall or esophagus, secondary to migrating grass awns or other foreign bodies, or as an extension of bacterial pneumonia. Sterile technique should be used during thoracocentesis and chest tube placement in all animals with pleural effusion or pneumothorax, to prevent iatrogenic infection.

Gram staining and both aerobic and anaerobic bacterial cultures with antibiotic sensitivity testing should be performed on the fluid. Prolonged incubation should be requested to increase the likelihood of identifying *Actinomyces* and *Nocardia spp*. Culture and sensitivity testing provide valuable information that can be used in selecting appropriate antibiotics and in monitoring therapy. Mixed bacterial infections are common. However, bacteria do not grow from cultures of all septic exudates, and results are not available for several days. Gram staining provides immediate information that can be used to help select antibiotics and is helpful in cases in which bacteria cannot be grown from the fluid.

CHYLOUS EFFUSIONS

Chylous effusion (chylothorax) results from leakage of fluid from the thoracic duct, which carries lipid-rich lymph from the body. Such leakage can be idiopathic or congenital, or it can occur secondary to trauma, neoplasia, cardiac disease, pericardial disease, dirofilariasis, lung lobe torsion, or diaphragmatic hernia. Chyle is usually milky white and turbid (see Fig. 23.1, *E*), largely as a result of chylomicrons that carry fats from the intestines. The fluid is occasionally blood tinged, although this finding may be an artifact from prior thoracocentesis. It is possible to obtain clear and colorless fluids, particularly in anorectic animals, but this is uncommon.

Chyle has the cytologic characteristics of a modified transudate or nonseptic exudate with moderate concentrations of protein, usually greater than 2.5 g/dL. The nucleated cell count is low to moderate, ranging from 400 to 10,000/μL. Early in the disease, the predominant cell type is the small lymphocyte. A few neutrophils may also be present. With time, nondegenerative neutrophils become more predominant, and lymphocytes are fewer. Macrophages also increase in number with time, and plasma cells may be present.

A diagnosis of chylothorax is confirmed by measuring the concentrations of triglycerides in pleural fluid and serum. Each specimen should be well mixed by the laboratory before a portion is analyzed because of the tendency for the lipid portion to rise to the surface. The triglyceride content in chyle is high compared with that in serum. Rarely, the test will need to be repeated after a meal in anorectic animals.

Most cases of chylothorax are idiopathic, but this diagnosis can be made only after other disorders have been ruled out. Treatment is most likely to be successful if an underlying problem is identified and treated directly. (See Chapter 24 for a complete discussion of chylothorax.)

HEMORRHAGIC EFFUSIONS

Hemorrhagic effusions are grossly red as a result of the large red blood cell content. Hemorrhagic effusions consist of more

than 3 g/dL of protein and more than 1000 nucleated cells/μL, with a distribution similar to that of peripheral blood. Over time the numbers of neutrophils and macrophages increase. Hemorrhagic effusions (except those obtained immediately after bleeding into the thorax) are readily distinguished from the recovery of peripheral blood through traumatic thoracocentesis by several features: hemorrhagic effusions show erythrophagocytosis and an inflammatory response on cytologic evaluation; hemorrhagic effusions do not clot; and the packed cell volume of hemorrhagic effusions is lower than that of peripheral blood.

Hypovolemia and anemia may contribute to clinical signs in patients with hemothorax (see Chapter 25). Hemothorax can result from trauma, systemic bleeding disorders, neoplasia, and lung lobe torsion. Rarely, septic exudates are grossly hemorrhagic (see Fig. 23.1, *F*) and are distinguished cytologically. Respiratory distress caused by hemothorax may be the only clinical sign in animals with some bleeding disorders, including rodenticide intoxication. An activated clotting time and platelet count should be performed early in the evaluation of these animals, followed by more specific clotting tests (i.e., prothrombin time and partial thromboplastin time). Hemangiosarcoma of the heart or lungs is a common neoplastic cause of hemorrhagic effusion, but malignant cells are rarely identified cytologically. Neoplastic effusions are discussed further in the next section.

EFFUSION CAUSED BY NEOPLASIA

Neoplasia within the thoracic cavity can result in most types of effusions (modified transudates, exudates, chylous effusion, or hemorrhagic effusion). Neoplasms may involve any of the intrathoracic structures, including lungs, mediastinal tissues, pleura, heart, and lymph nodes. In some cases, neoplastic cells exfoliate from the tumor into the effusion, and an early diagnosis can be made through fluid cytology. This is often possible in patients with mediastinal lymphoma. Unfortunately, other than in cases of lymphoma, it can be difficult or impossible to establish a definitive diagnosis of neoplasia on the basis of cytologic findings in the pleural fluid alone. Inflammation can result in considerable hyperplastic changes in mesothelial cells, which are easily confused with neoplastic cells. *A cytologic diagnosis of neoplasia other than lymphoma should be made with extreme caution.*

In most cases, neoplastic cells are not present in the fluid, or a cytologic diagnosis cannot be made. Thoracic radiography and ultrasonography should be performed to evaluate the thorax for evidence of neoplasia. Ultrasonography can be used to differentiate localized accumulations of fluid from soft tissue masses. If soft tissue masses are detected, aspirates or biopsy specimens are obtained for cytologic or histopathologic evaluation. A definitive diagnosis cannot be made on the basis of radiographic findings or ultrasound images alone.

Diffuse neoplastic infiltration of the pleura and some masses cannot be seen with these imaging techniques. Repeated CT, thoracoscopy, or surgical exploration may be necessary in such cases.

DIAGNOSTIC TESTS FOR THE PLEURAL CAVITY AND MEDIASTINUM

RADIOGRAPHY

Pleural Cavity

The pleura surrounds each lung lobe and lines the thoracic cavity. It is not normally visible radiographically, and individual lung lobes cannot be distinguished. Abnormalities of the pleura and pleural cavity include pleural thickening, pleural effusion, and pneumothorax. The mediastinum in the dog and cat is not an effective barrier between the left and right sides of the thorax, and effusion or pneumothorax therefore is usually bilateral.

Pleural Thickening

Pleural thickening results in a thin, fluid-dense line between lung lobes, where the pleura is perpendicular to the X-ray beam. These lines arc from the periphery toward the hilar region and are known as *pleural fissure lines.* The lines can occur as a result of prior pleural disease and subsequent fibrosis, mild active pleuritis, or low-volume pleural effusion. They can be an incidental finding in older dogs. Infiltration of the pleura with neoplastic cells generally results in effusion rather than thickening.

Pleural Effusion

Pleural effusion is visible radiographically after about 50 to 100 mL has accumulated in the pleural cavity, depending on the size of the animal. A mild effusion assumes the appearance of pleural fissure lines and can be confused with pleural thickening. As fluid accumulates, the lung lobes retract and the lung lobe borders become rounded. Rounding of the caudodorsal angles of the caudal lung lobes is especially noticeable. The fluid silhouettes the heart and the diaphragm, obscuring their borders. The lungs float on top of the fluid, displacing the trachea dorsally and causing the illusion of a mediastinal mass or cardiomegaly (Fig. 23.2, *A*). As more fluid accumulates, the lung parenchyma appears abnormally dense as a result of incomplete expansion. Collapsed lobes should be examined carefully for evidence of torsion (see Chapter 20). Pockets of fluid accumulation or unilateral effusion indicate the possibility of concurrent pleural adhesions (see Fig. 23.2, *B*).

Critical radiographic evaluation of intrathoracic structures, including lungs, heart, diaphragm, and mediastinum, cannot be performed in animals with pleural effusion until the fluid has been removed. Interpretation of radiographs obtained in the presence of fluid is prone to error. An exception to this rule is the finding of gas-filled intestinal loops in the thorax, which is diagnostic of diaphragmatic hernia. Both left and right lateral views should be evaluated, in addition to a ventrodorsal view, to improve the sensitivity of detecting masses.

Pneumothorax

Pneumothorax is the presence of air in the pleural space. Air opacity without vessels or airways can be seen between

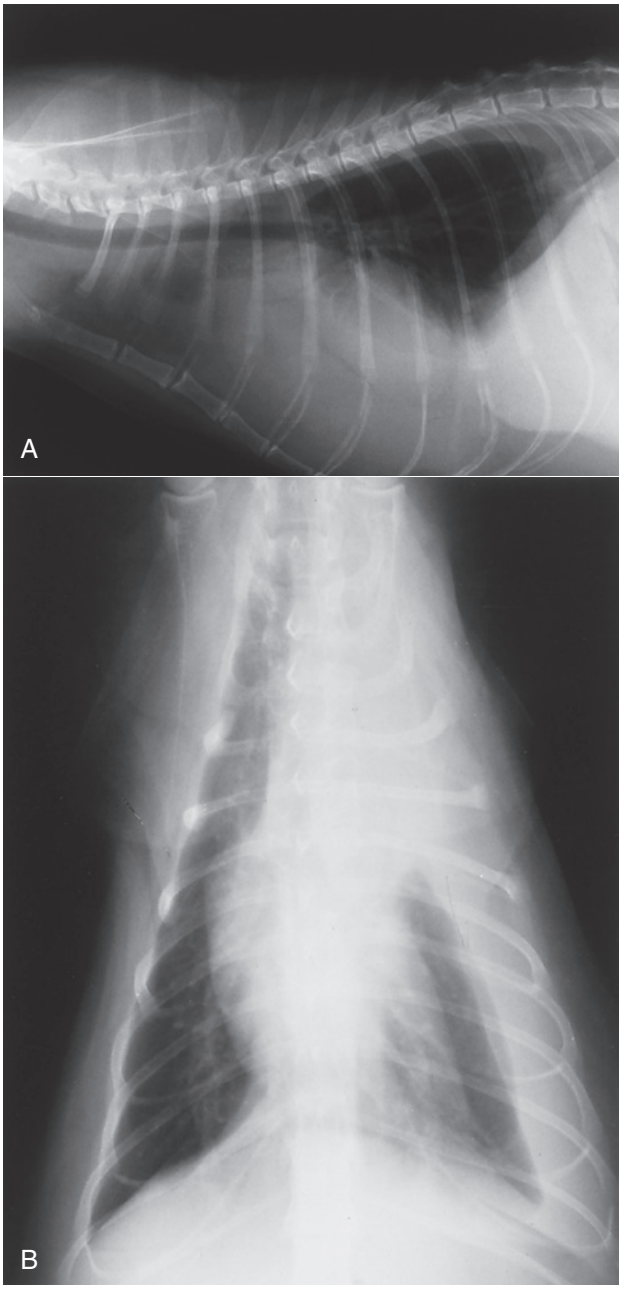


FIG 23.2
(A) Lateral thoracic view of a cat with pleural effusion. See text. **(B)** Ventrodorsal view showing that the effusion is unilateral.

the lung lobes and the chest wall on radiographs. It may be necessary to carefully scrutinize the radiographs with adjustments in contrast to detect mild pneumothorax. As a greater volume of air accumulates in the pleural space, the lung parenchyma becomes more dense because of incomplete expansion, facilitating the radiographic diagnosis. The heart is generally elevated above the sternum, with air opacity apparent between these two structures (Fig. 23.3). Radiographs should be examined carefully for evidence of possible causes of the pneumothorax, such as rib fractures

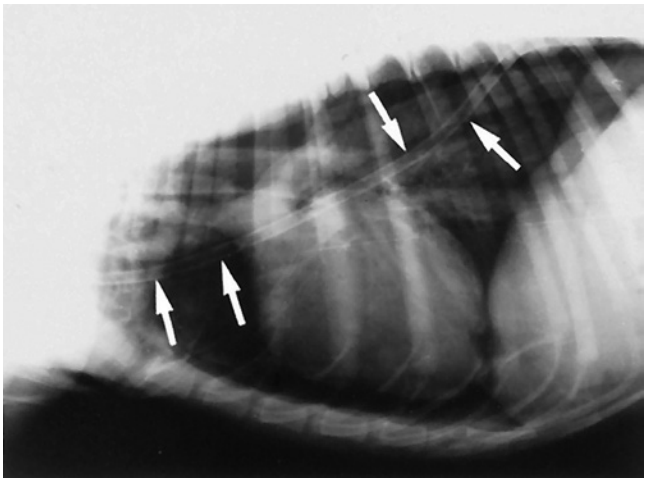


FIG 23.3
Lateral view of a dog with pneumothorax and pneumomediastinum. The pneumothorax is mild and demonstrated by elevation of the heart above the sternum. When the contrast of the original radiographs was decreased, retraction of lung borders could also be seen. It is possible to visualize the outer wall of the trachea and major blood vessels in the anterior mediastinum because of the pneumomediastinum. A chest tube placed to stabilize the dog's condition is also visible *(arrows)*.

(indicating trauma) or cavitary lesions. For accurate evaluation of the pulmonary parenchyma, the air must be removed and the lungs allowed to expand. Cavitary lesions are not always apparent radiographically. Further evaluation for cavitary lesions in patients with spontaneous pneumothorax includes CT.

Mediastinum

The cranial and caudal mediastinum contains the heart and great vessels, esophagus, lymph nodes, and associated support structures. Radiographic abnormalities involving the mediastinum include pneumomediastinum, alterations in size (e.g., mass lesions), displacement, and abnormalities involving structures within the mediastinum (e.g., megaesophagus).

Pneumomediastinum is the accumulation of air within the mediastinum. If pneumomediastinum is present, the outer wall of the trachea and other cranial mediastinal structures, such as the esophagus, major branches of the aortic arch, and the cranial vena cava, are contrasted against the air (see Fig. 23.3). These structures are not normally visible.

Abnormal soft tissue opacities can occur in the cranial mediastinum, although concurrent pleural effusion often obscures mass lesions. Localized lesions can represent neoplasia, abscesses, granulomas, or cysts. Less discrete disease can cause general widening of the mediastinum that is seen to exceed the width of the vertebra on ventrodorsal views. Exudates, edema, hemorrhage, tumor infiltration, and fat can cause a widened mediastinum. Megaesophagus can

often be observed in the cranial mediastinum, especially on lateral views.

The caudal vena cava and the aorta are normally visible in the caudal mediastinum. The most common caudal mediastinal abnormalities are megaesophagus and diaphragmatic hernia. Megaesophagus is an important consideration in animals with respiratory signs because it is a common cause of aspiration pneumonia.

The mediastinum is normally located in the center of the thoracic cavity. An abnormal shift of the mediastinum is identified by a lateral change in the position of the heart on ventrodorsal or dorsoventral views. Atelectasis (i.e., lung lobe collapse), lobectomy, and adhesions of the mediastinum to the chest wall can cause the mediastinum to shift toward the abnormality. Space-occupying lesions can cause the mediastinum to shift in the opposite direction.

The lymph nodes and the heart are mediastinal structures but are considered separately to ensure a careful evaluation. The sternal nodes are located immediately dorsal to the sternum near the thoracic inlet at the level of the first to third sternebrae (Fig. 23.4). Enlargement is seen on lateral views and has the appearance of a discrete mass lesion. The hilar nodes are located at the heartbase around the carina. Enlargement is seen as a generalized increased soft tissue opacity in the perihilar region and is most easily seen on the lateral view. Common differential diagnoses for hilar lymphadenopathy include lymphoma and fungal infection (especially histoplasmosis). Other differential diagnoses include metastatic neoplasia, eosinophilic pulmonary granulomatosis, and mycobacterial infection. Any inflammatory disease can potentially cause lymphadenopathy.

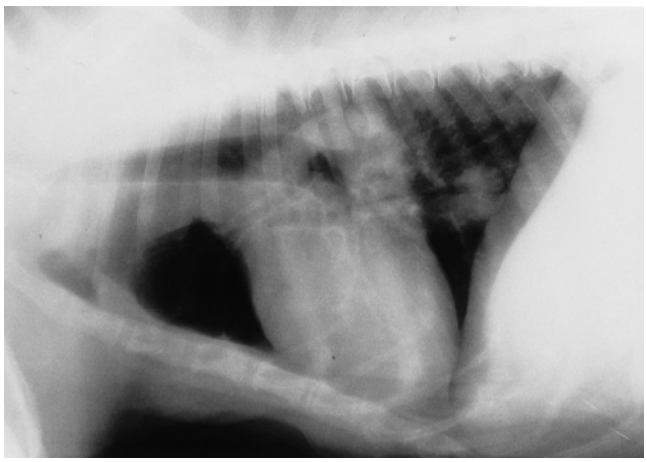


FIG 23.4
Lateral thoracic radiograph obtained in a dog with pulmonary neoplasia and sternal and hilar lymphadenopathy. The sternal node is the soft tissue opacity resting on the caudal half of the second sternebra. The hilar nodes are identified by increased soft tissue opacity around the carina. Several discrete pulmonary nodules are also present.

Other considerations in animals with increased perihilar opacity on radiographs include atrial enlargement and heartbase tumors.

Evaluation of the heart is described in Chapters 1 and 2. Right-sided heart failure and pericardial effusion can cause pleural fluid accumulation.

ULTRASONOGRAPHY

Ultrasonography is indicated in the diagnostic evaluation of dogs and cats with pleural effusion to search for masses, diaphragmatic hernia, lung lobe torsion, and cardiac disease. Mediastinal masses, masses involving the pulmonary parenchyma adjacent to the body wall, and masses extending into the thorax from the body wall may be identified and their echogenicity evaluated. Ultrasonography can also be used to guide aspiration needles or biopsy instruments to the lesion, although biopsies can be done safely only on solid masses. Ultrasonography is also useful for directing needle placement during thoracocentesis in animals with localized accumulations of pleural fluid. Air interferes with the sound waves, so structures surrounded by aerated lung cannot be examined.

In the emergency setting, ultrasonography can be used for rapid, minimally stressful assessment of the pleural space for fluid or air. The acronym for the examination is *TFAST,* which stands for *t*horacic *f*ocused *a*ssessment with *s*onography for *t*rauma. See the reference by Lisciandro (2011) for probe positions and characteristic sonographic signs.

COMPUTED TOMOGRAPHY

As discussed in Chapter 20, CT is more sensitive than radiography in evaluating the thorax. CT is useful for identifying abnormalities (e.g., masses, lung lobe torsion, thromboembolism), determining the extent of mass lesions before thoracotomy, and increasing the likelihood of identifying cavitary lesions in patients with spontaneous pneumothorax.

THORACOCENTESIS

Thoracocentesis is indicated for the collection of diagnostic specimens in dogs and cats with pleural effusion, for removal of pleural fluid or air to stabilize the condition of dogs and cats with impaired ventilation, and before radiographic evaluation of intrathoracic structures in dogs and cats with pleural fluid or air. Possible complications of thoracocentesis are pneumothorax caused by lung laceration, hemothorax, and iatrogenic pyothorax. Complications are rare if careful technique is used.

Thoracocentesis is performed with the animal in lateral or sternal recumbency, depending on which position is less stressful. Fluid or air is usually present bilaterally throughout the pleural space and can be retrieved from the seventh intercostal space (ICS) by placing the needle approximately two thirds of the distance from the costochondral junction toward the spine. If initial attempts are unsuccessful, other sites are tried or the animal's position is changed. Fluid may be more successfully retrieved from

gravity-dependent sites (i.e., closer to costochondral junctions) and air from nondependent sites. Thoracic radiographs are useful in choosing sides for thoracocentesis in the event of unilateral effusion. Ultrasonography is useful for guiding needle placement in patients in which fluid collection proves difficult.

A local anesthetic can be administered at the site of thoracocentesis. Sedation is rarely required but may be useful for decreasing patient stress. The site is shaved and surgically prepared, and the procedure is performed using sterile technique. Most often, a butterfly catheter, a three-way stopcock, and a syringe are used. Removal of fluid or air by syringe is associated with movement of the syringe, and the tubing of the butterfly catheter prevents this movement from affecting the position of the needle within the thoracic cavity. Air and most fluids can be retrieved through a 21-gauge butterfly catheter. A larger needle may be required to collect extremely viscous fluids, such as fluid from FIP or pyothorax. The three-way stopcock is attached to the catheter to keep air from entering the thorax during emptying or changing of the syringe.

With the syringe snugly attached and the stopcock open between the catheter and the syringe (closed to room air), the needle is advanced through the skin only. The needle and the skin are then moved about two rib spaces to the actual collection site. This technique prevents air from entering the chest through the needle tract after the procedure (an unlikely scenario). The needle is then advanced into the thorax immediately in front of the rib to avoid the intercostal vessels and nerves. The needle is held with a hand resting on the chest wall so it will not move relative to respirations or movement of the animal. Slight negative pressure is applied to the catheter by the syringe so that entry into the pleural space is immediately identified by the recovery of fluid or air. Once the needle has entered the pleural space, the tip is aimed away from the lung by lowering the wings of the catheter toward the body wall. Ideally, the bevel of the needle should face toward the lungs.

An alternative to a butterfly catheter is an intravenous over-the-needle catheter. In large dogs a 3¼ or 5¼ (8- or 13-cm) 14- to 16-gauge catheter can be used. These catheters are soft and produce less trauma than is produced by butterfly catheters while in the pleural space; they permit the animal to be repositioned or rolled to improve fluid or air removal. The longer length, compared with a butterfly needle, may be needed to reach the pleural space in large-breed or obese dogs. Extension tubing and a three-way stopcock are attached to the catheter immediately after placement. A small skin incision, just slightly larger than the catheter, will facilitate placement. As with the butterfly catheter, slight negative pressure is maintained by the syringe so that entry into the pleural space is immediately identified. The catheter tip is then directed cranially to allow positioning of the catheter between the lungs and the chest wall, preventing trauma to the lung tissue.

After fluid specimens are saved for cytologic and microbiologic analysis, as much fluid or air as possible is removed, except in patients with acute hemothorax (see Chapter 25).

THORACOSCOPY AND THORACOTOMY

A definitive diagnosis for the cause of pleural effusion is sometimes elusive. In such cases, thoracoscopy or thoracotomy may be necessary to allow visual assessment of the thoracic cavity and the collection of specimens for histologic and microbiologic analysis. Mesotheliomas and pleural carcinomatosis are often diagnosed through these methods.

CHEST TUBES: INDICATIONS AND PLACEMENT

Chest tube placement is indicated for the management of pneumothorax, if air continues to accumulate despite multiple thoracocenteses, and for the treatment of dogs and cats with pyothorax (see Chapter 24). If possible, needle thoracocentesis and therapy for shock are performed to stabilize dogs and cats in critical condition before chest tubes are placed.

The major complication of chest tubes is pneumothorax caused by a leak in the apparatus. Animals with chest tubes must be carefully monitored at all times to make sure that they do not disrupt the tubing connections, pull the tube part of the way out of the chest so that there are fenestrations outside the body wall, or bite through the tubing. Any leaks in the system can result in a life-threatening pneumothorax within minutes. If an animal with a chest tube must be left unattended, the tube should be clamped off close to the body wall and should be well protected by bandage material. Hemothorax or pneumothorax can be caused by lung laceration during tube placement. Iatrogenic pyothorax can result from bacteria introduced during placement or gaining entrance to the chest through the tube itself while it is in place. These complications are generally prevented through careful techniques and aseptic practices.

Pediatric chest tubes can be obtained from hospital supply companies. These tubes have multiple fenestrations, are calibrated along their length, and are radiopaque. For treating pyothorax, the tube should be as large as will fit between the ribs. The size of the tube is less critical for control of pneumothorax. Before placement, the end of the tube is occluded with a syringe adapter, a three-way valve, and a hose clamp (Fig. 23.5, *A*).

Sterile technique is used during placement of the chest tube. In an animal with unilateral disease, the tube is placed in the involved side of the thorax. Either side can be used in an animal with bilateral disease. The lateral side of the animal over the caudal rib cage is shaved and surgically prepared. The animal is anesthetized or heavily sedated. If the animal is sedated, a local anesthetic is placed subcutaneously at the tenth ICS and within the subcutaneous tissues, intercostal

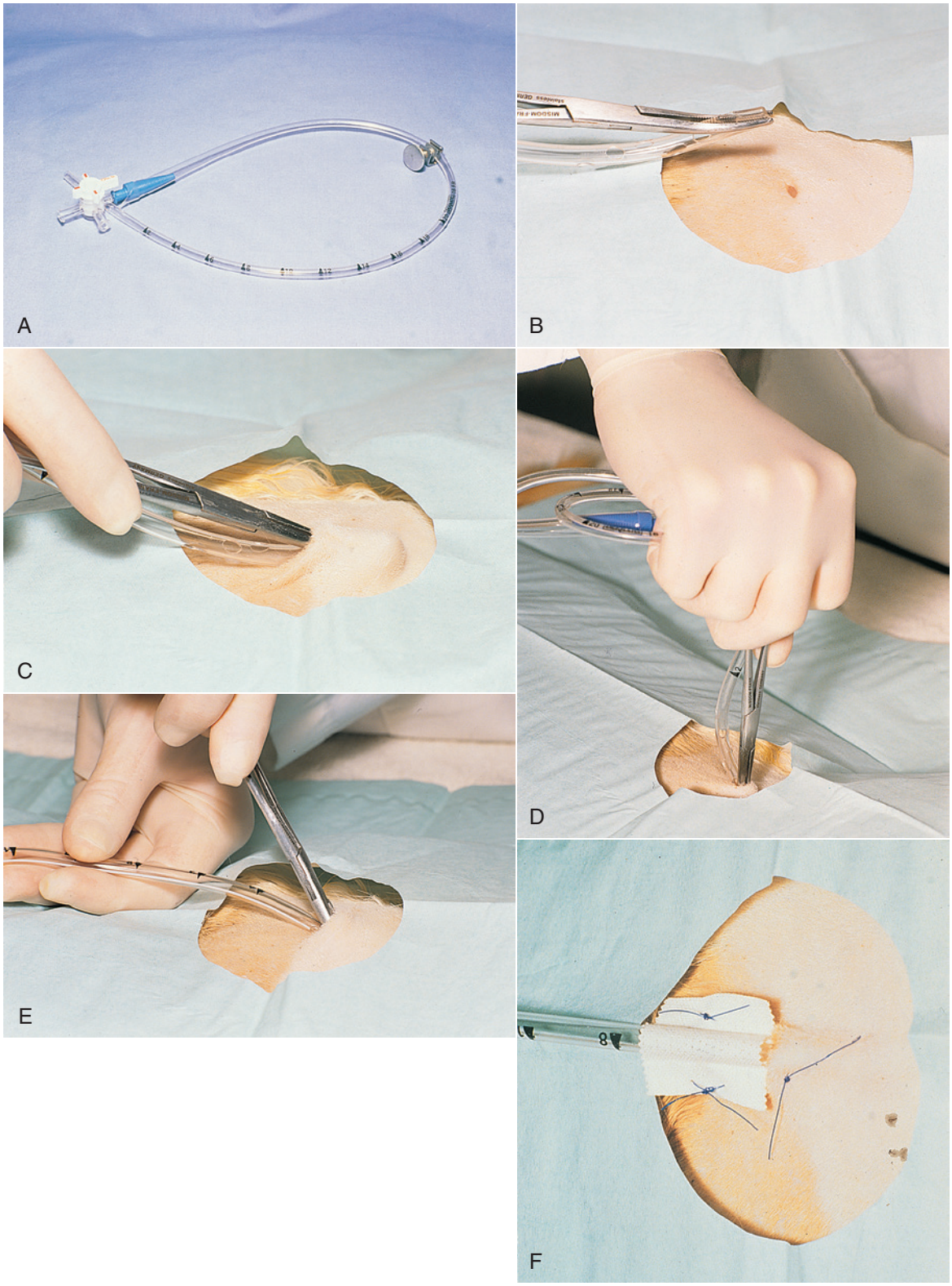


FIG 23.5
Placement of a chest tube. See text.

muscles, and pleura at the seventh ICS. The dorsoventral orientation is one half to two thirds the distance from the costochondral junction to the thoracolumbar musculature. This distance should correspond to the level where the ribs are maximally bowed.

The length of tube to be advanced into the chest must be determined from thoracic radiographs or by external landmarks on the animal. The tube should extend from the tenth ICS to the first rib. The fenestrations in the tube must not extend outside the point of exit from the pleural cavity.

A stab incision is made through the skin at the tenth ICS. A purse-string suture is then placed around the opening but is not tied. Some chest tubes made for humans contain a stylet. Smaller chest tubes are inserted with the aid of curved hemostats. The tip of the tube is grasped with the tip of the hemostats with the tube parallel to the body of the clamps (see Fig. 23.5, *B*).

The tube, with the stylet or hemostats, is then tunneled subcutaneously from the tenth to the seventh ICS. If hemostats are used, the tips are directed away from the animal's body (see Fig. 23.5, *C*). Once the tip reaches the seventh ICS, the stylet or hemostats are raised perpendicular to the chest wall. The palm of the hand is placed over the end of the stylet or the hemostat handles, and the tube is thrust through the body wall with one rapid motion (see Fig. 23.5, *D*). Once the tube has entered the pleural space, it is quickly advanced forward until a predetermined length has entered the chest while the stylet or hemostats are withdrawn (see Fig. 23.5, *E*).

An alternative technique can be used to minimize trauma to the lungs caused when the tube is thrust through the body wall. In this technique, after the skin incision has been made and a purse-string suture placed, an assistant standing at the head of the animal draws the skin of the thorax cranially to pull the skin opening forward from the tenth to the seventh ICS (Fig. 23.6). With the skin held in this position, hemostats are used to bluntly dissect through the thoracic and intercostal musculature to the pleura. At this point, the chest tube with the stylet or hemostats is easily popped through the pleura into the chest with minimal force. The tube is then advanced and the skin released.

Air will be sucked into the pleural cavity during tube placement regardless of the method used. This air is immediately removed through the tube using a 35-mL syringe. The purse-string suture is then tied around the tube. Immediately external to the skin entrance, the tube is attached to the body wall by suturing the tape that is formed as a butterfly around the tube to the skin on either side of it (see Fig. 23.5, *F*) or by using a Chinese finger trap suture around the tube and attached to the skin. This prevents the chest tube from being withdrawn if tension is accidentally applied to the tubing. The opening in the skin is covered with a sterile sponge with antiseptic ointment.

A light wrap is placed around the tube to hold it against the chest wall. *The wrap must not be too tight.* A wrap that is too tight can greatly decrease chest wall compliance and can increase the work of breathing in these compromised animals. The hose clamp is placed on the tube between the animal and the three-way valve to further protect against pneumothorax whenever suction is not being applied to the tube. An Elizabethan collar is always placed on the animal because a single bite through the tube can be fatal.



FIG 23.6
After an assistant pulls the skin forward, an incision can be made through the skin at the seventh intercostal space and blunt dissection is used to reach the pleura. A chest tube can be popped into the pleural space with minimal trauma to the underlying lung. When the skin is released, the tube will course through a subcutaneous tunnel to prevent air leaks around the tube.

Thoracic radiographs are taken to evaluate tube position and the effectiveness of drainage. Two views must be evaluated. Ideally, the tube should extend along the ventral aspect of the pleural space to the thoracic inlet. The most important sign of adequate tube placement is the absence of areas of persistent fluid or air accumulation. If areas of fluid or air persist, it may be necessary to replace the tube or place a second tube in the opposite side.

Once a chest tube is in place and determined to be in a satisfactory position, its effectiveness is monitored every 24 to 48 hours by thoracic radiography and by the gross and cytologic assessment of recovered fluid. The animal must also be monitored for the development of secondary complications. These include infection and leakage of air. The bandage should be removed at least daily. The site where the tube enters the skin should be evaluated for signs of inflammation or subcutaneous emphysema. The tube and skin sutures should be examined for signs of motion. The skin around the tube is kept clean, and a sterile sponge is replaced over the entry site of the tube before re-bandaging. Stopcock ports should be protected with sterile caps when not in use. Gloves should be worn and the stopcock ports wiped with hydrogen peroxide before use.

Suggested Readings

Case JB. Advances in video-assisted thoracic surgery, thoracoscopy. *Vet Clin Small Anim*. 2016;46:147.

LeBoedec K, et al. Relationship between paradoxical breathing and pleural diseases in dyspneic dogs and cats: 389 cases (2001-2009). *J Am Vet Med Assoc*. 2012;240:1095.

Lisciandro GR. Abdominal and thoracic focused assessment with sonography for trauma, triage, and monitoring in small animals. *J Vet Emerg Crit Care*. 2011;21:104.

Thrall D. *Textbook of veterinary diagnostic radiography*. 6th ed. St Louis: Saunders Elsevier; 2013.

CHAPTER 24

Disorders of the Pleural Cavity and Mediastinum



PYOTHORAX

Etiology

Septic exudate in the pleural cavity is referred to as *pyothorax*. It is most often idiopathic in origin, particularly in cats. Barrs et al. (2009) propose that the source of organisms in these cases is the oropharynx. Pyothorax can result from foreign bodies, puncture wounds through the chest wall, esophageal tears (usually from ingested foreign bodies), and extension of pulmonary infection. Thoracic foreign bodies are usually migrating grass awns. They are rare in cats and are most common in sporting breeds of dogs in states where there is a large concentration of foxtail grasses (e.g., California).

Clinical Features

Dogs and cats with pyothorax have clinical signs referable to a closed site of infection (abscess) and pleural effusion. Signs may be acute or chronic. Tachypnea, decreased lung sounds, increased abdominal excursions, and paradoxical breathing (abdomen and chest expanding asynchronously) are typical of pleural effusion. In addition, fever, lethargy, anorexia, and weight loss are common. Animals may be presented in septic shock or may demonstrate signs of systemic inflammatory response syndrome.

Diagnosis

The diagnosis of pyothorax is made through thoracic radiography and cytologic evaluation of pleural fluid. Thoracic radiographs are used to confirm the presence of pleural effusion and to determine whether the disease is localized, unilateral, or bilateral. In most animals, fluid is present throughout the pleural space. The finding of a localized accumulation of fluid indicates the possible presence of pleural fibrosis, mass lesions, or lung lobe torsion. Thoracic radiographs are taken again after removal of the fluid to evaluate the pulmonary parenchyma for evidence of underlying disorder (e.g., bacterial pneumonia, foreign body) that may have caused the pyothorax. Ultrasonography is also useful for identifying adhesions or pockets of fluid.

Identification of a septic exudate by pleural fluid analysis establishes the diagnosis of pyothorax. Septic suppurative inflammation is a consistent finding in pleural fluid examined cytologically, except in animals receiving antibiotics (Fig. 24.1; see also Chapter 23). Pleural fluid should be further evaluated by Gram staining, and aerobic and anaerobic bacterial cultures. These tests may identify organisms not apparent by routine cytologic staining and may provide valuable information for antibiotic selection. Anaerobes are usually present in the fluid, and in many dogs and cats more than one type of bacteria is present. All of the types of bacteria involved may not grow in the laboratory in spite of cytologic evidence of their presence, possibly because of competition between organisms or an inhibitory effect of the exudative fluid. Organisms such as *Actinomyces* and *Nocardia* particularly do not grow well if specimens have been cultured using routine procedures, and the laboratory should be notified of the possibility of these organisms. Absence of growth of bacteria does not rule out a diagnosis of pyothorax.

Evaluation of the patient's systemic status may reveal evidence of active inflammation, systemic inflammatory response syndrome, or sepsis. A normal leukogram does not rule out the possibility of pyothorax.

Treatment

Medical therapy for pyothorax includes antibiotics, drainage of the pleural cavity, and appropriate supportive care (e.g., fluid therapy). At first, empirically selected antibiotics are administered intravenously. Results of Gram staining and culture and sensitivity testing are helpful in adjusting antibiotic protocols as they become available. Recently published antimicrobial guidelines for the treatment of respiratory tract disease in dogs and cats (Lappin et al., 2017) recommend initial treatment of an injectable fluoroquinolone (e.g., enrofloxacin or marbofloxacin) with a penicillin (e.g., ampicillin with sulbactam) or clindamycin. The penicillin or clindamycin should be continued regardless of culture results because of the difficulty in growing some anaerobes in the laboratory.

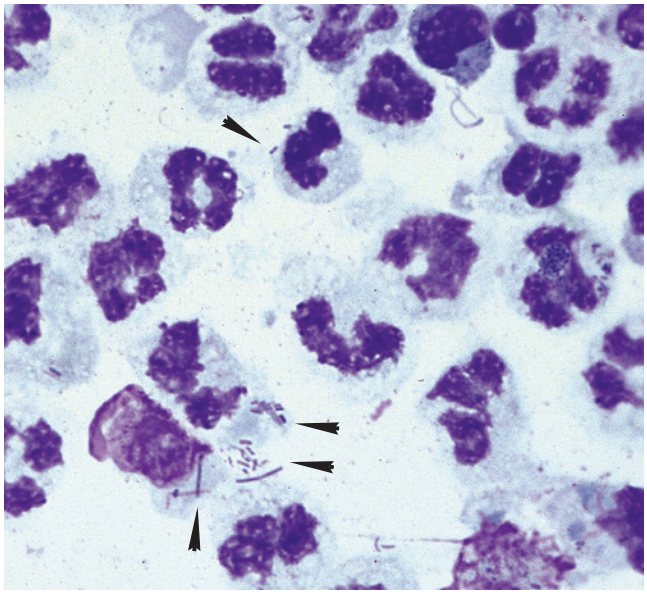


FIG 24.1
Cytologic preparation of a specimen of a pleural effusion from a cat with pyothorax. Degenerative neutrophils predominate, and intracellular and extracellular bacteria are prevalent *(arrowheads)*. Both rods and cocci are seen.

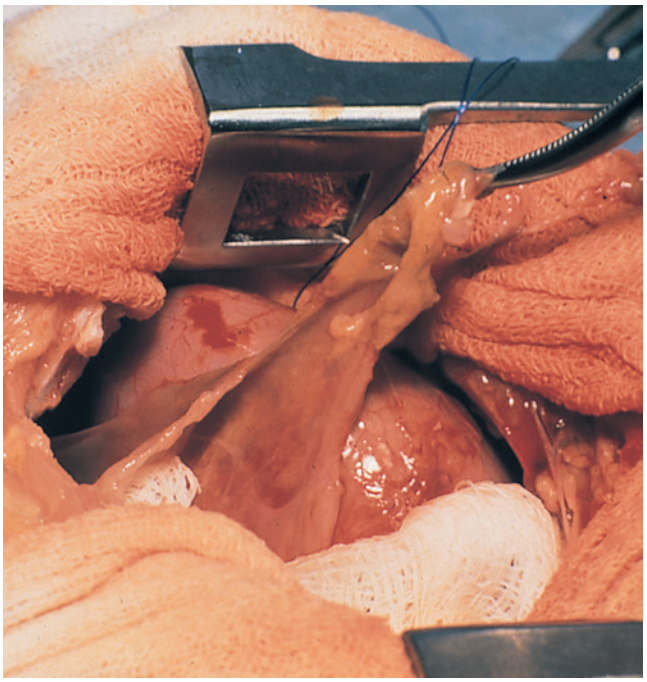


FIG 24.2
Pleural fibrosis manifested by markedly thickened pleura seen during thoracotomy in a cat with chronic pyothorax. Treatment with antibiotics alone was attempted, and several weeks later the cat's condition deteriorated. Fibrosis was too extensive to allow for routine drainage with chest tubes. Surgical debridement, several lobectomies, drainage through surgically placed tubes, and long-term antibiotic therapy resulted in a cure.

Oral antibiotics are used once significant improvement is noted, usually about the time of chest tube removal. Amoxicillin-clavulanate (dogs, 11 mg/kg q8h; cats, 12.5 mg/kg q8h) is used in patients that have responded with ampicillin with sulbactam. Oral antibiotic therapy is continued for an additional 4 to 6 weeks.

Drainage of the septic exudate is an essential part of the treatment of pyothorax. Although treatment with antibiotics alone often causes dramatic improvement in the animal's clinical condition initially, the signs generally recur, and complications of prolonged infection, such as fibrosis and abscessation requiring surgical debridement and drainage, are more likely (Fig. 24.2). Indwelling chest tubes provide the best drainage and can be used to keep the exudate from accumulating during the initial days of antibiotic therapy. Dogs and cats in critical condition at presentation are stabilized through the use of needle thoracocentesis and shock therapy before chest tube placement. Intermittent needle thoracocentesis is a poor substitute for chest tube draining in this setting and is rarely sufficient to achieve resolution of infection. Intermittent thoracocentesis is not recommended unless the owner cannot afford the expense of chest tube management and the remaining option is euthanasia.

Chest tube placement and assessment of positioning are discussed in Chapter 23. Animals probably respond most rapidly to constant suctioning of exudate from the chest, although intermittent suction is certainly adequate and often more feasible. Constant suction is applied with a suction pump and collection unit. Disposable pediatric cage-side collection units (e.g., Argyle Thora-Seal III, Medtronic) are available through hospital supply companies. These units allow monitoring of collected fluid volume and adjustment of suction pressure. An initial suction pressure of 10 to 15 cm H_2O is used, but more or less pressure may be necessary depending on the viscosity of the pleural fluid and the collapsibility of the tubes. The collection systems must be carefully monitored for leaks or malfunctions that could cause a fatal pneumothorax.

Intermittent suction by syringe is ideally performed every 2 hours for the first days of treatment, with arrangements made for drainage to continue during the night. Within a few days the volume of fluid produced will decrease, and the interval can then be lengthened. If such intensive care is not possible, an effort should still be made to empty the chest of fluid at least once late in the evening to minimize the accumulation of exudate overnight.

Lavage of the chest cavity is performed twice daily and consists of the removal of any fluid within the chest, followed by slow infusion of warmed sterile saline solution into the chest. A volume of approximately 10 mL/kg of body weight is infused, but the infusion should be discontinued if any distress is noted. After this the animal is gently rolled from side to side, and the fluid is removed. Sterile technique is used throughout the procedure. The volume recovered should be about 75% of the volume infused. If less fluid is retrieved, this may indicate that the chest tube is no longer providing

adequate drainage and should be assessed by radiography or ultrasonography. No obvious benefit is derived from the addition of antibiotics, antiseptics, or enzymes to the lavage solution. The addition of heparin (1000-1500 U/100 mL) to the lavage fluid may decrease fibrin formation and has been associated with better outcomes (Boothe et al., 2010).

All adapter ports connected to the chest tube should be covered with sterile caps when not in use. When accessing the ports, the clinician should wear gloves and remember to wipe the ports with hydrogen peroxide before use.

Thoracic radiographs are taken every 24 to 48 hours to ensure that the chest is being completely drained of fluid. Failure to monitor the effectiveness of drainage radiographically can lead to costly prolongation of the intensive care required for maintenance of the chest tube.

Serum electrolyte concentrations are also monitored. Many dogs and cats with pyothorax are dehydrated and anorectic at presentation and require intravenous fluid therapy. Supplementation of the intravenous fluid with potassium may be necessary.

The decision to discontinue drainage and remove the chest tube is based on fluid volume and cytologic characteristics. The volume of fluid recovered should have decreased to less than 2 mL/kg/day. Slides of the fluid are prepared daily and evaluated cytologically. Bacteria should no longer be visible intracellularly or extracellularly. Neutrophils will persist but should no longer appear degenerative (Fig. 24.3). When these criteria have been met and no pockets of fluid are seen on thoracic radiographs, the chest tube is removed and the animal is monitored clinically for at least 24 hours for the development of pneumothorax or the recurrence of effusion. Thoracic radiographs can be taken to more sensitively evaluate the animal for these potential problems.

Thoracic radiographs are evaluated 1 week after removal of the chest tube and 1 week and 1 month after discontinuation of antibiotic therapy. These radiographs are obtained so that a localized nidus of disease such as a foreign body or an abscess can be identified, and so that recurrence of a pyothorax can be detected before large volumes of pleural fluid accumulate. Such niduses are often invisible when large volumes of pleural fluid are present or when aggressive therapy is in progress.

Exploratory thoracotomy is indicated for the removal of a suspected nidus of infection and in those animals that do not respond to medical therapy. In the latter instance, surgery may be necessary to remove fibrotic and diseased tissue or a foreign body. Failure to respond is suggested by the continued need for a chest tube for longer than 1 week after the start of appropriate antibiotic treatment and drainage, although reported cases that have undergone complete recovery after medical management have required drainage by chest tubes for longer periods. Furthermore, persistence of large pockets of fluid in spite of appropriate chest tube placement may necessitate the decision to perform a thoracotomy earlier. Computed tomography of the chest may be a more sensitive method than thoracic radiography for

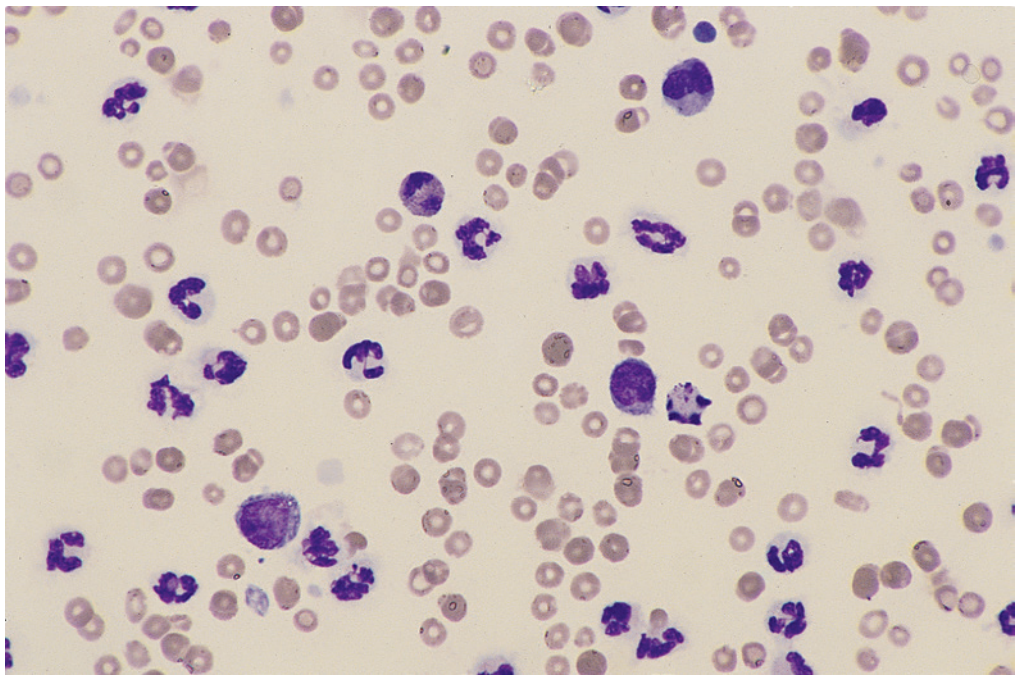


FIG 24.3
Cytologic preparation of a specimen of a pleural effusion from a cat being treated successfully for pyothorax with chest tube drainage and antibiotics. Compared with the fluid shown in Fig. 24.1, the nucleated cell count is low, the neutrophils are nondegenerative, organisms are not present, and mononuclear cells are appearing (cytocentrifuge prep).

detecting persistent pulmonary lesions. Rooney et al. (2002) recommended consideration for thoracotomy particularly in dogs that have radiographic evidence of mediastinal or pulmonary lesions, or if *Actinomyces* spp. are identified in the pleural fluid.

Prognosis

The prognosis for animals with pyothorax is fair to good if it is recognized early and treated aggressively. Waddell et al. (2002) reported a survival rate for cats of 66%, excluding those that were euthanized before treatment. In their report, 5 of 80 cats required thoracotomy. Boothe et al. (2010) reported a 1-year survival rate of 70% for dogs treated with chest tube drainage, with or without surgery, but only 29% for dogs treated with intermittent thoracocentesis. However, in a study by Rooney et al. (2002) of 26 dogs, only 25% of dogs were successfully treated medically, whereas 78% responded favorably to thoracotomy. One possible explanation for the poor success of medical management in the latter study is its geographic location in a region of the country where grass awn migration is common.

Exploratory surgery is necessary to ensure complete resolution of the problem in dogs or cats with foreign bodies in the thoracic cavity. Radiolucent foreign bodies can be difficult to find, however, and the prognosis for pyothorax secondary to them is more guarded. Long-term complications of pyothorax such as pleural fibrosis and restrictive lung disease are uncommon.

CHYLOTHORAX

Etiology

Chylothorax is the accumulation of chyle within the thoracic cavity. The chyle originates from the thoracic duct, which carries triglyceride-rich fluid from the intestinal lymphatics and empties it into the venous system in the anterior thorax. This fluid also contains lymphocytes, protein, and fat-soluble vitamins. Thoracic duct rupture after thoracic trauma can result in transient chylothorax. However, most cases are not the result of a ruptured duct. Possible causes of nontraumatic chylothorax include generalized lymphangiectasia, inflammation, and obstruction of lymphatic flow. Flow can be obstructed for physical reasons, such as neoplasia, or as a result of increased venous pressures.

Chylothorax can be categorized as congenital, traumatic, or nontraumatic. A congenital predisposition may exist in animals in which chylothorax develops later in life. Traumatic events that induce chylothorax can be surgical (e.g., thoracotomy) or nonsurgical (e.g., being hit by a car). Nontraumatic causes of chylothorax include neoplasia, particularly mediastinal lymphoma in cats; cardiomyopathy, dirofilariasis, pericardial disease, and other causes of right-sided heart failure; central venous thromboses; lung lobe torsion; diaphragmatic hernia; and systemic lymphangiectasia. No underlying disease can be identified in most animals, in which case idiopathic chylothorax is diagnosed.

Fibrosing pleuritis and pericarditis can be associated with chylothorax. Cats, in particular, may develop fibrosing pleuritis, which can interfere with normal expansion of the lungs even after thoracocentesis. Inflammation and thickening of the pericardium could contribute to the further formation of chylous effusion.

Clinical Features

Chylothorax can occur in dogs or cats of any age. Afghan Hounds and Shiba Inus appear to be predisposed to the disorder. The primary clinical sign is respiratory distress typical of pleural effusion. Although the distress is often acute in onset, more subtle signs have generally been present for longer than a month. Lethargy, anorexia, weight loss, and exercise intolerance are common. In some cases, cough is the only presenting sign.

Diagnosis

Chylothorax is diagnosed by thoracic radiography and by identification of chyle through cytologic and biochemical evaluation of pleural fluid obtained by thoracocentesis (see Chapter 23). Lymphopenia and panhypoproteinemia may be present in peripheral blood. The complication of fibrosing pleuritis is suspected when lung lobes have rounded borders radiographically and the degree of respiratory compromise subjectively exceeds that expected from the amount of fluid in the pleural space.

Once chylothorax has been diagnosed, further diagnostic tests are performed to identify potential underlying disease (Box 24.1). These tests include thoracic ultrasonography; echocardiography; microfilarial examination and adult antigen testing for heartworm disease; and, in cats, the measurement of thyroid hormone concentrations. Computed tomography will be more sensitive than thoracic radiography in identifying and characterizing localized disease and, when performed with contrast, may identify venous thromboses. Lymphangiography can be used to identify lymphangiectasia, sites of obstruction, and, rarely, sites of leakage from the thoracic duct. Lymphangiography is performed before surgical ligation of lymphatics is attempted.

Treatment

Thoracocentesis and appropriate fluid therapy are used to stabilize dogs and cats with chylothorax, as needed, at presentation. Electrolyte abnormalities may be present. A concerted effort is made to identify any underlying cause of the chylothorax, so that it can be directly treated. Elimination of the underlying problem may result in resolution of the chylothorax, although medical management (as described later for idiopathic chylothorax) is generally required for several weeks or even months. The exception is chylothorax of traumatic origin, which generally resolves within 1 to 2 weeks.

A routinely successful treatment for idiopathic chylothorax has not been established. Medical management is initially attempted because spontaneous remission occurs in some cases. In the absence of resolution with medical therapy,

BOX 24.1

Diagnostic Tests to Identify Underlying Diseases in Dogs and Cats With Chylothorax

Complete Blood Count, Serum Biochemical Panel, Urinalysis

Evaluation of systemic status

Cytologic Examination of Fluid

Infectious agents
Neoplastic cells (especially lymphoma)

Thoracic Radiographs (After Fluid Removal)

Anterior mediastinal masses
Other neoplasia
Cardiac disease
Heartworm disease
Pericardial disease

Ultrasonography (Ideally, in the Presence of Fluid)

Anterior mediastinum
  Mass
Heart (echocardiography)
  Cardiomyopathy
  Heartworm disease
  Pericardial disease
  Congenital heart disease
Other fluid densities adjacent to body wall
  Neoplasia
  Lung lobe torsion

Heartworm Antibody and Antigen Tests

Heartworm disease

Computed Tomography

Often more sensitive than radiography or ultrasonography
With contrast, to identify central venous thromboses

Lymphangiography

Preoperative and postoperative assessment of thoracic duct

surgical treatment that includes thoracic duct ligation and pericardectomy is recommended.

Medical management consists primarily of intermittent thoracocentesis and a low-fat diet. Thoracocentesis is performed as needed on the basis of the owner's observation of increased respiratory rate or effort or decreased activity or appetite. Initially, thoracocentesis may need to be performed every 1 to 2 weeks. The interval between thoracocenteses will gradually lengthen if the chylothorax is responsive to medical management. Ultrasound guidance of the needle during thoracocentesis is especially helpful in removing pockets of chyle from the pleural cavity. By increasing the effectiveness of drainage, it can prolong the interval between thoracocenteses.

Although the benefit of dietary management has been questioned, a low-fat, nutritionally complete diet is fed in patients with good body condition. In humans medium-chain triglyceride oil is absorbed directly into the bloodstream, bypassing the lymphatics, and can be used as a fat supplement. Unfortunately, in dogs these triglycerides have been shown to enter the thoracic duct. Studies have not been performed in cats.

Medical management may be facilitated by the administration of rutin, a benzopyrone drug. Rutin has been used in humans for the treatment of lymphedema. It is thought to decrease the protein content of the effusion by affecting macrophage function. The resorption of effusion may thereby be enhanced and fibrosis of the pleura minimized. The drug is available over the counter at health food stores. A dosage of 50 to 100 mg/kg given orally every 8 hours is recommended.

Surgical management is considered if clinical signs have not improved within 1 to 3 months of medical therapy, or if signs are intolerable. The recommended surgical management of chylothorax includes thoracic duct ligation and pericardectomy, with or without ablation of the cisterna chyli. Thoracic duct ligation is technically difficult and ideally performed by an experienced surgeon. Multiple ligations of the thoracic duct and its collaterals are performed. The ducts are identified by lymphangiography before surgery, and lymphangiography is repeated after ligation to assess the success of ligation. Pericardectomy is recommended at the time of thoracic duct ligation and is associated with an improved outcome (Fossum et al., 2004). Ablation of the cisterna chyli has also been reported to enhance success (McAnulty, 2011).

Placement of pleuroperitoneal or pleurovenous shunts or mesh within the diaphragm to allow fluid to drain away from the pleural space has also been recommended for the management of chylothorax and should be considered if medical and surgical treatment is unsuccessful. These drainage procedures provide a route by which the leaking chyle can reenter the circulation without producing the respiratory compromise associated with pleural effusion. Unfortunately, drains often become nonfunctional within months of placement.

Prognosis

The prognosis for chylothorax is fair, unless the chylothorax was traumatically induced or was the result of a reversible condition. Most studies report a positive response to surgical intervention in the range of 50% to 80% of patients (Singh et al., 2012b). It is not possible to predict the contribution of fibrosing pleuritis to clinical signs in cats with this complication. In cats with continued respiratory difficulties after resolution of effusion, decortication of the lung is considered.

NEOPLASTIC EFFUSION

Neoplastic effusions resulting from mediastinal lymphoma are treated with radiation or chemotherapy (see Chapter 79). Effusions caused by mesothelioma or carcinoma of the

pleural surfaces may respond to palliative therapy with intracavitary infusions of cisplatin or carboplatin (Moore, 1992), with or without concurrent chemotherapy. Placement of pleuroperitoneal shunts or intermittent thoracocentesis to alleviate the degree of respiratory compromise can be considered to prolong the life of patients that have no clinical signs beyond those resulting from the accumulation of pleural effusion.

PNEUMOTHORAX

Pneumothorax is the accumulation of air in the pleural space. The diagnosis is confirmed by means of thoracic radiography. The pleural cavity is normally under negative pressure, which keeps the lungs expanded in health. However, if an opening forms between the pleural cavity and the atmosphere or the airways of the lungs, air is transferred into the pleural space because of this negative pressure. A ***tension pneumothorax*** occurs if a one-way valve is created by tissue at the site of leakage, such that air can enter into the pleural space during inspiration but cannot return to the airways or atmosphere during expiration. Increased intrapleural pressure and resultant respiratory distress occur quickly.

Leaks through the thoracic wall can occur after a traumatic injury or as the result of a faulty pleural drainage system. Air can also enter the thorax during abdominal surgery through a previously undetected diaphragmatic hernia. These causes are readily identified.

Pneumothorax resulting from pulmonary air can occur after blunt trauma to the chest (i.e., traumatic pneumothorax) or as a result of existing pulmonary lesions (i.e., spontaneous pneumothorax). Traumatic pneumothorax occurs frequently, and findings of the history and physical examination allow this to be diagnosed. Pulmonary contusions are often present in these animals.

Less commonly, pneumothorax is a result of tracheal trauma. Tracheal tears within the thorax are usually the result of overinflation of endotracheal tube cuffs, a particular concern in cats. Trauma to the cervical trachea more often results in subcutaneous emphysema, though dissection of air can occur into the mediastinum or thorax.

Spontaneous pneumothorax occurs when preexisting pulmonary lesions rupture. Cavitary lung diseases include blebs, bullae, and cysts, which can be congenital or idiopathic, or can result from prior trauma, chronic airway disease (particularly in cats), or *Paragonimus* infection. Necrotic centers can develop in neoplasms, thromboembolized region (e.g., from dirofilariasis) abscesses, and granulomas involving the airways; these can rupture, allowing air to escape into the pleural space. (See Chapter 20 for further discussion of cavitary lesions.)

TRAUMATIC PNEUMOTHORAX

Dogs and cats with pneumothorax and a recent history of trauma are managed conservatively. Cage rest, removal of accumulating air by periodic thoracocentesis or by chest tube, and radiographic monitoring are indicated. If abnormal radiographic opacities persist without improvement for longer than several days in trauma patients, further diagnostic tests should be performed, as described for spontaneous pneumothorax. Failure of resolution of the pneumothorax over time may necessitate surgical intervention. Treatment with an autologous blood-patch has shown promise in patients for which surgery is not an option (Oppenheimer et al., 2014).

SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax is much less common than traumatic pneumothorax and occurs more often in dogs than in cats. Thoracocentesis is useful for initial stabilization of the animal's condition. If frequent thoracocentesis is needed to control the pneumothorax, a chest tube is placed (see Chapter 23).

Dogs and cats are evaluated for underlying disease with thoracic radiography (repeated after full lung expansion), computed tomography of the thorax, multiple fecal examinations for *Paragonimus* ova (see Chapter 20), heartworm testing, and possibly tracheal wash fluid analysis or bronchoscopy. Computed tomography is much more sensitive for the identification of bullae and should be performed before thoracotomy. In a study by Au et al. (2006), thoracic radiography identified bullae or blebs in only 2 of 12 dogs with spontaneous pneumothorax, whereas computed tomography was successful in identifying lesions in 9 of these dogs.

Pneumothorax in patients with *Paragonimus* infection may respond to treatment with anthelmintics (see Chapter 22) and supportive therapy as described for traumatic pneumothorax. Retrospective studies support surgical intervention for most dogs with spontaneous pneumothorax. In a review of 21 cases, Holtsinger et al. (1993) found that most dogs with spontaneous pneumothorax managed medically with chest tubes and suction ultimately required surgery during initial hospitalization or upon subsequent recurrence of pneumothorax to resolve the problem. Because unobserved recurrence of spontaneous pneumothorax can be fatal, conservative treatment is believed to carry greater risk than is associated with surgery. Furthermore, a report of 64 cases by Puerto et al. (2002) showed that recurrence and mortality rates for dogs with spontaneous pneumothorax were lower in dogs that had surgery compared with dogs that were treated conservatively. Similar data are not available to guide the management recommendations for cats with spontaneous pneumothorax, but supportive therapy is preferred for most cats. In a retrospective study of 35 cats, mortality was high regardless of treatment, with only 19 cats (54%) surviving to discharge (Mooney et al., 2012). Only 1 of 5 cats that had thoracotomy survived.

For patients undergoing thoracotomy, a median sternotomy is generally recommended to allow exposure of all lung lobes because it is often not possible to localize all cavitary lesions preoperatively (Fig. 24.4). Abnormal tissue is evaluated histologically and microbiologically for a definitive diagnosis.

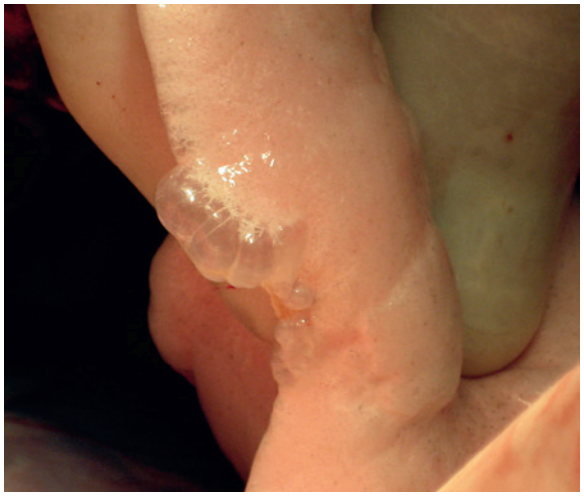


FIG 24.4
Blebs can be seen in this intraoperative image of the lung of a dog that presented with spontaneous pneumothorax. The size of these blebs precluded their identification by thoracic radiography or computed tomography. (Courtesy Dr. Guillaume Pierre Chanoit.)

Pleurodesis is used in the management of people with recurrent pneumothorax. Thus far, a consistently successful technique has not been found for obliterating the pleural space in dogs or cats. The infusion of autologous blood into the pleural cavity has shown some promise in dogs, perhaps functioning as a "patch" over an ongoing leak rather than obliterating the pleural space. Case reports are limited, and dogs with ongoing leakage from traumatic pneumothorax seemed most responsive (Oppenheimer et al., 2014).

Regardless of the treatment used, recurrence is a possibility. Accurate diagnosis of the underlying lung disease and determination of the extent of involvement through a thoracotomy assist in determining the prognosis.

MEDIASTINAL MASSES

Mediastinal masses can cause inspiratory distress as a result of displacement of lung tissue by the mass itself or by the secondary pleural effusion that may develop. Additional clinical signs such as coughing, regurgitation, and facial edema may be present. Neoplasia is the primary differential diagnosis. Lymphoma involving the mediastinum is common, particularly in cats. Other types of neoplasms include thymoma and rarely thyroid carcinoma, parathyroid carcinoma, and chemodectoma. Nonneoplastic mass lesions such as abscesses, granulomas, hematomas, and cysts are other possibilities.

Mediastinal masses in cats can sometimes be palpated during gentle compression of the anterior thorax. Radiographically, mediastinal masses appear as soft tissue opacities in the anterior mediastinum (Fig. 24.5). However, it can be difficult to accurately identify a mediastinal mass if pleural



FIG 24.5
Ventrodorsal view of the thorax of a cat with an anterior mediastinal mass. Soft tissue opacity fills the anterior mediastinum and obscures the border of the heart.

fluid is present. Pleural fluid can both mimic the appearance of a mass and obscure its borders. Ultrasonography done before removal of the pleural fluid is helpful in identifying a mass and determining the extent to which surrounding structures are involved.

Thoracocentesis and fluid analysis should be performed in animals with pleural effusion. Lymphoma can frequently be diagnosed through identification of malignant cells in the effusion. Transthoracic fine-needle aspiration or biopsy can be performed to obtain specimens for microscopic evaluation of the mass itself. Aspiration cytology is generally performed initially, followed by biopsy if a cytologic diagnosis is not obtained. Transthoracic biopsy specimens can often be obtained relatively safely with ultrasound guidance, particularly if the lesion is solid rather than cystic. A study by Lana et al. (2006) demonstrated the usefulness of flow cytometry of mediastinal mass aspirates in differentiating lymphoma from thymoma in dogs.

Surgical exploration or thoracoscopy may be necessary for biopsy of small lesions, cavitary lesions, and lesions adjacent to the heart or main blood vessels. Complete excision

of the mass should be attempted at that time, unless lymphoma is diagnosed. (Specific recommendations for the management of dogs and cats with mediastinal neoplasia are given in Chapter 78.)

PNEUMOMEDIASTINUM

Pneumomediastinum is identified radiographically. Subcutaneous emphysema or pneumothorax can occur concurrently or secondarily. Respiratory compromise most often results from pneumothorax. Mediastinal air commonly originates from rupture or tears in the trachea, bronchi, or alveoli. These leaks can occur as a result of bite wounds of the neck or sudden changes in intrathoracic pressure resulting from coughing, blunt trauma, or excessive respiratory efforts against obstructed airways. Potential iatrogenic causes include tracheal washing, tracheostomy, and endotracheal tube placement (usually by overinflation of the cuff). Air can enter the mediastinum through esophageal tears, generally resulting from foreign bodies.

Strict cage rest is indicated for animals with pneumomediastinum to facilitate natural sealing of the tear. If air continues to accumulate, causing respiratory compromise, bronchoscopy should be performed to identify tracheal or bronchial lacerations that may require surgical repair.

Suggested Readings

Au JJ, et al. Use of computed tomography for evaluation of lung lesions associated with spontaneous pneumothorax in dogs: 12 cases (1999-2002). *J Am Vet Med Assoc*. 2006;228:733.

Barrs VR, Beatty JA. Feline pyothorax—new insights into an old problem: part 1. Aetiopathogenesis and diagnostic investigation. *Vet J*. 2009;179:163.

Boothe HW, et al. Evaluation of outcomes in dogs treated for pyothorax: 46 cases (1983-2001). *J Am Vet Med Assoc*. 2010;236:657.

Fossum TW. *Small animal surgery*. 4th ed. St Louis: Elsevier Mosby; 2013.

Fossum TW, et al. Thoracic duct ligation and pericardectomy for treatment of idiopathic chylothorax. *J Vet Intern Med*. 2004;18:307.

Holtsinger RH, et al. Spontaneous pneumothorax in the dog: a retrospective analysis of 21 cases. *J Am Anim Hosp Assoc*. 1993;29:195.

Lana S, et al. Diagnosis of mediastinal masses in dogs by flow cytometry. *J Vet Intern Med*. 2006;20:1161.

Lappin MR, et al. Antimicrobial use guidelines for the treatment of respiratory tract disease in dogs and cats: antimicrobial guidelines working group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Liu DT, et al. Feline secondary spontaneous pneumothorax: a retrospective study of 16 cases (2000-2012). *J Vet Emerg Crit Care (San Antonio)*. 2014;24:316.

McAnulty JF. Prospective comparison of cisterna chyli ablation to pericardectomy for treatment of spontaneously occurring idiopathic chylothorax in the dog. *Vet Surg*. 2011;40:926.

Mooney ET, et al. Spontaneous pneumothorax in 35 cats (2001-2010). *J Feline Med Surg*. 2012;14:384.

Moore AS. Chemotherapy for intrathoracic cancer in dogs and cats. *Probl Vet Med*. 1992;4:351.

Oppenheimer N, et al. Retrospective evaluation of the use of autologous blood-patch treatment for persistent pneumothorax in 8 dogs (2009-2012). *J Vet Emerg Crit Care (San Antonio)*. 2014;24:215.

Puerto DA, et al. Surgical and nonsurgical management of and selected risk factors for spontaneous pneumothorax in dogs: 64 cases (1986-1999). *J Am Vet Med Assoc*. 1670;220:2002.

Rooney MB, et al. Medical and surgical treatment of pyothorax in dogs: 26 cases (1991-2001). *J Am Vet Med Assoc*. 2002;221:86.

Singh A, et al. Idiopathic chylothorax: pathophysiology, diagnosis, and thoracic duct imaging. *Compend Contin Educ Vet*. 2012a;34:E1.

Singh A, et al. Idiopathic chylothorax: nonsurgical and surgical management. *Compend Contin Educ Vet*. 2012b;34:E1.

Smeak DD, et al. Treatment of chronic pleural effusion with pleuroperitoneal shunts in dogs: 14 cases (1985-1999). *J Am Vet Med Assoc*. 1590;219:2001.

Stillion JR, et al. A clinical review of the pathophysiology, diagnosis, and treatment of pyothorax in the dog and cat. *J Vet Emerg Crit Care (San Antonio)*. 2015;25:113.

Thomas EK, Syring RS. Pneumomediastinum in cats: 45 cases (2000-2010). *J Vet Emerg Crit Care (San Antonio)*. 2013;23:429.

Thompson MS, et al. Use of rutin for the medical management of idiopathic chylothorax in four cats. *J Am Vet Med Assoc*. 1999;215:245.

Waddell LS, et al. Risk factors, prognostic indicators, and outcome of pyothorax in cats: 80 cases (1986-1999). *J Am Vet Med Assoc*. 2002;221:819.

Walker AL, et al. Bacteria associated with pyothorax of dogs and cats: 98 cases (1989-1998). *J Am Vet Med Assoc*. 2000;216:359.

CHAPTER 25

Emergency Management of Respiratory Distress



GENERAL CONSIDERATIONS

Respiratory distress, or *dyspnea,* refers to an abnormally increased effort in breathing. Some authors prefer to use terms such as *hyperpnea* and *increased respiratory effort* in reference to this abnormality because *dyspnea* and *distress* imply feelings that cannot be determined with certainty in animals. Breathing difficulties are extremely stressful for people and are likely so for dogs and cats as well. Dyspnea is also physically exhausting to the animal as a whole and to the respiratory musculature specifically. Animals in respiratory distress at rest should be managed aggressively, and their clinical status should be frequently assessed.

A dog or cat in respiratory distress may show orthopnea, which is difficulty breathing in certain positions. Animals with orthopnea will assume a sitting or standing position with their elbows abducted and neck extended. Movement of the abdominal muscles that assist ventilation may be exaggerated. Cats normally have minimal visible respiratory effort. Cats that show noticeable chest excursions or open-mouth breathing are severely compromised. Cyanosis, in which normally pink mucous membranes are bluish, is a sign of severe hypoxemia and indicates that the increased respiratory effort is not sufficiently compensating for the degree of respiratory dysfunction. Pallor of the mucous membranes is a more common sign of acute hypoxemia resulting from respiratory disease than is cyanosis.

Respiratory distress caused by respiratory tract disease most commonly develops as a result of large airway obstruction, severe pulmonary parenchymal or vascular disease (i.e., pulmonary thromboembolism), pleural effusion, or pneumothorax. Respiratory distress can also occur as a result of primary cardiac disease causing decreased perfusion, pulmonary edema, or pleural effusion (see Chapter 1). In addition, noncardiopulmonary causes of hyperpnea must be considered in animals with apparent distress, including severe anemia, hypovolemia, acidosis, hyperthermia, and neurologic disease. Pain and steroid administration can cause tachypnea and should be considered among the differential diagnoses in patients without other evidence of respiratory disease. Normal breath sounds may be increased in dogs and cats without respiratory disease, but crackles or wheezes are not expected.

A physical examination should be performed rapidly, with particular attention paid to the breathing pattern, auscultatory abnormalities of the thorax and trachea, pulses, and mucous membrane color and perfusion. Attempts at stabilizing the animal's condition should be made before further diagnostic testing is initiated.

Dogs and cats in shock should be treated appropriately (see Chapter 28). Most animals in severe respiratory distress benefit from decreased stress and activity, placement in a cool environment, and oxygen supplementation. Cage rest is extremely important, and the least stressful method of oxygen supplementation should be used initially. An oxygen cage achieves both of these goals, with the disadvantage that the animal is inaccessible. Sedation of the animal may be beneficial (Table 25.1). More specific therapy depends on the location and cause of the respiratory distress (Table 25.2). Ventilatory support is needed for patients that are not adequately oxygenating despite appropriate treatment or who have ventilatory failure. Oxygen supplementation and ventilator support are discussed later in this chapter.

EMERGENCY MANAGEMENT BASED ON LOCALIZATION

LARGE AIRWAY DISEASE

Diseases of the large airways result in respiratory distress by obstructing the flow of air into the lungs. For the purposes of these discussions, extrathoracic large airways (otherwise known as *upper airways*) include the pharynx, larynx, and trachea proximal to the thoracic inlet; intrathoracic large airways include the trachea distal to the thoracic inlet and bronchi. Animals presenting in respiratory distress caused by large airway obstruction typically have a markedly increased respiratory effort with a minimally increased respiratory rate (see Table 25.2). Excursions of the chest may

TABLE 25.1

Drugs Used to Decrease Stress in Animals With Respiratory Distress

Upper Airway Obstruction: Decreases Anxiety and Lessens Respiratory Efforts, Decreasing Negative Pressure Within Upper Airways		
Acepromazine	Dogs and cats	0.01-0.2 mg/kg IV, IM, SC (no more than 3 mg total dose)
Morphine	Dogs only, particularly brachycephalic dogs	0.2-2.0 mg/kg IM, SC; CRI, 0.1-0.3 mg/kg loading dose, then 0.1-0.3 mg/kg/h
Pulmonary Edema: Decreases Anxiety		
Morphine	Dogs only	0.2-2.0 mg/kg IM, SC; CRI, 0.1-0.3 mg/kg loading dose, then 0.1-0.3 mg/kg/h
Acepromazine	Dogs and cats	0.01-0.2 mg/kg IV, IM, SC (no more than 3 mg total dose)
Rib Fractures, After Thoracotomy, Other Trauma: Pain Relief		
Hydromorphone	Dogs and cats	0.1-0.2 mg/kg IV, IM, SC; CRI, 0.025-0.050 mg/kg IV loading dose, then 0.01-0.04 mg/kg/h
Butorphanol	Dogs and cats	0.1-0.8 mg/kg IV, IM, SC; CRI, 0.1-0.2 mg/kg IV loading dose, then 0.1-0.2 mg/kg/h
Buprenorphine	Dogs and cats	0.005-0.020 mg/kg IV, IM

CRI, Continuous-rate infusion; *IM,* intramuscularly; *IV,* intravenously; *SC,* subcutaneously.
Dosage recommendations from Quandt J: Analgesia, anesthesia, and chemical restraint in the emergent small animal patient, *Vet Clin North Am Small Anim Pract* 43:214, 2013.

TABLE 25.2

Localization of Respiratory Tract Disease by Physical Examination Findings in Dogs and Cats With Severe Respiratory Distress

	LARGE AIRWAY DISEASE		PULMONARY PARENCHYMAL DISEASE			
	EXTRATHORACIC (UPPER)	**INTRATHORACIC**	**OBSTRUCTIVE**	**RESTRICTIVE**	**OBSTRUCTIVE AND RESTRICTIVE**	**PLEURAL SPACE DISEASE**
Respiratory rate	Nl-↑	Nl-↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Relative effort	↑↑↑Inspiration	↑↑Expiration	↑Expiration	↑↑Inspiration	No difference	↑Inspiration
Audible sounds	Inpiratory stridor, stertor	Expiratory cough/wheeze	Rarely expiratory wheeze	None	None	None
Auscultable sounds	Referred upper airway sounds; ↑↑breath sounds	End expiratory click; ↑↑breath sounds	Expiratory wheezes or ↑↑breath sounds; rarely, ↓breath sounds with air trapping	↑↑Breath sounds; ±crackles	↑↑Breath sounds, crackles, and/or wheezes	↓Breath sounds

↑, Slightly increased; ↑↑, increased; ↑↑↑, markedly increased; ↓, decreased; *Nl,* normal. Normal respiratory rates for dogs and cats at rest are ≤ 20/min. In the hospital setting, rates of ≤ 30/min are generally accepted as normal.

be increased (i.e., deep breaths are taken). Breath sounds are often increased.

Extrathoracic (Upper) Airway Obstruction

Patients with extrathoracic (upper) airway obstruction typically exhibit the greatest breathing effort during inspiration, which is generally prolonged relative to expiration. Stridor or stertor is usually heard, generally during inspiration. A history of voice change may be present with laryngeal disease.

Laryngeal paralysis and brachycephalic airway syndrome are the most common causes of upper airway obstruction

(see Chapter 18). Other laryngeal and pharyngeal diseases are listed in Boxes 16.1 and 16.2. Severe tracheal collapse can result in extrathoracic or intrathoracic large airway obstruction, or both. Rarely, other diseases of the extrathoracic trachea, such as foreign body, stricture, neoplasia, granuloma, and hypoplasia, result in respiratory distress.

Patients with extrathoracic airway obstruction often present with acute distress in spite of the chronic nature of most of these diseases, because of a vicious cycle of increased respirations leading to increased obstruction, as described in Chapter 16. This cycle can almost always be broken with medical management (Fig. 25.1). The patient is sedated (see Table 25.1) and provided a cool, oxygen-rich environment (e.g., oxygen cage). For dogs with brachycephalic airway syndrome, morphine is given. Otherwise, acepromazine is used. Subjectively, dogs with brachycephalic airway syndrome seem to have greater difficulty maintaining a patent airway when sedated with acepromazine compared with morphine. Short-acting corticosteroids (e.g., dexamethasone, 0.1 mg/kg intravenously) are thought by some to be effective in decreasing local inflammation.

In rare cases, sedation and oxygen supplementation will not resolve the respiratory distress, and the obstruction must be physically bypassed. Placement of an endotracheal tube is generally effective. A short-acting anesthetic agent is administered. Long and narrow endotracheal tubes with stylets should be available to pass by large or deep obstructions. If an endotracheal tube cannot be placed, a transtracheal catheter can be inserted distal to the obstruction (see later in this chapter). If a tracheostomy tube is needed, it can then be placed under controlled, sterile conditions. It is rarely necessary to perform a nonsterile emergency tracheostomy.

Intrathoracic Large Airway Obstruction

Respiratory distress caused by intrathoracic large airway obstruction is rare. Patients with intrathoracic large airway obstruction typically exhibit the greatest breathing effort during expiration, which is generally prolonged relative to inspiration. The most common cause of intrathoracic large airway obstruction is collapse of the mainstem bronchi and/or intrathoracic trachea (tracheobronchomalacia; see Chapter 21). A high-pitched, wheezing, cough-like sound is often heard during expiration in these patients, and crackles or wheezes may be auscultated. Other differential diagnoses include foreign body, advanced *Oslerus* infection, tracheal neoplasia, tracheal stricture, and bronchial compression by extreme hilar lymphadenopathy.

Sedation, oxygen supplementation, and minimization of stress as described for the management of extrathoracic airway obstruction are often effective in stabilizing these patients as well. High doses of hydrocodone or butorphanol will provide cough suppression and sedation (see Chapter 21). Dogs with chronic bronchitis may benefit from bronchodilators and corticosteroids.

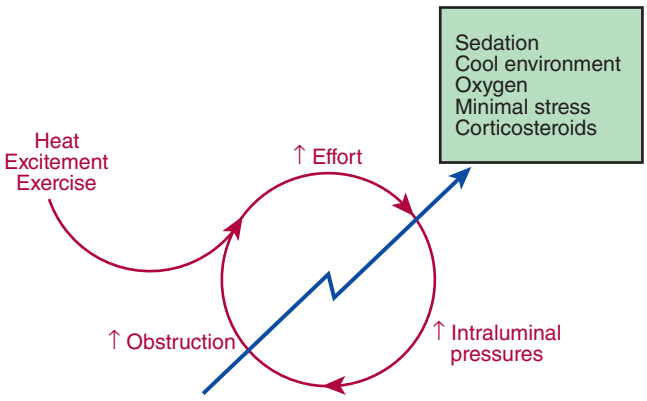


FIG 25.1
Patients with extrathoracic (upper) airway obstruction often present in acute respiratory distress because of progressive worsening of airway obstruction after an exacerbating event. Medical intervention is nearly always successful in breaking this cycle and stabilizing the patient's respiratory status.

PULMONARY PARENCHYMAL DISEASE

Diseases of the pulmonary parenchyma result in hypoxemia and respiratory distress through a variety of mechanisms, including obstruction of small airways (obstructive lung disease; e.g., idiopathic feline bronchitis); decreased pulmonary compliance (restrictive lung disease, "stiff" lungs; e.g., pulmonary fibrosis); and interference with pulmonary circulation (e.g., pulmonary thromboembolism). Most patients with pulmonary parenchymal disease, including those with pneumonia or pulmonary edema, develop hypoxemia through a combination of these mechanisms that contribute to $\dot{V}/\dot{Q}$ mismatch (see Chapter 20), including airway obstruction and alveolar flooding, and decreased compliance.

Animals that present in respiratory distress caused by pulmonary parenchymal disease typically have a markedly increased respiratory rate (see Table 25.2). Patients with primarily obstructive disease, usually cats with bronchial disease, may have prolonged expiration relative to inspiration with increased expiratory efforts. Expiratory wheezes are commonly auscultated. Patients with primarily restrictive disease, usually dogs with pulmonary fibrosis, may have prolonged inspiration relative to expiration and effortless expiration. Crackles are commonly auscultated. Occasionally, cats with severe bronchial disease will develop a restrictive breathing pattern in association with air trapping and hyperinflation of the lungs. Other patients, in which a combination of these processes is occurring, show increased effort during both phases of respiration; shallow breathing; and crackles, wheezes, or increased breath sounds on auscultation. Differential diagnoses for dogs and cats with pulmonary disease are provided in Box 19.1.

Oxygen therapy is the treatment of choice for stabilizing dogs or cats with severe respiratory distress believed to be caused by pulmonary disease. Bronchodilators, diuretics, or glucocorticoids can be considered as additional treatments if oxygen therapy alone is not adequate.

Bronchodilators, such as theophyllines or β-agonists, are used if obstructive lung disease is suspected because they

decrease bronchoconstriction. In combination with oxygen, they are the treatment of choice for cats with signs of bronchitis (see Chapter 21). Subcutaneous terbutaline (0.01 mg/kg, repeated in 5 to 10 minutes if necessary) or albuterol administered by metered dose inhaler (MDI) is most often used in emergency situations. Due to the airway obstruction, drug administered by MDI may not penetrate into deeper airways and often must be repeated numerous times before an effect is seen. Heart rate is used to monitor for toxicity. Bronchodilators are described in greater detail in Chapter 21.

Diuretics such as furosemide (2 mg/kg, administered intravenously) are indicated for the management of pulmonary edema. If edema is among the differential diagnoses of an unstable patient, a short trial of furosemide therapy is reasonable. However, potential complications of diuretic use resulting from volume contraction and dehydration should be taken into consideration. Continued use of diuretics is contraindicated in animals with exudative lung disease or bronchitis because systemic dehydration results in drying of airways and airway secretions. Mucociliary clearance of airway secretions and contaminants is decreased, and airways are further obstructed with mucus plugs.

Glucocorticoids decrease inflammation. Injectable formulations such as dexamethasone (0.1 to 0.5 mg/kg, administered intravenously) are indicated for animals in severe respiratory distress caused by the following conditions: idiopathic feline bronchitis, thromboembolism after adulticide treatment for heartworms, allergic bronchitis, pulmonary parasitism, and respiratory failure soon after initiation of treatment for pulmonary mycoses. Animals with other inflammatory diseases or acute respiratory distress syndrome (ARDS) may respond favorably to glucocorticoid administration. The potential negative effects of corticosteroids must be considered before their use. For example, the immunosuppressive effects of these drugs can result in exacerbation of an infectious disease. Although the use of short-acting corticosteroids for acute stabilization of such cases probably will not greatly interfere with appropriate antimicrobial therapy, long-acting agents and prolonged administration should generally be avoided. Glucocorticoid therapy potentially interferes with the results of future diagnostic tests, particularly if lymphoma or eosinophilic disease are differential diagnoses. Appropriate diagnostic tests are performed once the patient can tolerate the stress.

Broad-spectrum antibiotics are administered if there is evidence of sepsis (e.g., fever, neutrophilic leukocytosis with left shift, moderate to marked toxicity of neutrophils) or a high degree of suspicion of bacterial or aspiration pneumonia. Note that airway specimens (usually tracheal wash) should be obtained for culture if at all possible before broad-spectrum antibiotics are initiated to confirm the diagnosis of bacterial infection and to obtain susceptibility data. Specimens obtained after antibiotics are initiated may not be diagnostic, even with continued progression of signs. However, airway sampling may not be possible in these unstable patients. If sepsis is suspected, blood and urine cultures may be useful. The diagnosis and treatment of bacterial and aspiration pneumonia are described in Chapter 22.

If the dog or cat does not respond to this management, it may be necessary to intubate the patient and institute positive-pressure ventilation until a diagnosis can be established and specific therapy initiated.

PLEURAL SPACE DISEASE

Pleural space diseases cause respiratory distress by preventing normal lung expansion. Animals presenting in respiratory distress as a result of pleural space disease typically have a markedly increased respiratory rate (see Table 25.2). Relatively increased inspiratory efforts may be noted but are not always obvious. Decreased lung sounds on auscultation distinguish patients with tachypnea caused by pleural space disease from patients with tachypnea caused by pulmonary parenchymal disease. Increased abdominal excursions during breathing may be noted.

Paradoxical breathing refers to a breathing pattern in which the abdominal walls are "sucked in" during inspiration. Paradoxical breathing has been associated with pleural diseases in dogs and cats presented for respiratory distress (LeBoedec et al., 2012). The authors of this study attribute the paradoxical breathing to decreased inhibition of contraction of the intercostal muscles secondary to increased pleural pressure. The reported sensitivity and specificity of the finding as a predictor of pleural disease were 0.67 and 0.83 in dyspneic dogs, and 0.90 and 0.58 in dyspneic cats, respectively.

Most patients in respiratory distress resulting from pleural space disease have pleural effusion or pneumothorax (see Chapter 23). Other differential diagnoses are diaphragmatic hernia and mediastinal masses. If pleural effusion or pneumothorax is suspected to be causing respiratory distress, needle thoracocentesis (see Chapter 23) should be performed immediately before further diagnostic testing is conducted or any drugs are administered. Where available, ultrasonography can be used for rapid, minimally stressful assessment of the pleural space for fluid or air. The acronym for the examination is *TFAST,* which stands for *t*horacic *f*ocused *a*ssessment with *s*onography for *t*rauma. See the Lisciandro (2011) reference for probe positions and characteristic sonographic signs. Oxygen can be provided by mask while thoracocentesis is performed, but successful drainage of the pleural space will quickly improve the animal's condition. Occasionally, emergency placement of a chest tube is necessary to evacuate rapidly accumulating air (see Chapter 23).

As much fluid or air should be removed as possible. The exception is for animals with acute hemothorax. Hemothorax is usually the result of trauma or rodenticide intoxication. The respiratory distress associated with hemothorax is often the result of acute blood loss rather than an inability to expand the lungs. In this situation, as little volume as is needed to stabilize the animal's condition is removed. The remainder will be reabsorbed (autotransfusion) to the benefit of the animal. Aggressive fluid therapy is indicated.

OXYGEN SUPPLEMENTATION AND VENTILATION

OXYGEN SUPPLEMENTATION

Oxygen supplementation is generally indicated to maintain arterial blood oxygen pressures (Pa_{O_2}) at greater than 60 mm Hg. Oxygen supplementation is indicated in every dog or cat with signs of respiratory distress or labored breathing. Cyanosis is another clear indication. Whenever possible, the cause of hypoxemia should be identified and specific treatment initiated as well. Assisted ventilation is indicated for animals with an inadequate arterial oxygen concentration despite supplementation, and for animals with arterial carbon dioxide pressures exceeding 60 mm Hg (see Chapter 20).

The inhaled concentration of oxygen can be supplemented by the administration of 100% oxygen by mask, hood, nasal catheter, transtracheal catheter, endotracheal tube, tracheal tube, or oxygen cage. Administration of oxygen by nasal catheter is very well suited to most practices.

When administering 100% oxygen to an animal, the clinician must consider the anhydrous nature of pure oxygen and the toxic effects of oxygen in a high concentration. Because oxygen from tanks contains no water, drying of the airways can occur quickly, particularly if the nasal cavity has been completely bypassed by catheters or tubes. All animals with respiratory tract diseases should be systemically hydrated. Moisture must be added to the airways of animals who have been receiving oxygen by catheter or tube for longer than a few hours. Ventilators designed for long-term use have a heated humidifier incorporated into their design. Humidity exchange filters, which can also be attached to tracheal and endotracheal tubes, function by retaining moisture from exhaled air and adding it to inhaled air. These filters can support bacterial growth and must be replaced daily. Nebulization can also be used to add moisture to the airways. Less effective methods of hydration, such as instillation of sterile 0.9% sodium chloride solution directly into tubes or catheters, can be used if other options are not available. Some water vapor can also be added to the oxygen by incorporating pass-over or bubble humidifiers in the system.

Inhalation of air with greater than 50% oxygen is toxic to the pulmonary epithelium. Pulmonary function deteriorates, and death can result. Air with greater than 50% oxygen is therefore not provided for longer than 12 hours. If higher concentrations are necessary to maintain adequate arterial oxygen concentrations, ventilatory support is initiated.

Oxygen Masks

Oxygen masks are useful for short-term supplementation. The animal experiences minimal stress, and manipulations such as venous catheter placement and thoracocentesis can be performed. A snug fit is desirable to decrease the volume of dead space, and a relatively high flow rate is necessary (Table 25.3). Sterile eye ointment is applied to prevent desiccation of the corneas.

TABLE 25.3

Maximum Achievable Oxygen Concentrations and Associated Flow Rates for Various Methods of Supplementation

METHOD OF ADMINISTRATION	MAXIMUM OXYGEN CONCENTRATION (%)	FLOW RATE
Mask	50-60	8-12 L/min
Nasal catheter	50	6-8 L/min or 50-150 mL/kg/min
Transtracheal catheter	30-40	1-2 L/min
Endotracheal tube	100	0.2 L/kg/min
Tracheal tube	100	0.2 L/kg/min
Oxygen cage	60	2-3*

*After cage is filled, flow is adjusted on the basis of oxygen concentration as measured by oxygen sensor.
From Court MH et al.: Inhalation therapy: oxygen administration, humidification, and aerosol therapy, *Vet Clin North Am Small Anim Pract* 15:1041, 1985.

Oxygen Hoods

Oxygen hoods that can be placed over the animal's head are available. With some, the animals must be laterally recumbent and still, limiting the use of hoods to animals recovering from anesthesia, those that are severely depressed, and those that are heavily sedated (Fig. 25.2). Others are designed to completely surround the animal's head and are attached around the neck. One design is an adaptation of an Elizabethan collar (OxyHood, JorVet). In some situations, oxygen hoods may be better tolerated than oxygen masks, and it may take less manpower to care for an animal for which one is being used than an animal with an oxygen mask. A means for escape of exhaled air must always be provided to prevent the buildup of CO_2 within the hood.

Nasal Catheters

Nasal catheters can be used for long-term oxygen supplementation (Fig. 25.3). The animal is relatively free to move and is accessible for evaluation and treatment. Most animals tolerate the catheter well. Catheters can become obstructed with nasal secretions, however. Soft red rubber or infant feeding tubes or polyurethane catheters can be used. Tube size is based on patient size. In general, a 3.5 to 5F tube is used for cats, and a 5 to 8F tube is used for dogs.

Sedation is rarely necessary for catheter placement. First, the length of tubing to be inserted into the nasal cavity is measured against the head of the animal. The tubing should reach the level of the carnassial tooth. A water-soluble lubricant or 0.2% lidocaine jelly is applied to the length of the catheter that will be within the nasal cavity. Next, 0.2%



FIG 25.2
An oxygen hood can be used for recumbent animals as a substitute for an oxygen mask. In this patient, oxygen is being delivered through an opening in the top of the hood, and the light blue opening that will accommodate standard anesthesia tubing is left open for circulation of air. Regardless of the method used to increase the oxygen in inspired air, a means for escape of expired CO_2 is essential (Disposa-Hood, Utah Medical Products, Inc.).



FIG 25.3
Dog with intranasal catheter in place for delivery of oxygen. The catheter is sutured to the muzzle less than 1 cm from its exit from the naris and is further anchored with sutures to the face so that it exits behind the animal's head. An Elizabethan collar is routinely used to prevent the animal from removing the catheter.

lidocaine is dripped gently into the nasal cavity through the naris with the animal's nose pointed upward. The catheter is then passed through the naris and is initially aimed dorsomedially through the naris, then immediately ventromedially. Once the correct length of catheter has been inserted, it is gently bent beneath the lateral cartilage and sutured to the muzzle no farther than 1 cm caudal to the exit from the naris. The catheter can be further anchored to the face with sutures securing its path between the eyes to behind the animal's head. An Elizabethan collar is placed on the patient to prevent the animal from removing the catheter.

A sterile intravenous set can be connected to the catheter. The intravenous line can be attached to a half-filled bottle of sterile saline solution and positioned above the fluid level. Oxygen is then delivered through the bottle, below the fluid level, providing some moisture as the oxygen bubbles through the saline.

Transtracheal Catheters

Oxygen can be administered through a jugular catheter placed with sterile technique through the trachea. This approach is particularly useful for the emergency stabilization of animals with an upper airway obstruction. The catheter is placed as for transtracheal washing (see Chapter 20).

Endotracheal Tubes

Endotracheal tubes are used to administer oxygen during surgical procedures and cardiopulmonary resuscitation. They can be used to bypass most upper airway obstructions for emergency stabilization. Pure oxygen can be administered for short periods. Longer supplementation requires the mixing of 100% oxygen with room air. Ventilation can be provided with a cuffed endotracheal tube. Trauma to the trachea is decreased by using high-volume, low-pressure cuffs and by inflating the cuff with the least amount of pressure necessary to create a seal. If positive-pressure ventilation is not being used, the cuff can remain deflated.

Because endotracheal tubes are not tolerated by alert animals, tracheal tubes are preferred for long-term management. Conscious animals in which endotracheal tubes are used must be given sedatives, analgesics, paralyzing agents, or a combination of these drugs. The cuff should be deflated when possible to minimize tracheal damage. The tube must be cleaned periodically to remove secretions (see the recommendations for tracheal tube cleaning), and frequent flushing of the oral cavity is performed. Moisture must be added to the inspired gases, as previously discussed.

Tracheal Tubes

Tracheal tubes are placed through the tracheal rings and are readily tolerated by conscious animals. It is rare that an animal requires an emergency tracheostomy. Nearly all such animals can be stabilized by other techniques, allowing the tracheal tube to be subsequently placed using a careful, sterile surgical technique. Tracheal tubes are generally used for the management of animals with an upper airway obstruction. Room air often contains adequate oxygen for

use in animals with an upper airway obstruction once the obstruction has been bypassed.

The tube itself should have a diameter nearly as wide as the tracheal lumen and a length of 5 to 10 rings. It is necessary to use high-volume, low-pressure cuffs to prevent tracheal damage and subsequent stricture. Double-lumen tubes are ideal for this method. The inner tube can be removed for cleaning and can be replaced easily. Single-lumen tubes also work and may be necessary in small animals.

Tracheal tubes are usually placed with the animal anesthetized with a short-acting agent. The trachea is exposed through a ventral midline incision made just beneath the larynx. The trachea is entered through an incision made a few rings below the cricoid cartilage, parallel to the trachea and perpendicular to the rings, and through just enough rings to allow passage of the tube. Either end of the incision can be widened with a small transverse incision. Stay sutures are placed on each side of the incision to facilitate initial placement of the tube as well as later replacement if the tube is accidentally or intentionally removed. The tube is then inserted into the opening. With minimal pressure on the airway, it is tied with gauze around the neck of the animal. Few or no sutures are used to close the incision to prevent the collection of air subcutaneously. A gauze sponge with a slit cut in it and coated with antiseptic ointment can be placed over the incision and around the tube.

The tube must be monitored for obstruction and cleaned. The inner tube of double-lumen tubes can be easily removed for this purpose. The tube is cleaned every 30 to 60 minutes initially, with the interval increased as fewer secretions accumulate. Sterile technique is used when the tubes are handled, and they must be replaced if they become contaminated.

Single-lumen tubes are difficult to remove and replace safely for the first few days unless stay sutures are left in place. Periodic cleaning can be performed with the tube in place. Sterile saline solution is instilled into the tube for this purpose. To perform suctioning, a sterile urinary catheter with several openings at the end is attached to a suction unit and passed through the tube. The trachea and tracheal tube are then suctioned to remove secretions. Suctioning is performed for short intervals to allow the lungs to reinflate. Cleaning is performed every few hours initially, then less frequently if secretions are not accumulating.

A smaller tube can be used once the animal is able to oxygenate adequately with room air. The tube can be removed when the animal can oxygenate by breathing around a small tube with the lumen obstructed. The incision is allowed to heal without suturing. The tip of the tube is cultured for bacteria.

Antibiotics are not administered prophylactically. Any existing infection or infections that occur during therapy are treated on the basis of culture and sensitivity information.

Complications of tracheal tubes are common. In a report of temporary tracheostomy tubes by Nicholson and Baines (2012), complications occurred in 36 of 42 (86%) patients. Most of these complications were clinically insignificant (e.g., pneumomediastinum, subcutaneous emphysema) or correctable. The most common complications were tube obstruction (26%), dislodgment (21%), aspiration pneumonia (21%), and stoma swelling (21%). Overall, 34 of the dogs (81%) had a successfully managed temporary tracheostomy tube.

Oxygen Cages

Oxygen cages provide an oxygen-enriched environment with minimal stress to animals. However, the animal is isolated from direct contact, which can be a disadvantage. Other environmental factors, such as humidity, temperature, and carbon dioxide concentration, must be monitored and controlled, or extreme stress and even death can occur. The animal is totally dependent on proper cage function. The ability of the cage to maintain the correct environment varies with the specific cage as well as with each animal. Commercial cages are available for veterinary use. Incubators from human hospitals can be modified for small animals.

VENTILATORY SUPPORT

The purposes of ventilatory support are to decrease the retention of carbon dioxide and to improve oxygenation. Ventilatory support is labor intensive and associated with complications. It is used when other means of respiratory support are not adequate.

Retention of carbon dioxide, or hypercapnia, occurs in animals unable to ventilate adequately. Spontaneous ventilation can be impaired by neurologic dysfunction, such as that which occurs with severe head trauma, polyneuropathies, and some toxicities. Ventilatory support is recommended in such animals if the $Paco_2$ level increases to greater than 60 mm Hg. Hypoventilation caused by a pleural effusion or pneumothorax is treated by removing the fluid or air, not by positive-pressure ventilation. Hypoventilation caused by an upper airway obstruction is treated by establishing a patent airway.

Animals with severe lung disease may be unable to maintain adequate oxygenation without ventilatory support. Positive-pressure ventilation is routinely necessary for the management of patients with ARDS (see Pulmonary Edema, Chapter 22). As previously noted, long-term administration of air with an oxygen concentration greater than 50% results in serious lung damage. If the Pao_2 cannot be maintained at greater than 60 mm Hg without excessive oxygen supplementation, ventilatory support is indicated.

The delivery of air by positive pressure is different from normal inhalation of air by negative pressure. With positive pressure, the distribution of ventilation within the lungs is altered. The intrathoracic pressure increases each time the lungs are filled with air, which results in decreased venous return to the heart. Along with other effects, systemic hypotension results and can be severe enough to cause acute renal failure. Compliance of the lungs also decreases over time in animals receiving positive-pressure ventilation. As the lungs

become stiffer, greater pressures are necessary to expand them. Careful monitoring of animals is essential during ventilation. Important variables to monitor include blood gas values, compliance, mucous membrane color, capillary refill time, pulse quality, arterial blood pressure, central venous pressure, lung sounds, and urine output. The extensive nursing care and monitoring required for these patients usually limit the use of long-term ventilatory support to large referral hospitals.

Suggested Readings

Hopper K, Powell LL. Basics of mechanical ventilation for dogs and cats. *Vet Clin North Am Small Anim Pract*. 2013;43:955.

LeBoedec K, et al. Relationship between paradoxical breathing and pleural diseases in dyspneic dogs and cats: 389 cases (2001-2009). *J Am Vet Med Assoc*. 2012;240:1095.

Lisciandro GR. Abdominal and thoracic focused assessment with sonography for trauma, triage, and monitoring in small animals. *J Vet Emerg Crit Care*. 2011;21:104.

Nicholson I, Baines S. Complications associated with temporary tracheostomy tubes in 42 dogs (1998 to 2007). *J Small Anim Pract*. 2012;53:108.

Quandt J. Analgesia, anesthesia, and chemical restraint in the emergent small animal patient. *Vet Clin North Am Small Anim Pract*. 2013;43:214.

Sigrist NE, et al. Evaluation of respiratory parameters at presentation as clinical indicators of respiratory localization in dogs and cats with respiratory distress. *J Vet Emerg Crit Care*. 2011; 21:13.

Drugs Used in Respiratory Disorders*

GENERIC NAME	PURPOSE	DOGS (mg/kg†)	CATS (mg/kg†)
Acepromazine	Sedation	0.01-0.2 IV, IM, SC (maximum, 3 mg)	Same
Albuterol	Bronchodilator	0.02-0.05 PO, SC q8-12h	Same
Amikacin	Antibiotic	15 IV, IM, SC q24h	10 IV, SC q24h
Aminophylline	Bronchodilation; other potential benefits for canine bronchitis patients	11 PO, IV, IM q8h	5 PO, IV, IM q12h
Amoxicillin	Antibiotic	22 PO q8-12h	Same
Amoxicillin-clavulanate	Antibiotic	11 PO q8-12h	12.5 q8-12h
Ampicillin	Antibiotic	22-30 PO, IV, SC q8h	Same
Ampicillin-sulbactam	Antibiotic	20 mg/kg (ampicillin) IV q6-8h	Same
Atropine	Anti-cholinergic	0.04 SC	Same
Azithromycin	Antibiotic	5-10 mg/kg PO q12h for 1 day, then q3d	Same
Buprenorphine	Analgesic	0.005-0.02 IV, IM; duration 4-8h	Same
Butorphanol	Antitussive	0.5 PO q6-12h	Not recommended
Cefadroxil	Antibiotic	11-22 PO q12h	22 PO q24h
Cefazolin	Antibiotic	25 SC, IM, IV q6	Same
Cefoxitin	Antibiotic	10-20 IV, IM q6-8h	Same
Cefovecin	Antibiotic	8 SC once; can be repeated once in 7-14 d	Same
Cephalexin	Antibiotic	22-25 PO q12h	Same
Cetirizine	Antihistamine	2 q12h	1 PO q24h
Chloramphenicol	Antibiotic	50 PO, IV, SC q8h	50 mg/cat PO, IV, SC q12h
Chlorpheniramine	Antihistamine	4-8 mg/dog q12h	2 mg/cat q12h
Clindamycin	Antibiotic	10 PO, SC q12h	10-15 PO, SC q12h



Drugs Used in Respiratory Disorders*—cont'd

GENERIC NAME	PURPOSE	DOGS (mg/kg†)	CATS (mg/kg†)
Cyclophosphamide	Alkylating chemotherapeutic and immunosuppressant	50 mg/m^2 PO q48h	Same
Dexamethasone	Glucocorticoid	0.1-0.5 IV q12h	Same
Dextromethorphan	Cough suppressant	1-2 PO q6-8h	Not recommended
Diazepam	Sedation	0.2-0.5 IV	Same
Diphenhydramine	Antihistamine	1 IM; 2-4 PO q8h	Same
Doxapram	Respiratory stimulant for laryngeal motion examination	1-2 mg/kg IV	—
Doxycycline	Antibiotic	5 PO, IV q12h OR 10 q24h	Same
Enrofloxacin	Antibiotic	5-20 PO, IV, IM q24h	5 PO q24h
Famcyclovir	Antiherpetic	—	90 PO q12h
Fenbendazole	Anthelmintic for lungworms	25-50 mg/kg PO q12h for 14 days	Same
Furosemide	Diuretic	2 PO, IV, IM q8-12h	Same
Glycopyrrolate	Anticholinergic	0.005 IV, SC	Same
Hydrocodone bitartrate	Antitussive	0.25-0.5 PO q6-12h	Not recommended
Hydromorphone	Analgesic	0.1-0.2 IV, IM, SC. CRI: See Table 25.1	Same
Itraconazole (for aspergillosis)	Antifungal	5 PO q12h with food	—
Ivermectin	Anthelmintic	See text for specific parasites	See text for specific parasites
Ketamine	Anesthetic	—	4-11 IV
L-Lysine	Inhibits herpesvirus replication in vitro	—	500 mg/cat PO q12h
Marbofloxacin	Antibiotic	2.7-5.5 PO q24h	Same
Meropenem	Antibiotic	24 IV q12h or 8.5 SC q12h	10 IV, IM, SC q12h
Methylprednisolone acetate	Glucocorticoid	—	10 mg/cat IM q2-4 weeks
Metronidazole	Antibiotic	10 PO q8h PO q12h	Same
Milbemycin	Anthelmintic for nasal mites	0.5-1 PO q7-10d for 3 treatments	—
Minocycline	Antibiotic	5 PO q12h	8.8 PO q24h OR 50 mg/cat q24h
Morphine	—	0.2-2 IM,SC; duration 1-4h. CRI: See Table 25.1	—
Orbifloxacin	Antibiotic	2.5-7.5 PO q12h for tablets	7.5 PO q12h of oral suspension
Oxymetazoline 0.025%	Topical decongestant	—	1 drop/nostril q24h for 3 days, then withhold for 3 days
Phenylephrine 0.25%	Topical decongestant	—	1 drop/nostril q24h for 3 days, then withhold for 3 days
Pradofloxacin	Antibiotic	5 PO q24h	7.5 PO q24h for oral suspension; 5 q24h for tablets

Continued

Drugs Used in Respiratory Disorders*—cont'd

GENERIC NAME	PURPOSE	DOGS (mg/kg†)	CATS (mg/kg†)
Praziquantel	Anthelmintic for *Paragonimus*	23-25 mg/kg PO q8h for 3 days	Same
Prednisone, prednisolone	Glucocorticoid	0.25-2 PO q12h	Same. Prednisolone preferred for cats.
Rutin	Benzopyrone with potential benefit for chylothorax	50-100 q8h	Same
Sildenafil	Phosphodiesterase type 5 inhibitor for pulmonary hypertension	1 q12h; increase to effect up to 3 q8-12h	—
Terbinafine	Antifungal	30 q12h	Same
Terbutaline	Bronchodilator	1.25-5 mg/dog PO q8-12h	1/8-1/4 of 2.5-mg tablet/cat PO q12h to start; 0.01 mg/kg SC, repeat once
Tetracycline ophthalmic ointment	Antibiotic ophthalmic ointment	—	q4-8h
Theophylline base (immediate release)	Bronchodilation; other potential benefits in canine bronchitis	9 PO q8h	4 PO q12h
Trimethoprim-sulfadiazine	Antibiotic	15 PO q12h	Same

IM, Intramuscularly; *IV,* intravenously; *PO,* by mouth; *SC,* subcutaneously.
*Antimicrobial dosages from Lappin MR, et al.: Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases, *J Vet Intern Med* 31:279, 2017.
†Unless otherwise noted.

PART THREE ▪ Digestive System Disorders

Michael D. Willard

CHAPTER 26

Clinical Manifestations of Gastrointestinal Disorders



DYSPHAGIA, HALITOSIS, AND DROOLING

Dysphagia, halitosis, and drooling often coexists in animals with oral disease. Dysphagia (i.e., difficulty in eating) usually results from oral pain, masses, foreign objects, trauma, neuromuscular dysfunction, or a combination of these (Box 26.1). Halitosis typically signifies an abnormal bacterial proliferation secondary to tissue necrosis, tartar, periodontitis, or oral/esophageal retention of food (Box 26.2). Drooling occurs because animals are unable or unwilling to swallow (i.e., pseudoptyalism). Excessive salivation is often due to nausea; animals that are not nauseated rarely produce excessive saliva (Box 26.3). Although any disease causing dysphagia may have an acute onset, clinicians usually should first consider foreign objects or trauma as the cause in acutely dysphagic patients. The environmental and vaccination history should always be assessed to determine whether rabies is a reasonable possibility.

The next step is a thorough oral, laryngeal, and cranial examination. This examination is often the most important diagnostic step because most problems producing oral pain can be partially or completely defined at physical examination. Ideally, this is done without chemical restraint to facilitate detection of pain. However, many animals must be anesthetized for an adequate oral examination to search for anatomic abnormalities, inflammatory lesions, pain, and discomfort. If pain is found, the question is whether it occurs when the mouth is opened (e.g., retrobulbar inflammation), is associated with extraoral structures (e.g., muscles of mastication), or originates from the oral cavity. The clinician must search for fractures, lacerations, crepitus, masses, enlarged lymph nodes, inflamed or ulcerated areas, draining tracts, loose teeth, excessive temporal muscle atrophy, inability to open the mouth while the animal is under anesthesia, and ocular problems (e.g., proptosis of the eye, inflammation, or strabismus suggestive of retrobulbar disease). If oral pain is apparent but cannot be localized, retrobulbar lesions, temporomandibular joint disease, and posterior pharyngeal lesions should be considered. A concurrent clinicopathologic evaluation may be useful, especially if oral examination findings indicate systemic disease (e.g., lingual necrosis resulting from uremia, chronic infection secondary to hyperadrenocorticism).

Mucosal lesions (e.g., masses, inflamed or ulcerated areas) and painful muscles of mastication should be biopsied. Masses that do not disrupt the mucosa, especially those on the midline and dorsal to the larynx, can be difficult to discern and are often best found by digital palpation. Fine-needle aspiration and cytologic evaluation are reasonable first steps for diagnosing masses. Remember that fine-needle aspirates can only find disease; they do not exclude disease (i.e., they are not sensitive tests). Subtle masses or those dorsal to the larynx are often best aspirated with ultrasonographic guidance. Multiple aspirations are usually done before a wedge or punch biopsy is performed.

Incisional biopsy specimens must include generous amounts of submucosal tissues. Many oral tumors cannot be diagnosed with superficial biopsy specimens because normal oral flora cause superficial necrosis and inflammation obscuring the lesion. Clinicians are often afraid to biopsy aggressively because these lesions bleed profusely and are hard to suture. The clinician should avoid major vessels (e.g., the palatine artery) and use silver nitrate to stop hemorrhage. It is better to have difficulty stopping hemorrhage after obtaining an adequate biopsy specimen than to have less difficulty stopping hemorrhage after obtaining a nondiagnostic specimen. If diffuse oral mucosal lesions are noted, search carefully for vesicles (e.g., pemphigus); if found, remove them intact for histopathologic and immunofluorescent studies. If vesicles are not found, then at least two or three tissue samples representing a spectrum of new and old lesions should be obtained.

BOX 26.1

Causes of Dysphagia

Oral Pain

Fractured bones or teeth
Trauma
Periodontitis or caries (especially cats)
Mandibular or maxillary osteomyelitis
Other causes
  Retrobulbar abscess/inflammation
  Various other abscesses or granulomas of the oral cavity
  Temporal-masseter myositis
Stomatitis, glossitis, pharyngitis, gingivitis, tonsillitis, or sialoadenitis
  Immune-mediated disease
  Feline viral rhinotracheitis, calicivirus, leukemia virus, or immunodeficiency virus
  Lingual foreign objects, other foreign objects, or granulomas
  Tooth root abscess
  Uremia
  Electrical cord burn
  Miscellaneous causes
  - Thallium
  - Caustics
Pain associated with swallowing: esophageal stricture or esophagitis

Oral Mass

Tumor (malignant or benign)
Eosinophilic granuloma
Foreign object (oral, pharyngeal, or laryngeal)
Retropharyngeal lymphadenomegaly
Inflammatory polyp of middle ear (primarily cats)
Sialocele

Oral Trauma

Fractured bones (e.g., mandible, maxilla)
Soft tissue laceration
Hematoma

Neuromuscular Disease

Localized myasthenia
Temporal-masseter myositis
Temporomandibular joint disease
Oral, pharyngeal, or cricopharyngeal dysfunction
  Cricopharyngeal achalasia
Tick paralysis
Rabies
Tetanus
Botulism
Various cranial nerve dysfunctions/central nervous system disease

BOX 26.2

Causes of Halitosis

Bacterial Causes

Food retained in the mouth
  Anatomic defect allowing retention (exposed tooth roots, tumor, large ulcer)
  Neuromuscular defect allowing retention (pharyngeal dysphagia)
Food retained in the esophagus
Tartar or periodontitis
Damaged oral tissue
  Neoplasia/granuloma of mouth or esophagus
  Severe stomatitis/glossitis

Eating Noxious Substances

Necrotic or odoriferous food
Feces

BOX 26.3

Major Causes of Drooling

Ptyalism

Nausea
Hepatic encephalopathy (especially feline)
Seizure activity
Chemical or toxic stimulation of salivation (organophosphates, caustics, bitter drugs [e.g., atropine, metronidazole])
Behavior
Hyperthermia
Salivary gland hypersecretion

Pseudoptyalism

Oral pain, especially stomatitis, glossitis, gingivitis, pharyngitis, tonsillitis, or sialoadenitis (see Box 26.1)
Oral or pharyngeal dysphagia (see Box 26.1)
Facial nerve paralysis

If oral examination findings are not helpful, plain oral and laryngeal radiographs are usually the best next steps. Oral cultures are rarely helpful because normal oral flora makes interpretation of results difficult. Even animals with severe halitosis or stomatitis secondary to bacterial infection rarely benefit from bacterial culture, unless there is a draining tract or abscess.

Halitosis often accompanies dysphagia, in which case it is usually more productive to determine the cause of the dysphagia. If halitosis occurs without dysphagia, the clinician should first be sure that the odor is abnormal and then check for the ingestion of odoriferous substances (e.g., feces). A thorough oral examination is still the most important test. Halitosis not attributable to an oropharyngeal lesion may be

originating from the esophagus. Radiographs (plain and/or contrast) or esophagoscopy may reveal a tumor or retained food secondary to stricture or weakness. If the history and oral examination are unrevealing except for mild to moderate tartar accumulation, the teeth should be cleaned to try to resolve the problem.

Drooling is usually caused by nausea, oral pain, or dysphagia. The approach to the diagnosis of oral pain and dysphagia is described under the appropriate headings. Nausea is considered in the section on vomiting.

Dysphagic animals without demonstrable lesions or pain may have neuromuscular disease. Dysphagia of muscular origin usually results from atrophic myositis (see Chapter 67). Finding swollen, painful temporal muscles suggests acute myositis. Finding severe temporal-masseter muscle atrophy plus difficulty opening the mouth (even when the animal is anesthetized) suggests chronic temporal-masseter myositis. Biopsy of affected muscles is indicated. It is critical that muscle tissue be retrieved; it is easy to obtain only fibrous scar tissue. A positive test for antibodies to type 2M muscle fibers is consistent with masticatory muscle myositis but not polymyopathy.

Neurogenic dysphagia is caused by disorders in the oral (i.e., also called *prehensile*), pharyngeal, or cricopharyngeal phases of swallowing (disorders of the latter two phases are discussed in the section on regurgitation). Rabies should always be considered, despite its relative rarity. After rabies is presumptively ruled out, cranial nerve deficits (especially deficits of cranial nerves V, VII, IX, XII) should be considered. Because clinical signs vary depending on the nerve (or nerves) affected, a careful neurologic examination is indicated.

Inability to pick up food or having food drop from the mouth while eating usually indicates a prehensile disorder. Dysphagia may be noticeable in dogs and cats with pharyngeal and cricopharyngeal dysfunction, but regurgitation is often more prominent. Dynamic contrast-enhanced cinefluoroscopy or fluoroscopy is best for detecting and defining neuromuscular dysphagia. Localized myasthenia is an important cause of pharyngeal dysphagia and should be ruled out with serology. If neuromuscular problems are seemingly ruled out by imaging and serology, then anatomic lesions and occult causes of pain (e.g., soft tissue inflammation or infection) must be reconsidered.

DISTINGUISHING REGURGITATION FROM VOMITING FROM EXPECTORATION

Regurgitation is expulsion of material (i.e., food, water, saliva) from the mouth, pharynx, or esophagus and must be differentiated from vomiting (expulsion of material from the stomach and/or intestines) and expectoration (expulsion of material from the respiratory tract). Historical and physical examination findings sometimes allow differentiation (Table 26.1). Expectoration is generally associated with coughing at the time of the event. However, because dogs that cough and gag excessively may stimulate themselves to vomit as well, careful history taking is important. Animals that regurgitate and some that vomit may cough due to aspiration.

TABLE 26.1

Aids to Differentiate Regurgitation From Vomiting*

SIGN	REGURGITATION	VOMITING
Prodromal nausea†	No	Usually
Retching‡	No	Usually
Material produced		
Food	±	±
Bile	No	±
Blood	± (undigested)	± (digested or undigested)
Amount of material	Any amount	Any amount
Time relative to eating	Anytime	Anytime
Distention of cervical esophagus	Rare	No
Dipstick analysis of material		
pH	≥7	≤5 or ≥8
Bile	No	±

*These are *guidelines* that often help distinguish vomiting from regurgitation. However, occasional animals will require plain and/or contrast-enhanced radiographs to distinguish between the two. In particular, animals that are vomiting may appear to be regurgitating. The reverse is less common.
†May include salivation, licking lips, pacing, and an anxious expression. The owner may simply state that the animal is aware that it will soon "vomit."
‡These are usually forceful, vigorous abdominal contractions or dry heaves. This is not to be confused with gagging, which is common in regurgitation.

The criteria in Table 26.1 are guidelines. Some animals that appear to be regurgitating are vomiting and vice versa. In particularly severe cases of esophageal weakness, one may see the cervical esophagus balloon in and out during respiration (Video 26.1). If the clinician cannot distinguish between two based on history and physical examination findings, a urine dipstick may be used to determine pH and whether there is bilirubin in *freshly* "vomited" material. If the pH is 5 or less, the material is probably gastric in origin, resulting from vomiting. A pH of 7 or greater without evidence of bilirubin is most consistent with regurgitation. Finding bilirubin means the material is duodenal in origin (i.e., vomiting). Finding blood in the urine dipstick test is not helpful.

If vomiting and regurgitation still cannot be distinguished, plain thoracic radiographs ± a barium-contrast esophagram will detect most esophageal lesions. However, some esophageal disorders (e.g., hiatal hernia, partial stricture, segmental motility defects) are easily missed unless a careful radiographic technique and/or fluoroscopy is used. Endoscopy is sometimes required to detect esophageal lesions missed by imaging (e.g., esophagitis).

REGURGITATION

If regurgitation is confirmed, the disease should be localized to the oropharynx or esophagus (Fig. 26.1). History or observing the pet eating should allow the clinician to detect dysphagia (e.g., undue stretching or flexing of the neck during swallowing, repeated efforts at swallowing, food falling from the mouth during swallowing). Some animals with dysphagia associated with neuromuscular disorders have more difficulty swallowing liquids than solid foods, probably because it is easier to aspirate liquids. Oropharyngeal dysphagic animals in particular often cough when swallowing water.

If a regurgitating animal is dysphagic, then oral, pharyngeal, and cricopharyngeal dysfunctions must be considered; the latter two clinically mimic each other. Fluoroscopic evaluation of swallowing a barium meal is necessary to differentiate pharyngeal from cricopharyngeal dysfunction. If they are not accurately differentiated, inappropriate therapy may cause morbidity or mortality.

Two main reasons for esophageal regurgitation are obstruction and muscular weakness. Plain thoracic radiographs are the initial step for defining these problems. Barium-contrast esophagrams are often necessary because plain films do not detect many esophageal lesions. Using liquid barium sulfate can miss partial strictures, but mixing barium with canned food or kibble typically reveals these lesions. Fluoroscopy may be necessary to detect partial loss of peristalsis, segmental aperistalsis, gastroesophageal reflux, or sliding hiatal hernias. Sometimes the lower esophageal sphincter must be fluoroscopically observed for several minutes to detect frequency and severity of gastroesophageal reflux (normal animals may show occasional reflux). If the animal seems to be regurgitating but contrast-enhanced radiographs fail to reveal esophageal dysfunction, either the assessment of regurgitation is wrong or there is occult esophageal disease requiring esophagoscopy for diagnosis (e.g., esophagitis, gastroesophageal reflux).

Esophageal obstruction is principally caused by foreign objects, vascular anomalies, cicatrix, and tumors. Achalasia

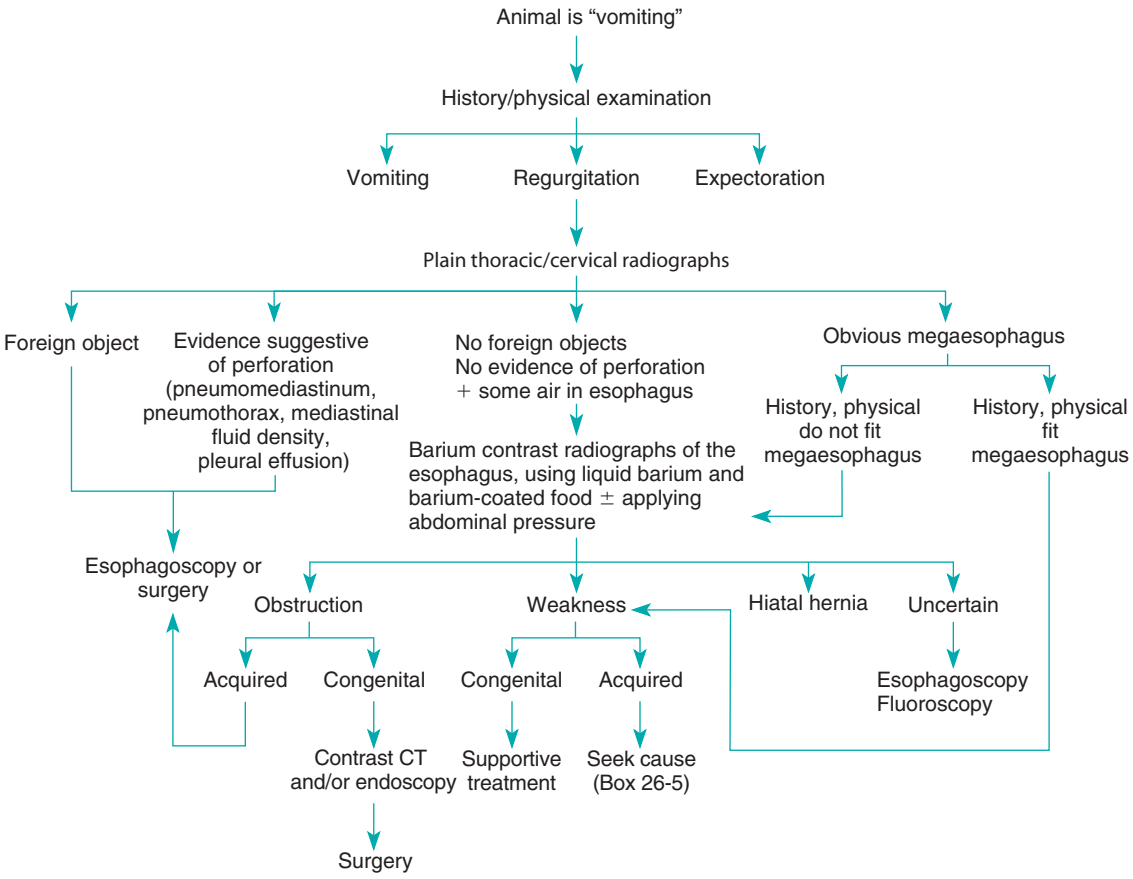


FIG 26.1
General diagnostic approach to regurgitation in the dog and cat.

of the lower esophageal sphincter may sometimes be responsible (Box 26.4). Obstruction should be characterized as congenital or acquired and as intraluminal, intramural, or extraesophageal. Congenital obstructions are usually extraesophageal vascular ring anomalies. Acquired intraluminal obstructions are usually foreign objects or cicatrix secondary to esophagitis. The clinician should always determine whether animals with esophageal foreign objects (especially small foreign objects that would have been expected to have passed) have a partial esophageal stricture that predisposed them to obstruction. Endoscopy may be both diagnostic and therapeutic in these animals; thoracotomy is seldom needed for management of cicatrix or intraluminal foreign objects.

Esophageal weakness may be congenital or acquired. Congenital weakness is typically idiopathic, and further diagnostics are unfruitful. Acquired esophageal weakness usually results from an underlying neuromuscular problem. Although an underlying cause is infrequently diagnosed, finding one may lead to a permanent cure as opposed to supportive therapy of the symptoms. A complete blood count (CBC), serum biochemistry profile, determination of serum antibody titers to acetylcholine receptors, resting serum cortisol (see Chapter 50), serum creatine kinase, and/or fecal examination for *Spirocerca lupi* ova are performed to look for causes of acquired esophageal weakness (Box 26.5). One may also consider searching for lead intoxication (nucleated red blood cells and basophilic stippling in the CBC, serum and urine lead concentrations), canine distemper (retinal lesions), and various neuropathy-myopathies (electromyography, nerve biopsy, muscle biopsy). Chagas disease causes esophageal disease in people but has not been reported to cause esophageal weakness in dogs. Lower esophageal achalasia-like syndrome has been identified in dogs with congenital and acquired weakness. The prevalence of this syndrome is currently uncertain, but assumed to be low. Fluoroscopic examination is necessary for diagnosis.

Esophagoscopy may detect esophagitis or small lesions (e.g., partial strictures) that contrast-enhanced esophagrams do not reveal. If esophagitis is found, the clinician should look carefully for a cause (e.g., hiatal hernia, gastric outflow obstruction). After entering the stomach, the endoscopist must retroflex the tip of the endoscope and examine the gastric side of the lower esophageal sphincter for leiomyomas or malformation (e.g., hiatal hernia). Gastroduodenoscopy is performed concurrently to look for gastric and duodenal reasons for gastroesophageal reflux or vomiting.

BOX 26.4

Causes of Esophageal Obstruction

Congenital Causes

Vascular ring anomaly
- Persistent fourth right aortic arch (most common type)
- Other vascular rings

Esophageal web (rare)

Acquired Causes

Foreign object (especially when there is a sudden onset)
Cicatrix/stricture (not common but very important)
Neoplasia
- Esophageal tumors
  - Carcinoma
  - Sarcoma caused by *Spirocerca lupi*
  - Leiomyoma of lower esophageal sphincter
- Extraesophageal tumors
  - Thyroid carcinoma
  - Pulmonary carcinoma
  - Mediastinal lymphosarcoma

Achalasia of the lower esophageal sphincter (sometimes found in dogs)
Gastroesophageal intussusception (very rare)

BOX 26.5

Causes of Esophageal Weakness

Congenital Causes

Idiopathic
Achalasia-like syndrome (not sure how common)

Acquired Causes

Myasthenia (generalized or localized) (important)
Hypoadrenocorticism (uncommon but important)
Severe esophagitis
- Gastroesophageal reflux
  - Hiatal hernia
  - Anesthesia-associated reflux (uncommon but important)
  - Spontaneous reflux
- Foreign body (uncommon but important)
- Caustic ingestion
  - Iatrogenic (e.g., doxycycline, clindamycin, ciprofloxacin, nonsteroidal anti-inflammatory drugs [NSAID])
  - Disinfectants, chemicals, etc.
- Persistent vomiting
- Excessive gastric acidity
  - Gastrinoma
  - Mast cell tumor
- Fungal organisms (e.g., pythiosis)

Myopathies (including muscular dystrophy)/neuropathies
Miscellaneous causes
- Achalasia-like syndrome
- Dysautonomia
- *Spirocerca lupi*
- Dermatomyositis (principally in Collies)
- Botulism
- Tetanus
- Lead poisoning
- Canine distemper

Idiopathic

VOMITING

Vomiting is usually caused by (1) motion sickness, (2) ingestion of emetogenic substances (e.g., drugs), (3) gastrointestinal (GI) tract obstruction, (4) abdominal (especially alimentary tract) inflammation or irritation, and (5) extragastrointestinal tract diseases that may stimulate the medullary vomiting center region or the chemoreceptor trigger zone (Box 26.6). Occasionally, central nervous system (CNS) disease, behavior, and learned reactions to specific stimuli may cause vomiting. If the cause of the vomiting is inapparent on history and physical examination, the next step depends on whether the vomiting is acute or chronic and whether there is hematemesis (Figs. 26.2 and 26.3). Remember that blood in vomitus may be fresh (i.e., red) or digested to varying degrees (i.e., "coffee grounds" or "dregs").

In animals with acute vomiting without hematemesis, clinicians should first search for obvious causes (e.g., ingestion of a foreign body, intoxication, organ failure, parvovirus) as well as for secondary fluid, electrolyte, or acid-base abnormalities or sepsis that require prompt, specific therapy. If the animal appears stable and there is no obvious cause, symptomatic treatment is often first tried for 1 to 2 days. If the animal is too sick for the clinician to take a chance on

BOX 26.6

Causes of Vomiting

- Motion Sickness (Acute) (Important)
- Diet (Important)
  - Dietary indiscretion
  - Dietary intolerance
- Emetogenic Substances (Acute)
  - Drugs: almost any drug can cause vomiting (especially drugs administered orally [PO]), but the following drugs seem especially likely to cause vomiting:
    - Digoxin
    - Chemotherapeutics (e.g., cyclophosphamide, cisplatin, dacarbazine, doxorubicin)
    - Selected antibiotics (e.g., erythromycin, tetracycline/doxycycline, amoxicillin plus clavulanic acid)
    - Penicillamine
    - Nonsteroidal antiinflammatory drugs
    - Apomorphine
    - Xylazine
  - Toxic chemicals
    - Strychnine
    - Heavy metals
- Gastrointestinal Tract Obstruction (Acute or Chronic) (Important)
  - Gastric Outflow Obstruction
    - Benign pyloric stenosis (uncommon)
    - Foreign object (common)
    - Gastric antral mucosal hypertrophy
    - Neoplasia
    - Nonneoplastic infiltrative disease (e.g., pythiosis)
    - Gastric malpositioning
      - Gastric dilation or volvulus (see nonproductive retching)
      - Partial gastric dilation/volvulus (does not always cause clinical signs)
  - Intestinal Obstruction
    - Foreign object (very common)
      - Nonlinear objects
      - Linear objects
    - Neoplasia
    - Intussusception
    - Cicatrix (rare)
    - Torsion/volvulus (very rare)
- Gastrointestinal/Abdominal Inflammation (Acute or Chronic) (Important)
  - Gastritis (common)
    - Without ulcers/erosions
    - With ulcers/erosions
    - Non-obstructing foreign body
    - Parasitic (i.e., *Physaloptera, Ollulanus*)
  - Enteritis (acute)
    - Parvovirus (common)
    - Acute hemorrhagic diarrheal syndrome (common)
    - Parasites (acute or chronic)
    - Inflammatory bowel disease (IBD) (more common in cats)
  - Pancreatitis (common and very important in dogs)
  - Peritonitis (acute or chronic; septic or nonseptic)
  - Colitis (acute or chronic)
  - Splenitis
- Extraalimentary Tract Diseases (Acute or Chronic) (Important)
  - Uremia (common)
  - Adrenal insufficiency (uncommon but important)
  - Hypercalcemia
  - Hepatic insufficiency or disease (Important)
  - Cholecystitis
  - Diabetic ketoacidosis
  - Pyometra
  - Endotoxemia/septicemia
- Miscellaneous Causes (Acute or Chronic)
  - Dysautonomia
  - Feline hyperthyroidism (Important)
  - Postoperative nausea/ileus (uncommon)
  - Overeating
  - Idiopathic hypomotility
  - Central nervous system disease
    - Tumor
    - Meningitis
    - Increased intracranial pressure
  - Sialoadenitis/sialoadenosis*
  - Behavior
  - Physiologic (epimeletic in female dogs)

*It is important to determine whether this is the cause of vomiting or an effect of vomiting.

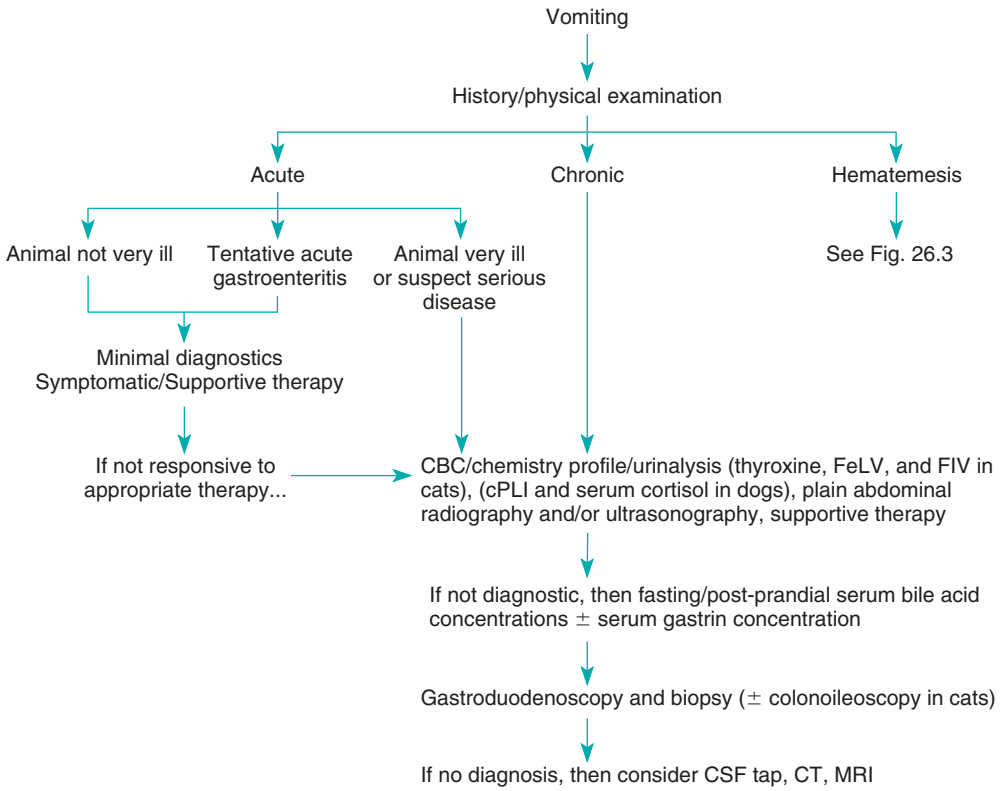


FIG 26.2
General diagnostic approach to vomiting in the dog and cat. *CBC,* Complete blood count; *cPLI,* canine pancreatic lipase immunoreactivity; *CSF,* cerebrospinal fluid; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *MRI,* magnetic resonance imaging.

guessing wrong, if the vomiting persists for 2 to 4 days after the start of symptomatic therapy, or if the condition worsens during this initial time, then more aggressive diagnostic testing is usually appropriate.

The clinician should search for historical evidence of ingested foreign objects, toxins, inappropriate food, or drugs. Physical examination is used to look for abdominal abnormalities (e.g., masses, pain) and evidence of extraabdominal disease (e.g., uremic glossitis, a thyroid nodule indicative of hyperthyroidism). Clinicians should always look for linear foreign bodies in vomiting cats and carefully examine the base of the tongue; chemical restraint (e.g., ketamine HCl, 2.2 mg/kg of body weight given intravenously) may be necessary to examine this area properly. The abdomen is palpated to search for masses or pain, but even careful palpation may miss short ileocolic intussusceptions in the craniodorsal abdomen. It is reasonable to perform fecal examination for parasites because they can cause vomiting. If a cause cannot be found and the animal is not unduly ill, the clinician may prescribe a therapeutic trial (e.g., pyrantel and a dietary trial; see Table 28.7). Therapeutic trials should be designed so that failure of the therapy allows the clinician to exclude at least one disease.

If acute vomiting does not respond to symptomatic therapy or if the animal is so sick that the clinician cannot take a chance on symptomatic therapy being ineffective, aggressive diagnostic testing is appropriate. Animals with acute or chronic vomiting without hematemesis should undergo abdominal radiography and/or ultrasonography to look for intestinal obstruction, foreign objects, masses, pancreatitis, peritonitis, poor serosal contrast, alimentary tract ileus, free abdominal fluid, or free abdominal gas. Abdominal ultrasonography can be more revealing than plain radiographs, but radiographs may be more sensitive in revealing free air and some foreign bodies. A CBC, serum biochemistry profile, and urinalysis are also indicated. Cats should be tested for feline leukemia virus, feline immunodeficiency virus, and hyperthyroidism. It may be necessary to measure serum bile acid concentrations (or blood ammonia concentrations) or resting serum cortisol concentrations to screen for hepatic or adrenal insufficiency, respectively, that can be unsuspected based on serum biochemistry profiles. Immunoreactive pancreatic lipase activity can be helpful in diagnosing otherwise occult canine pancreatitis, but it must be remembered that the test cannot be used as a simple litmus test for clinically important pancreatitis.

If results of extensive clinical pathology testing and abdominal imaging are not diagnostic in a patient with chronic vomiting, the next diagnostic step is usually upper GI endoscopy. If endoscopy is not available, then exploratory laparotomy may be substituted, but surgery can miss gastric lesions that will be picked up endoscopically. Contrast gastrograms

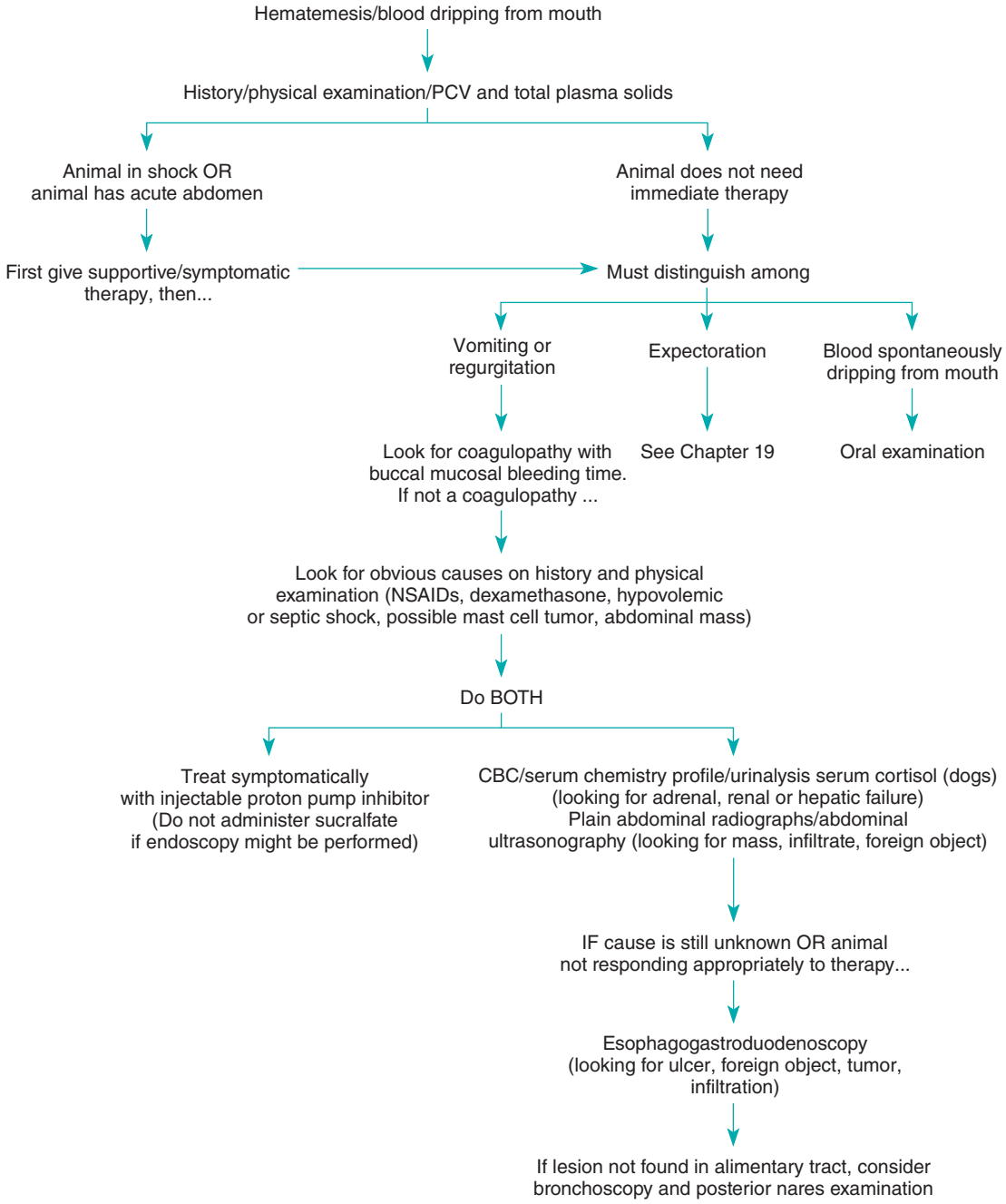


FIG 26.3
General diagnostic approach to hematemesis in the dog and cat. *CBC,* Complete blood count; *PCV,* packed cell volume.

are occasionally helpful; however, endoscopy is usually more cost-effective. During endoscopy, the clinician should biopsy the stomach and duodenum, regardless of normal gross mucosal appearance. In cats, endoscopic biopsy of the ileum and ascending colon may occasionally be required to find the cause of vomiting. If laparotomy is chosen over endoscopy, the entire abdomen should be examined. The stomach, duodenum, jejunum, ileum, mesenteric lymph nodes, liver, and, in cats, the pancreas should typically be biopsied.

If the cause of vomiting is undiagnosed after biopsy, the basis for previously excluding the different diseases should be reviewed. Diseases may be inappropriately ruled out (or diagnosed) because the clinician does not understand the limitations of certain tests. For example, dogs with hypoadrenocorticism may have normal electrolyte concentrations; inflammatory gastric and bowel disease may be localized to one area of the stomach or intestine and rarely causes significant changes in the white blood cell count; hyperthyroid cats may have normal serum thyroxine concentrations; dogs and cats with hepatic failure may have normal serum bilirubin concentrations as well as normal serum alanine aminotransferase and alkaline phosphatase activities; dogs

and cats with pancreatitis may have normal immunoreactive pancreatic lipase activities and normal abdominal ultrasound examinations; and *Physaloptera* infections are almost never diagnosed by fecal examination. Finally, the clinician may have to consider uncommon diseases that are more difficult to diagnose (e.g., idiopathic gastric hypomotility, occult CNS disease).

HEMATEMESIS

Clinicians must often use history and physical examination to help identify hematemesis as well as distinguish it from other problems. Hematemesis is expulsion of digested (i.e., "coffee grounds") or fresh blood. Animals with oral lesions that have blood dripping from their lips do not have hematemesis. Likewise, hemoptysis (i.e., coughing up blood) is not hematemesis.

Clinicians should distinguish vomiting that produces specks of blood from vomiting in which there is substantial blood present. The former may be caused by gastric mucosal trauma secondary to vigorous vomiting from any cause, and animals with such "hematemesis" should generally be treated as described in the previous section on vomiting. Patients that produce more substantial amounts of blood generally should be approached differently. Although hematemesis is usually caused by gastroduodenal ulceration and erosion (GUE), clinicians should not make this assumption and automatically treat for such. The clinician should first check the hematocrit and plasma total protein concentration to determine whether a blood transfusion is necessary (see Fig. 26.3). The clinician should next try to determine whether there is a coagulopathy (uncommon but important), ingestion of blood from another site (including the respiratory tract), or a gastrointestinal tract (GIT) lesion (e.g., GUE) (Box 26.7). Platelet counts and a measure of clotting capability (e.g., buccal mucosal bleeding time) are strongly recommended. The clinician should next look for obvious causes of GIT hemorrhage (e.g., acute gastritis, acute hemorrhagic diarrheal syndrome [used to be called *hemorrhagic gastroenteritis*], or GUE due to ulcerogenic drugs [e.g., nonsteroidal

BOX 26.7

Causes of Hematemesis

Coagulopathy (Uncommon)

Thrombocytopenia/platelet dysfunction
Clotting factor deficiency
Disseminated intravascular coagulation

Alimentary Tract Lesion

Gastrointestinal tract ulceration/erosion (common and important)
  Infiltrative disease (important)
  - Neoplasia
    - Leiomyoma
    - Carcinomas
    - Lymphomas
  - Pythiosis (especially younger dogs in the southeastern United States)
  - Inflammatory bowel disease (uncommon)

  "Stress" ulceration
  - Hypovolemic shock
  - Septic shock (i.e., systemic inflammatory response syndrome)
  - After gastric dilation or volvulus
  - Neurogenic "shock"
  - Extreme or sustained exertion (common in select working animals)

  Hyperacidity
  - Mast cell tumor
  - Gastrinoma (rare)

  Iatrogenic causes
  - Nonsteroidal antiinflammatory drug (common and important)
  - Glucocorticoids (especially dexamethasone) (important)

  Other causes
  - Hepatic disease (common and important)
  - Hypoadrenocorticism (uncommon but important)
  - Pancreatitis (common disease but uncommonly causes ulceration or hematemesis)
  - Renal disease (common disease but uncommonly causes ulceration or hematemesis)
  - Inflammatory diseases

  Foreign objects (rarely a primary cause of hematemesis, but will worsen preexisting ulceration or erosion)

Gastritis
  Acute gastritis (common)
  Acute hemorrhagic diarrheal syndrome (common)
  Chronic gastritis (uncommon in dogs)
  Helicobacter-associated disease (doubtful association with hematemesis in dogs and cats)

Gastric mucosal trauma from vigorous vomiting*
Gastric polyps
Esophageal disease (uncommon)
  Tumor
  Severe esophagitis
  Trauma

Bleeding oral lesion
Gallbladder disease (especially tumors) (rare)

Extraalimentary Tract Lesion (Blood Is Swallowed and Then Vomited) (Rare)

Respiratory tract disorders
  Lung lobe torsion
  Pulmonary tumor
  Posterior nares lesion

Dietary indiscretion

*Hematemesis caused by vigorous vomiting usually consists of specks of blood as opposed to larger quantities.

antiinflammatory drugs, dexamethasone] or recent severe hypovolemic shock or systemic inflammatory response syndrome or abdominal masses that may involve the gastric mucosa or cutaneous mast cell tumors). Remember: mast cell tumors can grossly mimic almost any other benign or malignant neoplasm, especially lipomas.

If acute gastritis, acute hemorrhagic diarrheal syndrome, nonsteroidal antiinflammatory drug or dexamethasone–induced GUE, or GUE resulting from shock is strongly suspected, the clinician may elect a limited diagnostic workup (e.g., CBC, serum biochemistry panel) to define the degree of blood loss and look for evidence of renal, hepatic, or adrenal failure. Then the animal can be treated symptomatically for 3 to 5 days (see Chapter 28, pp. 437-440) to see what effect this has in controlling clinical signs. Endoscopy is not necessary or helpful in many of these cases because it cannot reliably distinguish between ulcers that will heal with medical therapy and those that will require surgical resection. However, if the cause of hematemesis or GUE is unknown, more aggressive diagnostic tests (e.g., abdominal ultrasound and gastroduodenoscopy) should be considered (see Fig. 26.3). The stomach and duodenum should be imaged, preferably by ultrasonography, to look for alimentary tract infiltrations, foreign objects, and masses. Endoscopy is the most sensitive and specific means of finding and evaluating GUE. The principal indications for endoscopy in animals with upper GI blood loss include (a) distinguishing potentially resectable ulcers from widespread, unresectable erosions in patients with life-threatening GI bleeding; (b) localizing ulcers when considering surgical resection; and (c) determining the cause of GUE in patients with upper GI blood loss of unknown cause. Abdominal exploratory surgery may be performed instead of endoscopy, but it is easy to miss bleeding mucosal lesions when examining the serosal surface of the GIT. Intraoperative endoscopy (i.e., endoscopic examination of the mucosal surface of the stomach and duodenum while the abdomen is opened) may sometimes be useful in finding lesions that the surgeon cannot discern from the serosal surface.

If the source of bleeding cannot be found using gastroduodenoscopy, the clinician should consider possible bleeding sites beyond the reach of the endoscope; blood being swallowed from a lesion in the mouth, posterior nares, trachea, or lungs; hemorrhage from the gallbladder; or an intermittently bleeding gastric or duodenal lesion. Capsule endoscopy has recently become available for dogs and can also be used to look for bleeding lesions throughout the GI tract. It can be used when endoscopy is not available or when the bleeding lesion is suspected to be beyond the reach of the endoscope. Endoscopy of the trachea and choana can be diagnostic in some cases of occult respiratory hemorrhage.

DIARRHEA

Diarrhea is nothing more than excessive fecal water. This explains why many animals with severe small bowel disease do not have diarrhea. When diarrhea is present, one should first distinguish acute from chronic problems.

Acute diarrhea is usually caused by diet, parasites, or infectious diseases (Box 26.8). Dietary problems are often detected by history; parasites by fecal examination; and infectious diseases by history (i.e., evidence of contagion or exposure), CBC, fecal enzyme–linked immunosorbent assay for canine parvoviral antigen, and exclusion of other causes.

BOX 26.8

Causes of Acute Diarrhea

Diet (Common and Important)

Intolerance/allergy
Poor-quality food
Rapid dietary change (especially in puppies and kittens)
Bacterial food poisoning
Dietary indiscretion

Parasites (Common and Important)

Helminths
Protozoa
- *Giardia*
- *Tritrichomonas* (feline)
- *Coccidia*

Infectious Causes

Viral causes
- Parvovirus (canine, feline) (dogs: common and important)
- Coronavirus (canine, feline) (infrequent, not important)
- Feline leukemia virus (including infections secondary to it)
- Feline immunodeficiency virus (specifically infections secondary to it)
- Various other viruses (e.g., rotavirus, canine distemper virus)

Bacterial causes
- *Salmonella* spp. (uncommon)
- *Clostridium perfringens* (common and important in large bowel diarrheas)
- Verotoxin-producing *Escherichia coli*
- *Campylobacter jejuni* (uncommon)
- *Yersinia enterocolitica* (questionable)
- Various other bacteria

Rickettsial infection
- Salmon poisoning (regionally important)

Other Causes

Acute hemorrhagic diarrheal syndrome
Intussusception
Ingestion of "toxins"
- "Garbage can" intoxication (spoiled foods)
- Chemicals
- Heavy metals
- Various drugs (antibiotics, antineoplastics, anthelmintics, antiinflammatories, digitalis, lactulose)

Acute pancreatitis (diarrhea is usually a modest component of clinical signs but it can be major)
Hypoadrenocorticism

If acute diarrhea becomes unduly severe or persistent (i.e., chronic), then additional diagnostic tests are recommended.

Animals with chronic diarrhea should be examined for parasites. Typically multiple fecal examinations looking for nematodes, *Giardia,* and *Tritrichomonas* are indicated. The in-house enzyme-linked immunosorbent assay (ELISA) "snap" tests for Giardia are more sensitive than fecal examination and have excellent negative predictive values. The indirect fluorescent antibody test (IFA) test for *Giardia* is considered the "gold standard" test, but requires feces to be sent off to a laboratory. Next, the clinician should determine whether the diarrhea originates from the small or large intestine. History is often the best tool (Table 26.2). Failure to lose weight or body condition despite chronic diarrhea almost always indicates large bowel disease. Weight loss usually indicates small bowel disease although severe large bowel diseases (e.g., pythiosis, histoplasmosis, protothecosis, malignancy) may cause weight loss; however, animals with large bowel disease causing weight loss usually have obvious signs of colonic involvement (e.g., fecal mucus, tenesmus, hematochezia). Whenever tenesmus is present, the clinician should ascertain whether or not it was present when the disease began. If tenesmus did not begin until late in the course of the diarrhea, it may be due simply to perineal scalding or anal soreness resulting from chronic irritation.

Chronic small intestinal diarrhea can be categorized as maldigestion, nonprotein-losing malabsorptive disease, and protein-losing enteropathy. Maldigestion is principally caused by exocrine pancreatic insufficiency (EPI) and infrequently causes marked hypoalbuminemia (i.e., < 2.0 g/dL with a normal range 2.5-4.4 g/dL). Film digestion tests for fecal trypsin activity, Sudan staining of feces for undigested fats, and fat absorption tests yield many false-negative and false-positive results. The most sensitive and specific test for EPI is the serum trypsin-like immunoreactivity (TLI; see Chapter 27, p. 423), which is indicated in patients with chronic small intestinal diarrhea.

Attempting to diagnose EPI by supplementing pancreatic enzymes is strongly discouraged. If a dog's diarrhea ameliorates in response to pancreatic enzyme supplementation, it might be due to EPI or antibiotic-responsive enteropathy (ARE; i.e., dysbiosis) or it might just be a fortuitous, temporal effect. A false-positive diagnosis of EPI results in the unnecessary supplementation of expensive enzymes. Up to 15% of dogs with EPI do not respond when enzymes are added to their diet; therefore if EPI is incorrectly ruled out in such a case, unnecessary endoscopies or operations often result. Therefore the clinician should definitively diagnose or rule out EPI before proceeding with other diagnostic tests or treatments.

Malabsorptive intestinal disease may be protein-losing enteropathy (PLE) or nonprotein-losing (Fig. 26.4). Diarrhea occurs only if the absorptive capacity of the colon is exceeded. Therefore a dog or cat can be losing weight and/or albumin because of small intestinal disease and not have diarrhea (see the section on Weight Loss). The serum albumin concentration can be mildly or markedly decreased (i.e., 2.0 g/dL or less [normal range 2.5-4.4 g/dL]) in patients with PLE. If an animal has marked hypoalbuminemia not caused by protein-losing nephropathy, hepatic insufficiency, or skin lesions, then PLE is diagnosed by process of exclusion. If the serum albumin is mildly decreased (i.e., 2.1-2.4 g/dL), then other causes (e.g., sequestration in third space, nutrition) should also be considered. Hypoglobulinemia sometimes develops in patients with PLE, but many patients with PLE do not have panhypoproteinemia. In general, dogs with PLE are preferably approached with aggressive diagnostics.

In patients with nonprotein-losing malabsorptive disease, the clinician may perform additional diagnostic tests (e.g., intestinal biopsy) or perform therapeutic trials. If the patient

TABLE 26.2

Differentiation of Chronic Small Intestinal From Large Intestinal Diarrheas

SIGN	SMALL INTESTINAL DIARRHEA	LARGE INTESTINAL DIARRHEA
Weight loss*	Expected	Uncommon*
Polyphagia	Sometimes	Rare to absent
Frequency of bowel movements	Often near normal	Sometimes very increased but often normal
Volume of feces	Often increased, but can be normal volume	Sometimes decreased (because of the increased frequency) but can be normal
Blood in feces	Melena (rare)	Hematochezia (sometimes†)
Mucus in feces	Uncommon	Sometimes
Tenesmus	Uncommon (but may occur later in chronic cases)	Sometimes
Vomiting	May be seen	May be seen

*Failure to lose weight or condition is the most reliable indication that an animal has large bowel disease. However, animals with colonic histoplasmosis, pythiosis, lymphoma, protothecosis, or similar severe infiltrative diseases may have weight loss due to large bowel disease.
†Hematochezia becomes much more important as a differentiating feature in animals that are losing weight. Its presence in such animals confirms the presence of large bowel involvement (either by itself or in combination with small bowel disease) despite weight loss.

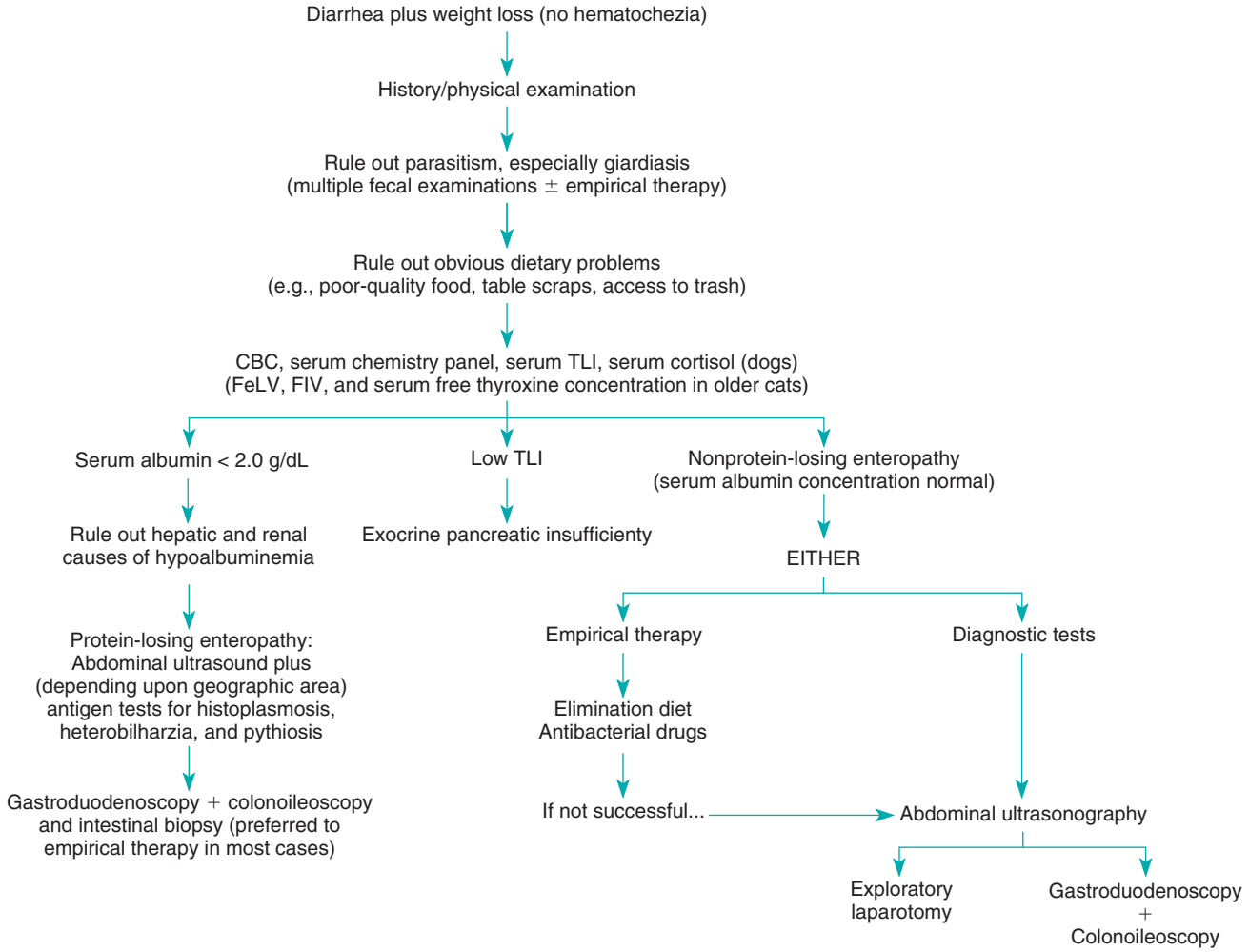


FIG 26.4
General diagnostic approach to small intestinal diarrhea in the dog and cat. *CBC,* Complete blood count; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus, *TLI,* trypsin-like immunoreactivity.

is not emaciated or rapidly losing weight and is not hypoalbuminemic, then biopsy is seldom the best next step. Screening for atypical hypoadrenocorticism with resting serum cortisol concentrations is appropriate. Testing for histoplasmosis, pythiosis, and heterobilharziasis can be appropriate, depending upon geographical location. Therapeutic trials are the best way to diagnose dietary-responsive diarrhea and ARE (also called *antibiotic-responsive diarrhea* and/or *dysbiosis*), which are two of the most common causes of chronic small bowel diarrhea in dogs. ARE cannot be diagnosed by measuring serum cobalamin and folate concentrations. If a therapeutic trial is performed, the clinician must be sure that it is done properly (e.g., long enough, correct dose) so that it has a high likelihood of succeeding if the animal has the suspected disease. If the patient seems particularly ill (e.g., severe or rapid weight loss), or is hypoalbuminemic, or has failed well-implemented clinical trials and is negative for infectious causes (i.e., histoplasmosis, heterobilharziasis, pythiosis) and atypical hypoadrenocorticism, then abdominal ultrasonography is the next step. Ultrasonography should always precede biopsy because it may be diagnostic if it shows dilated lymphatics in the intestinal mucosa (i.e., lymphangiectasia) or lymphadenopathy or intestinal infiltrates that can be aspirated percutaneously. If ultrasonography is not diagnostic, then biopsy is the next step (Boxes 26.9 and 26.10). Either laparotomy or endoscopy can be performed to biopsy the bowel. If ultrasonography reveals a localized lesion that cannot be reached with an endoscope, then laparotomy is indicated. Otherwise, endoscopy is quicker and safer than laparotomy and may allow the clinician to biopsy lesions not discernable from the serosal surface. Endoscopic biopsy specimens can easily be nondiagnostic if the endoscopist has not been carefully trained in biopsy techniques. If laparotomy is performed in hypoalbuminemic animals, it may be prudent to use nonabsorbable suture material and/or perform intestinal serosal patch grafting. Distended intestinal lymphatics or lipogranulomas in the intestinal wall are suggestive of lymphangiectasia. If intestinal biopsy specimens are not helpful, the main possibilities are that the tissue specimens were inadequate (e.g., not deep enough, from

BOX 26.9

Major Causes of Malabsorptive Disease

Dog

Parasitism: giardiasis, nematodes (common and important)
Dietary responsive (food intolerance or allergy; common and important)
Antibiotic-responsive enteropathy (also called "dysbiosis") (common and important)
Inflammatory bowel disease
Neoplastic bowel disease (especially lymphoma; important but not common)
Fungal infections (regionally important)
- Pythiosis
- Histoplasmosis

Cat

Dietary responsive (food intolerance or allergy; common and important)
Parasitism: giardiasis
Inflammatory bowel disease: lymphocytic-plasmacytic enteritis (common and important)
Neoplastic bowel disease (especially lymphoma; common and important)

BOX 26.10

Major Causes of Protein-Losing Enteropathy*

Dog

Intestinal lymphangiectasia (common and important)
Alimentary tract lymphoma (important)
Severe inflammatory bowel disease
Alimentary tract fungal infections
- Histoplasmosis (regionally important)
- Pythiosis (regionally important)

Chronic intussusception (especially young dogs)
Alimentary tract hemorrhage (e.g., ulceration or erosion, neoplasia, parasites)
Unusual enteropathies (e.g., chronic purulent enteropathy, severe ectasia of mucosal crypts)
Massive hookworm or whipworm infestation (regionally important)

Cat

Alimentary tract lymphoma (important)
Severe inflammatory bowel disease (common and important)
Alimentary hemorrhage (e.g., neoplasia, duodenal polyps, idiopathic ulceration)

*Any gastrointestinal disease can cause protein-losing enteropathy, but these are the most common causes. Except for lymphangiectasia, these diseases do not consistently produce protein-losing enteropathy.

BOX 26.11

Major Causes of Chronic Large Intestinal Diarrhea

Dog

Dietary responsive (intolerance or allergy; important and common)
Fiber-responsive (important and common)
Parasitism
- Whipworms (regionally important and common)
- *Heterobilharzia* (regionally important)

Bacterial diseases
- "Clostridial" colitis (important and common)
- Histiocytic ulcerative colitis (usually Boxers and French Bulldogs)

Fungal infections (regionally important and common)
- Histoplasmosis
- Pythiosis

Inflammatory bowel disease (uncommon in dogs)
Neoplasia
- Lymphoma
- Adenocarcinoma

Cat

Dietary responsive (intolerance or allergy; important and common)
Fiber-responsive (important and common)
Inflammatory bowel disease (important)
Tritrichomonas (especially important in exotic cats and in catteries)
Feline leukemia virus infection (including infections secondary to it)
Feline immunodeficiency virus infection (specifically infections secondary to it)

the wrong place, too much artifact), the pathologist did not recognize the lesion, the animal has occult giardiasis or ARE or dietary intolerance, or there is disease (e.g., lymphangiectasia, neoplasia, inflammation) localized to where the clinician did not biopsy.

There are some differences in cats with chronic small bowel disease compared with dogs. PLE is less common in cats, and when present typically indicates severe infiltrative disease (usually not lymphangiectasia) and the need for biopsy. Nematode infections causing chronic diarrhea are much less common in cats than in dogs.

Dogs with chronic large intestinal diarrhea (Box 26.11) should first undergo a digital rectal examination to search for mucosal thickening or proliferation. The rectum is the most common site of canine colonic neoplasia, and finding obvious mucosal lesions indicates the need for biopsy. If the rectal mucosa seems normal, the animal has not lost weight,

and the serum albumin is well within the normal range (a serum albumin at the lower end of the reference range may not be "normal" enough), then it is often most appropriate to try therapeutic trials after a few basic diagnostic tests. Fecal examination to detect whipworms, fecal ELISA to detect *Giardia* (a small bowel problem that can mimic large bowel disease), and fecal PCR to detect *Tritrichomonas* (cats) are indicated. Therapeutic trials usually consist of high-fiber diets, elimination diets, antibacterials to control "clostridial" colitis, and/or treatment for parasites.

Additional diagnostic tests that may be done instead of therapeutic trials principally include biopsying colonic mucosa by colonoscopy, and fecal assays for toxins (e.g., clostridial toxin) and/or specific organisms (e.g., *Campylobacter, Salmonella*). Fecal cultures and antigen tests for specific pathogens should be considered if history indicates a strong likelihood of a contagious disorder. Fecal ELISA and PCR assays should be done before performing enemas or administering lavage solutions. Unless there is a good epidemiologic reason to strongly suspect infectious bacteria, fecal cultures and antigen/DNA tests tend to be very low-yield procedures that are difficult to interpret. Colonoscopy/biopsy is principally useful to diagnose histoplasmosis, histiocytic ulcerative colitis, protothecosis, Heterobilharzia, or neoplasia in dogs, whereas cats are often diagnosed with colonic inflammatory bowel disease.

If the results of these tests are not diagnostic, the clinician must consider three main possibilities. First, the biopsy specimens may not be representative of the entire colonic mucosa. For example, if the disease is localized to the region of the ileocolic valve, it will be necessary to use a flexible endoscope to reach the area. Second, the pathologist may not have recognized the lesions. Third, there may be no mucosal lesions. This typically occurs in animals with a dietary intolerance or allergy, "clostridial" colitis, or fiber-responsive diarrhea, all common problems in dogs.

HEMATOCHEZIA

If the patient has hematochezia (fresh blood in the feces) and diarrhea, the problem should usually be approached in the same manner as for animals with large bowel diarrhea (see Chapter 26, pp. 401-402). The patient with normal stools plus hematochezia is approached slightly differently. Streaks of blood on the outside of otherwise normal feces usually indicates a distal colonic or rectal lesion, whereas blood mixed into feces suggests that bleeding is occurring higher in the colon. Coagulopathies rarely cause bleeding from the rectum only. Focal bleeding lesions in the distal colon, rectum, or perineal region (Box 26.12) are especially important. Acute hematochezia may also result from trauma (e.g., passing a foreign body).

A thorough digital rectal examination is the best initial step (even if anesthesia is necessary). The clinician should express each anal sac repeatedly and examine the contents. If the problem is chronic and digital rectal examination is not helpful, then colonoscopy and biopsy are indicated. Barium enema is not recommended. Biopsy specimens of masses must include submucosa or many neoplastic lesions will be missed. Hematochezia is rarely severe enough to cause anemia; however, a CBC can be performed to look for and characterize anemias.

BOX 26.12

Major Causes of Hematochezia*

Dog

Anal-rectal disease

Anal sacculitis (important and common)
Neoplasia
- Rectal adenocarcinoma (important)
- Rectal polyp (important)
- Colorectal leiomyoma or leiomyosarcoma

Perianal fistulas (important)
Anal foreign body
Rectal prolapse
Anal-rectal trauma (e.g., foreign body, thermometer, enema tube, fecal loop, pelvic fractures)

Colonic/intestinal disease

Parasitism
- Whipworms (important and common)
- Hookworms (severe infections can involve the colon)

Dietary responsive (intolerance or allergy; common)
"Clostridial" colitis (common disease but uncommonly causes hematochezia)
Acute hemorrhagic diarrheal syndrome (important and common)
Parvoviral enteritis (important and common)
Histoplasmosis (regionally important and common)
Pythiosis (regionally important)
Intussusception (more common in young animals)
- Ileocolic
- Cecocolic

Inflammatory bowel disease
Colonic trauma
Coagulopathy
Colonic vascular ectasia

Cat

Dietary responsive (intolerance or allergy)
Inflammatory bowel disease (important)
Coccidia
Rectal tumors (uncommon)

*These diseases do not consistently produce hematochezia, but when hematochezia is present, these are the most common causes.

MELENA

Melena is caused by digested blood and is seen as "coal tar"-black (not just "dark") feces. Clinicians must distinguish melena from stools that are intensely dark green. Melena is strongly suggestive of upper alimentary tract bleeding or

ingestion of blood (Box 26.13). However, a lot of blood must enter the GI tract in a relatively short time to produce melena, which is why most animals with upper GI hemorrhage do not have melena. A CBC is indicated to look for iron deficiency anemia (i.e., microcytosis, hypochromasia). Measuring total serum iron concentration and total iron-binding capacity plus staining the bone marrow for iron are more definitive tests for iron deficiency anemia. Ultrasonography is helpful when looking for infiltrated, bleeding lesions (e.g., an intestinal tumor). Gastroduodenoscopy is the most sensitive test for GUE (which is often missed by ultrasonography). If ultrasound and gastroduodenoscopy are nonrevealing, then one must suspect small intestinal lesions beyond the reach of the endoscope. If imaging reveals a lesion beyond the reach of the endoscope, exploratory laparotomy is required. The clinician may elect to perform exploratory surgery immediately, but it is easy to miss bleeding mucosal lesions when examining the serosa or palpating the bowel. Intraoperative endoscopy (i.e., having the surgeon manually advance the tip of the endoscope while pushing the intestines onto the endoscope) may be helpful if no lesion is detected at surgery. Capsule endoscopy may be helpful in confirming that there is a bleeding lesion in the distal small intestines before laparotomy (or in finding a more orad lesion previously missed). Contrast radiographs rarely detect bleeding lesions and are not recommended

TENESMUS

Tenesmus (i.e., ineffectual or painful straining at urination or defecation) and dyschezia (i.e., painful or difficult elimination of feces from the rectum) are principally caused by obstructive or inflammatory distal colonic or urinary bladder or urethral lesions (Box 26.14). Colitis, constipation, perineal hernias, perianal fistulas, prostatic disease, and cystic/urethral disease are the most common causes of tenesmus. Most rectal masses and strictures cause hematochezia; however, some do not disrupt the colonic mucosa and cause only tenesmus.

The first goal (especially in cats) is to distinguish lower urinary tract from alimentary tract disease. In cats tenesmus secondary to a urethral obstruction is often misinterpreted as constipation. By observing the patient, the clinician may be able to determine whether the animal is attempting to urinate or defecate. Palpating the bladder is important; a distended urinary bladder often indicates an obstruction whereas a small, painful bladder often indicates cystitis. A urinalysis can also be helpful. If necessary, one can catheterize the urethra to determine if it is patent.

If the clinician suspects tenesmus resulting from alimentary tract disease, the next steps are to palpate the abdomen, perform a digital rectal examination, and visualize the anus and perineal areas even if this requires sedation/anesthesia.

BOX 26.13

Major Causes of Melena*

Dog

- Hookworms (important)
- Gastroduodenal tract ulceration/erosion (see Box 26.7) (important)
- Gastric or small intestinal tumor (important)
  - Lymphoma
  - Adenocarcinoma
  - Leiomyoma or leiomyosarcoma
  - Polyp
- Ingested blood
  - Oral lesions
  - Nasopharyngeal lesions
  - Pulmonary lesions
  - Diet
- Hypoadrenocorticism (uncommon but important)
- Coagulopathies (uncommon but important)

Cat (Rare)

- Gastrointestinal tumor
  - Lymphoma
  - Duodenal polyps
  - Other tumors (adenocarcinoma, mast cell tumor)
- Coagulopathies: vitamin K deficiency (intoxication or resulting from malabsorption)

*These diseases do not consistently produce melena, but if melena is present, these are the most common causes.

BOX 26.14

Major Causes of Tenesmus and/or Dyschezia

Dog

- Perineal inflammation or pain: anal sacculitis (common and important)
- Rectal inflammation/pain
  - Perianal fistulae (important)
  - Tumor (important)
  - Proctitis (either primary disease or secondary to diarrhea or prolapse)
  - Histoplasmosis/pythiosis
- Colonic/rectal obstruction
  - Rectal neoplasia
  - Rectal granuloma
  - Perineal hernia (important)
  - Constipation
  - Prostatomegaly (common and important)
  - Pelvic fracture
  - Other pelvic canal masses
  - Rectal foreign object

Cat

- Urethral obstruction (common and very important)
- Rectal obstruction
  - Pelvic fracture
  - Perineal hernia
- Constipation
  - Abscess near rectum

The clinician should not assume that constipation, if present, is causing the tenesmus. Severe pain (e.g., that resulting from proctitis) may make the animal refuse to defecate and cause secondary constipation. Most rectal strictures, perineal hernias, masses, enlarged prostates, pelvic fractures, and rectal tumors can be detected during a digital rectal examination. The clinician may need to use two fingers to detect partial strictures when examining large dogs. Perianal fistulae are usually visible but may be detected only as perirectal thickenings. Next, the clinician expresses the anal sacs and examines their contents. Finally, the clinician evaluates the feces to determine whether they are excessively hard or have abnormal contents (e.g., hair, trash).

A biopsy should be done of any mass, stricture, or infiltrative lesion found by rectal examination. A rectal scraping is sometimes sufficient (e.g., histoplasmosis), otherwise biopsy specimens taken with rigid biopsy forceps that include submucosa are preferred. Fine-needle aspiration should be performed on extracolonic masses because abscesses occasionally occur.

If the clinician is confused by physical examination findings, observing the animal defecate may help define the underlying process. Animals with inflammation often continue to strain after defecating, whereas a constipated animal strains before feces are produced. Tenesmus that occurs when an animal is in a squatting position often results from colitis, whereas tenesmus that occurs when an animal is in a semiwalking or partial squatting position usually results from constipation.

CONSTIPATION

Constipation (infrequent and difficult evacuation of feces) and obstipation (intractable constipation) have several causes (Box 26.15). The initial use of symptomatic therapy is often successful, but it is important to look for causes because some problems may become harder to treat if symptomatic therapy masks signs while the underlying disease progresses.

Iatrogenic, dietary, environmental, or behavioral causes should be sought on history. Feces should be examined to determine whether they contain plastic, bones, hair, popcorn, or other such material. Physical and digital rectal examinations are done to search for rectal obstruction or infiltration. Plain pelvic radiographs can help show whether the animal has anatomic abnormalities or a previously undetected

BOX 26.15

Causes of Constipation

Iatrogenic Causes

Drugs
- Opiates
- Anticholinergics
- Carafate (sucralfate)
- Barium sulfate

Behavioral/Environmental Causes

Change in household/routine (especially cats)
Soiled litter box/no litter box (especially cats)
House training
Inactivity

Refusal to Defecate

Behavioral
Pain in rectal/perineal area (see Box 26.14)
Inability to assume position to defecate
- Orthopedic problem
- Neurologic problem

Dietary Causes

Excessive fiber in dehydrated animal
Abnormal diet (especially dogs)
- Hair
- Bones
- Indigestible material (e.g., plants, plastic)

Colonic Obstruction

Pseudocoprostasis
Deviation of rectal canal: perineal hernia (important)
Intraluminal and intramural disorders
- Tumor
- Granuloma
- Cicatrix
- Rectal foreign body
- Congenital stricture

Extraluminal disorders
- Tumor
- Granuloma
- Abscess
- Healed pelvic fracture
- Prostatomegaly (common and important)
- Prostatic or paraprostatic cyst
- Sublumbar lymphadenopathy

Colonic Weakness

Systemic disease
- Hypothyroidism (important)
- Hypercalcemia
- Hypokalemia

Localized neuromuscular disease
- Spinal cord trauma
- Pelvic nerve damage
- Dysautonomia
- Chronic, massive dilation of the colon causing irreversible stretching of the colonic musculature

Miscellaneous Causes

Severe dehydration
Idiopathic megacolon (especially cats)

colonic obstruction (e.g., prostatomegaly, enlarged sublumbar lymph node). Ultrasonography is the preferred technique when looking for infiltrates. A serum biochemistry panel may reveal causes of colonic inertia (e.g., hypothyroidism, or rarely hypercalcemia or hypokalemia,).

Colonoscopy is indicated if the clinician suspects an obstruction too orad to be detected by digital examination. Ultrasound-guided fine-needle aspiration of infiltrative colonic lesions sometimes yields diagnostic findings, but colonoscopy (especially rigid) allows a more reliable biopsy specimen to be obtained. If a thorough diagnostic workup fails to identify a cause in a patient with a grossly dilated colon, idiopathic megacolon may be present.

FECAL INCONTINENCE

Fecal incontinence is typically caused by lower motor neuron disease (e.g., cauda equina syndrome, lumbosacral stenosis) or a partial rectal obstruction. Severe irritative proctitis may cause urge incontinence. Animals with rectal obstructions continually try to defecate because the anal canal is filled with feces. Proctitis is suspected on the basis of rectal examination findings and confirmed by proctoscopy and biopsy findings. Neuromuscular disease is suspected if an abnormal anal reflex is found, usually in conjunction with other neurologic defects in the anal, perineal, hindlimb, or coccygeal region. Defects in the coccygeal region are discussed in Chapter 65.

WEIGHT LOSS

Weight loss may be due to any of several categories of problems (Box 26.16). If other problems with more restrictive lists of differentials (e.g., ascites, vomiting, diarrhea, polyuria/polydipsia) are also present, they should usually be investigated first because it may be easier to find the cause. If there are no other concurrent problems that facilitate localization of the disease, then the clinician should determine what the animal's appetite was when the weight loss *began* (Fig. 26.5). Almost any disease can eventually cause anorexia/hyporexia. Weight loss despite an adequate caloric intake (or failure to gain weight despite an excessive caloric intake) usually indicates maldigestion, malabsorption, excessive utilization (e.g., hyperthyroidism, lactation) or inappropriate loss (e.g., diabetes mellitus) of calories. If the patient is hyporexic, it is important to determine if the hyporexia is severe enough that the weight loss can reasonably be attributed to the decreased caloric intake.

The animal's history should be reviewed for evidence of dietary problems, dysphagia, regurgitation, vomiting, or increased use of calories (e.g., lactation, strenuous work, extreme temperatures). Signalments suggestive of particular diseases (e.g., hyperthyroidism in older cats, hepatic failure in young Yorkshire Terriers with signs of portosystemic shunts) should be recognized. It is important to remember that diarrhea may be absent in animals with severe small intestinal disease.

BOX 26.16

Causes of Weight Loss

- **Food**
  - Not enough (especially if there are multiple animals)
  - Poor quality food or low-caloric-density food
  - Inedible
- **Anorexia** (see Box 26.17)
- **Dysphagia** (see Box 26.1)
- **Regurgitation/Vomiting** (i.e., must be losing enough calories to account for weight loss; see Boxes 26.4 to 26.6)
- **Maldigestive Disease**
  - Exocrine pancreatic insufficiency (usually but not always associated with diarrhea)
- **Malabsorptive Disease** (see Box 26.9)
  - Small intestinal disease (may be associated with normal stools)
- **Malassimilation**
  - Organ failure
    - Cardiac failure
    - Hepatic failure
    - Renal failure
    - Adrenal failure
- **Excessive Utilization of Calories**
  - Lactation
  - Increased work
  - Extremely cold environment
  - Pregnancy
  - Increased catabolism resulting from fever/inflammation
  - Hyperthyroidism
- **Increased Loss of Nutrients**
  - Diabetes mellitus
  - Protein-losing nephropathy
  - Protein-losing enteropathy
- **Neuromuscular Disease**
  - Lower motor neuron disease
- **Cancer Cachexia**

Physical examination might identify abnormalities that localize the problem to a particular body system (e.g., nasal disease preventing normal olfaction, dysphagia, arrhythmia suggestive of cardiac failure, weakness suggestive of neuromuscular disease, abnormally sized or shaped organs, abnormal fluid accumulations). Retinal examination may identify inflammatory or infiltrative diseases, especially in cats.

A CBC, serum biochemistry profile, and urinalysis should be done next to search for evidence of inflammation, organ failure, or a paraneoplastic syndrome. Cats should be tested for circulating feline leukemia virus antigen and antibodies to feline immunodeficiency virus. Serum T_4 (and sometimes fT_4) concentrations should be determined in middle-aged to older cats. If clinical pathology data are not helpful, imaging is usually the next step. Thoracic radiographs (ventrodorsal and both lateral views) are important because significant

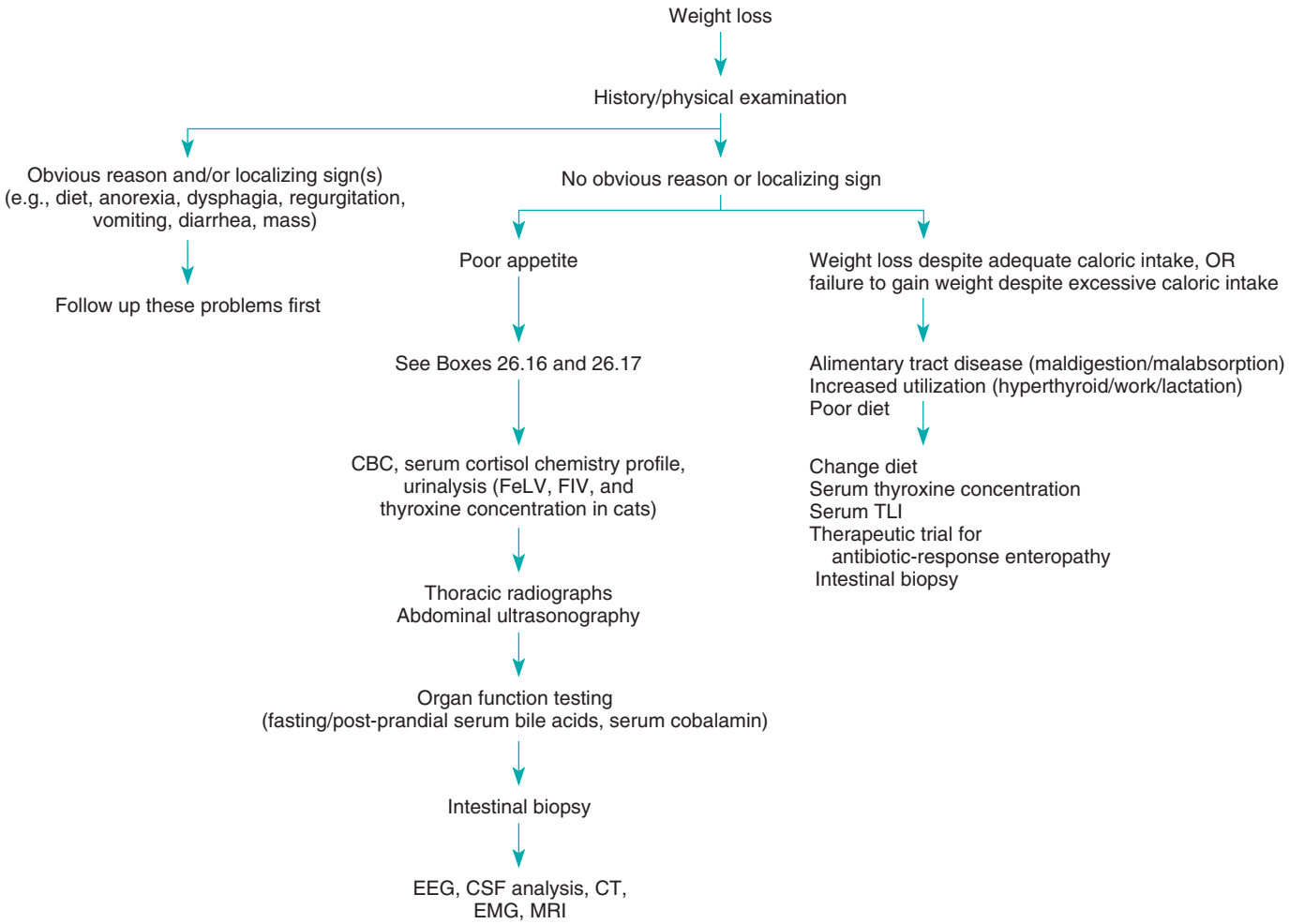


FIG 26.5
General diagnostic approach to weight loss in the dog and cat. *ACTH,* Adrenocorticotropic hormone; *CBC,* complete blood count; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *EEG,* electroencephalography; *EMG,* electromyography; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *MRI,* magnetic resonance imaging.

thoracic disease cannot be ruled out because of normal physical examination findings. Computed tomography (CT) is more sensitive for thoracic disease than plain radiographs, but three-view radiographic examinations are usually adequate. Most cats and some dogs can be palpated well enough that abdominal radiographs are not cost-effective early in the workup. However, abdominal ultrasonography may reveal infiltrative lesions that cannot be palpated or seen radiographically.

If the cause of weight loss remains unknown after these tests, additional diagnostics are necessary. Daily physical examinations can be an important means of localizing the problem. Fever of unknown origin may be noted (see Chapter 90). Organ function testing (e.g., serum bile acid concentrations, serum cortisol, serum TLI, serum cobalamin) is reasonable. Likewise, if serum T_4 concentrations are normal in a cat with suspected hyperthyroidism, the serum fT_4 concentration should be determined or other tests (e.g., nuclear scintigraphy) performed (see Chapter 48).

If the cause of weight loss still remains undiagnosed, the clinician should consider performing therapeutic trials (e.g., for ARE) or gastric/intestinal biopsy. If a laparotomy is performed instead of endoscopy, the entire abdomen should be examined and multiple biopsy samples of the alimentary tract, liver, and mesenteric lymph nodes obtained. Pancreatic biopsy should be considered in cats.

Other possible diagnostic tools include tests to evaluate the CNS (i.e., cerebrospinal fluid analysis, CT, magnetic resonance imaging). Animals that are hyporexic due to CNS disease do not always have obvious cranial nerve deficits or seizures. Peripheral nerves and muscles may be evaluated by serum creatine kinase, electromyography, and muscle/nerve biopsies. Sometimes the weakness associated with neuropathies and myopathies is mistaken for lethargy; see Chapter 59). If the cause of the weight loss still remains undiagnosed and the history and physical examination findings are still noncontributory, occult cancer becomes a major differential diagnosis. In such cases, the clinician may have to wait and

retest later with the hope that the disease will progress enough to be detected.

Causes of weight loss that can be particularly difficult to diagnose include gastric disease not causing vomiting, intestinal disease not causing vomiting or diarrhea, hepatic disease with normal serum chemistries, occult inflammatory disease, atypical hypoadrenocorticism with normal serum electrolyte concentrations, occult cancer, "dry" feline infectious peritonitis, and CNS disease without cranial nerve deficits or seizures.

ANOREXIA/HYPOREXIA

The diagnostic approach and differential diagnoses for animals with hyporexia of uncertain cause is similar to that for animals with weight loss (see Fig. 26.5) (Box 26.17). Inflammatory disease is often detected by the CBC or by finding fever. GI disease may produce hyporexia without vomiting or diarrhea. Cancer cachexia (with anorexia as the predominant sign) may stem from relatively small tumors that are not grossly detectable, although this is rare. Finally, CNS disease must be considered, especially if there is altered mentation. However, altered mentation may resemble the depression and lethargy commonly seen in animals with other diseases.

ABDOMINAL EFFUSION

Abdominal effusion is usually caused by hypoalbuminemia, portal hypertension, and/or increased vascular/lymphatic permeability (i.e., inflammation). Effusions resulting from alimentary tract disorders are primarily caused by PLE (pure low protein transudate due to severe hypoalbuminemia) or alimentary tract rupture (i.e., septic peritonitis). Some animals with PLE have normal stools, ascites being the only abnormality on history or physical examination. Malignant tumors may obstruct lymphatic flow or increase vascular permeability, causing transudates, modified transudates or nonseptic peritonitis. Modified transudates usually result from hepatic or cardiac disease or from abdominal malignancies. For further information on abdominal effusions, see Chapters 33 and 34.

ACUTE ABDOMEN

Acute abdomen refers to various abdominal disorders producing shock (hypovolemic or septic), sepsis, and/or severe pain (Box 26.18). Causes may include alimentary tract obstruction or leakage, vascular compromise (e.g., congestion, torsion, volvulus, ischemia), inflammation, neoplasia, or sepsis. The approach to this problem is determined by the severity of clinical signs (Fig. 26.6).

Shock and gastric dilation or volvulus (GDV) must be identified and treated immediately. Once these conditions are eliminated, the next major decision is whether to perform exploratory surgery or initiate medical therapy. Animals with abdominal masses, foreign objects, bunched-up loops of painful small intestine suggestive of linear foreign body, or spontaneous septic peritonitis should typically undergo surgery as soon as they are acceptable anesthetic risks. If the cause of the acute abdomen is uncertain, it can be difficult to decide whether to do surgery. Surgery is not necessarily beneficial and may be detrimental to animals with pancreatitis, parvoviral enteritis, pyelonephritis, or prostatitis. Typically, abdominal imaging (i.e., plain abdominal radiography,

BOX 26.17

Major Causes of Anorexia/Hyporexia

Inflammatory Disease (Anywhere in Body) (Common and Important)

- Bacterial infections
- Viral infections
- Fungal infections
- Rickettsial infections
- Protozoal infections
- Sterile inflammation
  - Immune-mediated disease
  - Neoplastic disease
  - Necrosis
  - Pancreatitis
- Fever of unknown origin

Dysphagia (Especially Resulting From Pain)

- Nausea (common and important)
  - Stimulation of the medullary vomiting center for any reason but especially gastric or intestinal disease, even if it is not sufficient to cause vomiting (common with gastric disease; see Box 26.6)
- Metabolic Disease
  - Organ failure (e.g., kidney, adrenal, liver, heart)
  - Hypercalcemia
  - Diabetic ketoacidosis
  - Hyperthyroidism (usually causes polyphagia, but some cats have apathetic hyperthyroidism)
- Central Nervous System Disease (often without obvious neurologic abnormalities)
- Cancer Cachexia
- Anosmia (rare)
- Psychological Causes

BOX 26.18

Major Causes of Acute Abdomen

Septic Inflammation

Septic peritonitis (common and important)
- Perforated gastric ulcer (NSAIDs, tumor) (important)
- Perforated intestines (tumor, post-op dehiscence, linear foreign body, severe inflammation) (common and important)
- Devitalized intestines (intussusception, thrombosis/infarct)
- Ruptured gallbladder (e.g., septic cholecystitis, mucocele) (uncommon but important)
- Abscess/infection
  - Splenic
  - Hepatic
  - Cholecystitis
  - Prostatic
  - Renal
- Pyometra (ruptured) (important)

Nonseptic Inflammation

Pancreatitis (common and important)
Uroabdomen (important)
Pansteatitis

Organ Distention or Obstruction

Gastric dilation or volvulus (common and important)
Intestinal obstruction resulting from many causes (common and important)
Intussusception (important, especially younger animals)
Dystocia
Mesenteric volvulus (rare)
Incarcerated obstruction (rare)

Ischemia

Torsion of spleen, liver lobe, testicle, or other organ (rare)
Thromboembolism of abdominal organ(s) (rare)

Other Causes of Abdominal Pain (see Box 26.19)

Abdominal Hemorrhage

Abdominal neoplasia (hemangiosarcoma, hepatocellular carcinoma) (common and important)
Trauma
Coagulopathy (important)

Abdominal Neoplasia

NSAIDs, Nonsteroidal antiinflammatory drugs.

ultrasonography) and clinical pathologic studies (i.e., CBC, chemistry panel) should be performed before a laparotomy is performed. Ultrasound can reveal infiltrates that radiographs cannot detect, sometimes allowing diagnosis via aspiration. However, radiographs occasionally detect lesions (e.g., small foreign bodies, free abdominal gas) that were missed ultrasonographically. Imaging may reveal spontaneous pneumoperitoneum, abdominal masses, foreign objects, alimentary tract obstruction, gastric or mesenteric torsion (these require surgical treatment), or free peritoneal fluid (this requires abdominocentesis and fluid analysis for management). Radiographic contrast series are seldom appropriate and may complicate later therapy/surgery.

If optimal medical therapy is being given and the animal's condition is clearly deteriorating or does not improve after 2 to 5 days of therapy, or if the animal continues to have excruciating pain, it is often appropriate to recommend exploratory surgery. Inform the client that you may discover the animal has a disorder not surgically correctable (e.g., pancreatitis) or that nothing abnormal may be found. In the latter case, the clinician should biopsy various abdominal organs and then treat the animal's symptoms while awaiting biopsy results.

ABDOMINAL PAIN

"Abdominal" pain must first be determined to be abdominal and not extraabdominal in origin (e.g., thoracolumbar pain is often erroneously assessed as being abdominal in origin). An animal with true abdominal pain may show obvious discomfort (e.g., it paces or repeatedly assumes different positions, repeatedly looks at or licks its abdomen) and may whine, growl, or snap if the abdomen is touched. Some dogs stretch out and assume a "praying" position (i.e., the "position of relief"). Other animals have inconspicuous signs (e.g., the animal grunts or tries to walk away when palpated, the abdomen is tensed) that are easily missed. On the other hand, rough abdominal palpation technique in normal animals may elicit a guarding response that can mimic abdominal pain. Main causes of abdominal pain are listed in Box 26.19.

If the patient has abdominal pain, the goal is to determine the source. If the pain is originating from within the abdominal cavity, the diagnostic approach depends on its severity, progression of disease, and whether there are any obvious causes. The steps taken in diagnosing the cause of abdominal pain are similar to those taken in an animal with acute abdomen. Some causes of abdominal pain can be difficult to diagnose (e.g., acute pancreatitis, localized peritonitis).

ABDOMINAL DISTENTION OR ENLARGEMENT

Abdominal distention or enlargement may be associated with an acute abdomen, but these conditions are typically separate problems. It is best to believe clients who claim

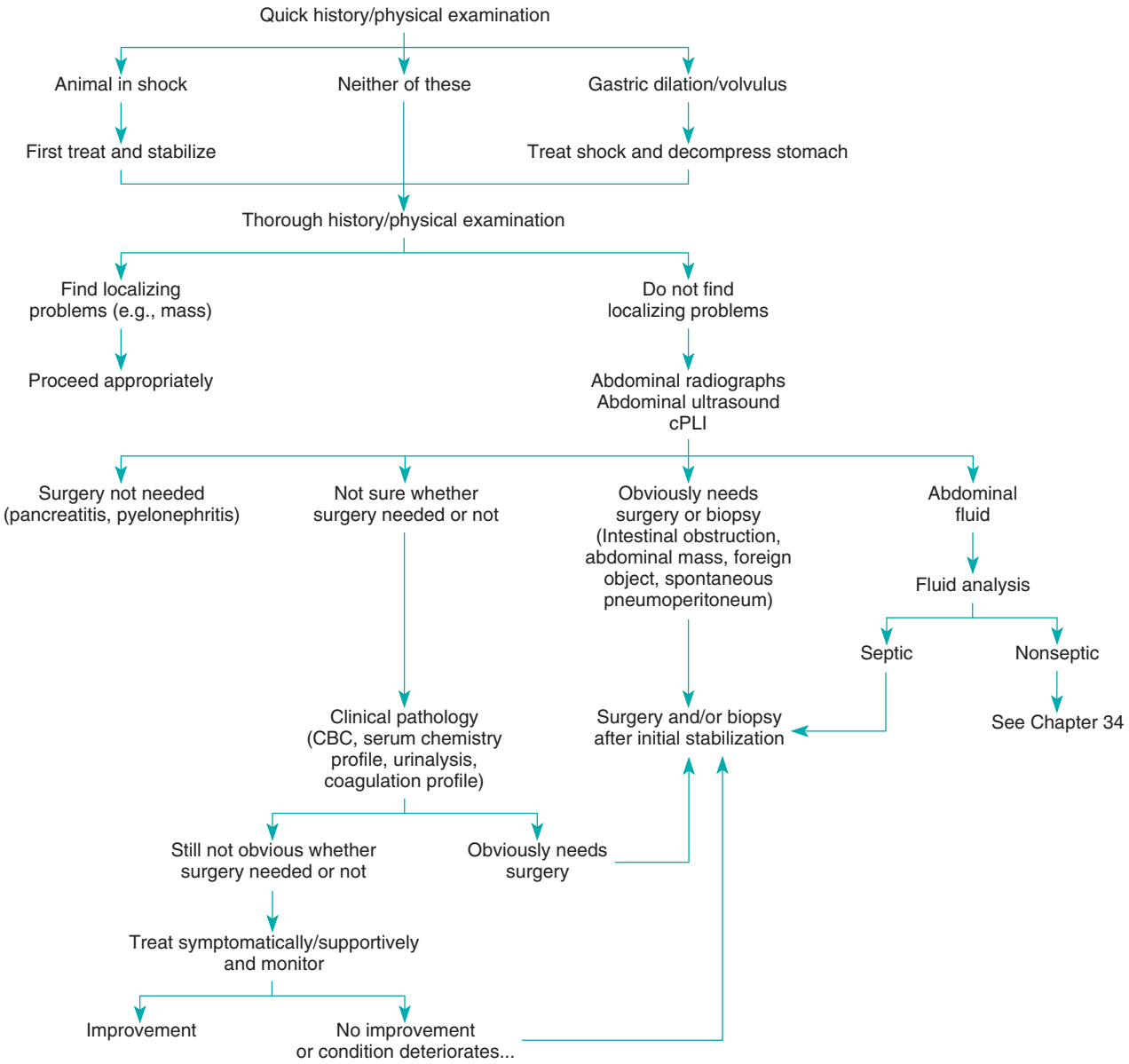


FIG 26.6
General diagnostic approach to acute abdomen in the dog and cat. *CBC,* Complete blood count; *PLI,* pancreatic lipase immunoreactivity.

there is abdominal enlargement until good cause is found to believe otherwise. There are six main causes of abdominal distention (Box 26.20).

The first concern is whether an acute abdomen is present (e.g., GDV, septic peritonitis, hemoabdomen plus shock). After an acute abdomen is ruled out, it should be possible to classify enlargement on the basis of physical examination and abdominal imaging (i.e., radiography or ultrasonography), according to the criteria in Box 26.20. Obesity and pregnancy should be obvious. Specimens of free abdominal fluid should be obtained and analyzed as described in Chapter 34. Biopsy should be performed on abdominal masses and enlarged organs, unless there is a reason not to (e.g., hepatomegaly caused by severe right-sided heart failure). Fine-needle aspiration is typically safe, although leakage of septic contents or implantation of neoplastic cells may rarely occur. Ultrasonography helps determine potential for hemorrhage or leakage (e.g., cyst, mass with ultrasonographic characteristics of hemangiosarcoma). Finding spontaneous pneumoperitoneum suggests alimentary tract rupture or septic peritonitis and is usually an indication for prompt surgical exploration. A hollow viscus dilated with gas may indicate obstruction (i.e., gastric dilation, intestinal obstruction) or physiologic ileus (see p. 420 and pp. 467-468; Figs. 27.5 and 30.3. Surgery is indicated if an obstruction seems likely. If abdominal musculature weakness is suspected, hyperadrenocorticism may be considered. Results of a CBC, serum biochemistry panel, and urinalysis are used to

BOX 26.19

Causes of Abdominal Pain

- Poor Palpation Technique ("Pseudo-pain")
- Musculoskeletal System (Mimics Abdominal Pain)
  - Fractures
  - Intervertebral disk disease (common and important)
  - Diskospondylitis (important)
  - Abscesses
- Peritoneum
  - Peritonitis
    - Septic (common and important)
    - Nonseptic (e.g., uroabdomen) (important)
  - Adhesions (rare)
- Gastrointestinal Tract
  - Gastrointestinal ulcer
  - Foreign object (especially linear)
  - Neoplasm
  - Adhesions (rare)
  - Intestinal ischemia (rare)
  - Intestinal spasm (rare)
  - See also Box 26.18, under Organ Distention or Obstruction
- Hepatobiliary Tract
  - Hepatitis
  - Cholelithiasis or cholecystitis
- Pancreas
  - Pancreatitis (common and important)
- Spleen
  - Torsion (rare)
  - Rupture
  - Neoplasm
  - Infection (rare)
- Urogenital System
  - Pyelonephritis (important)
  - Lower urinary tract infection
  - Prostatitis (important in dogs)
  - Nonseptic cystitis (common and important in cats)
  - Cystic or ureteral obstruction or rupture (common, especially after trauma)
  - Urethritis or obstruction (common)
  - Metritis
  - Uterine torsion (rare)
  - Neoplasm
  - Testicular torsion (rare)
  - Mastitis (does not cause true abdominal pain but mimics abdominal pain)
- Miscellaneous Causes
  - Postoperative pain (especially if animal has a tight suture line)
  - Iatrogenic causes
  - Drugs (e.g., misoprostol, bethanechol)
  - Adrenalitis (associated with hypoadrenocorticism) (rare)
  - Heavy metal intoxication (rare)
  - Vasculopathy (rare)
    - Rocky Mountain spotted fever vasculitis
    - Infarct

BOX 26.20

Causes of Abdominal Enlargement

- Tissue
  - Pregnancy (common and important)
  - Hepatomegaly (infiltrative or inflammatory disease, lipidosis, neoplasia)
  - Splenomegaly (infiltrative or inflammatory disease, neoplasia, hematoma)
  - Renomegaly (neoplasia, infiltrative disease, compensatory hypertrophy)
  - Miscellaneous neoplasia
  - Granuloma (e.g., pythiosis)
- Fluid
  - Contained in organ(s)
  - Congestion resulting from torsion, volvulus, or right-sided heart failure
  - Spleen
  - Liver
  - Cysts
  - Paraprostatic cyst
  - Perinephric cyst
  - Hepatic cyst
  - Hydronephrosis
  - Intestines or stomach (resulting from obstruction or ileus)
  - Pyometra
  - Free in abdomen (common and important)
    - Transudate, modified transudate, exudate, blood, chyle
- Gas
  - Contained in organ(s)
  - Stomach (gastric dilation or volvulus) (common and important)
  - Intestines (resulting from obstruction)
  - In parenchymatous organs (e.g., liver) resulting from infection with gas-producing bacteria
  - Free in abdomen
  - Iatrogenic (after laparoscopy or laparotomy)
  - Alimentary tract or female reproductive tract rupture
  - Bacterial metabolism (peritonitis)
- Fat
  - Obesity
  - Lipoma
- Weak Abdominal Muscles
  - Hyperadrenocorticism (important)
- Feces

look for specific organ involvement (e.g., hyperadrenocorticism). Contrast-enhanced alimentary or urinary tract radiographs are generally not appropriate; ultrasonography typically makes such techniques unnecessary. Sometimes abdominal CT examination will be required.

Suggested Readings

Anderson KL, Feeney DA. Radiography. In: Washabau RW, et al., eds. *Canine and feline gastroenterology*. St Louis: WB Saunders; 2013.

Jergens AE. Dyschezia and tenesmus. In: Washabau RW, et al., eds. *Canine and feline gastroenterology*. St Louis: WB Saunders; 2013.

Marks SL. Diarrhea. In: Washabau RW, et al., eds. *Canine and feline gastroenterology*. St Louis: WB Saunders; 2013.

Washabau RJ. Regurgitation. In: Washabau RW, et al., eds. *Canine and feline gastroenterology*. St Louis: WB Saunders; 2013.

Washabau RJ. Vomiting. In: Washabau RW, et al., eds. *Canine and feline gastroenterology*. St Louis: WB Saunders; 2013.

CHAPTER 27

Diagnostic Tests for the Alimentary Tract



PHYSICAL EXAMINATION

Routine physical examination is the first step in evaluating animals with alimentary tract disease. If oral, abdominal, or rectal disease is a concern and the patient refuses to allow examination of the area, it is usually appropriate to use chemical restraint to adequately examine the area. A common example is a vomiting cat with a possible linear foreign body lodged under the tongue; the clinician should thoroughly examine the mouth and base of the tongue, even if it requires strong sedation.

The clinician should methodically identify individual organs during abdominal palpation. In dogs the small intestine, large intestine, and urinary bladder can usually be found (unless there is pain, effusion, or obesity). In cats both kidneys are usually palpable. In both species clinicians should usually be able to detect substantial splenomegaly, hepatomegaly, intestinal or mesenteric masses, and intestinal foreign objects. Abdominal pain may be subtle; some animals cry out during gentle palpation, whereas others just tense their abdomen (i.e., guarding) or try to move away. Rough palpation technique can cause a normal animal to tense up or vocalize during palpation, mimicking abdominal pain. Light, careful palpation permits the definition of more of the abdominal contents. If there is sufficient abdominal fluid to prevent meaningful abdominal palpation, ballottement of the abdomen should produce a fluid wave.

During digital rectal examination, the examiner should be able to identify and evaluate the colonic mucosa, anal sphincter, anal sacs, pelvic canal bones, muscular support for the rectum, urogenital tract, and luminal contents. It is easy to misinterpret small mucosal polyps as mucosal folds and to miss partial strictures large enough to allow a single digit to pass through easily.

ROUTINE LABORATORY EVALUATION

COMPLETE BLOOD COUNT

Complete blood counts are important in animals at risk for neutropenia (e.g., parvoviral enteritis, severe sepsis), infection (e.g., aspiration pneumonia), or anemia (e.g., pale mucous membranes, melena, hematemesis) and also in those that have fever, severe weight loss, or hyporexia of occult cause. The clinician should always consider absolute numbers of the different types of white blood cells. If the animal is anemic, the clinician should look for evidence of regeneration (i.e., reticulocytes, polychromasia) and iron deficiency (e.g., hypochromasia, microcytosis, increased red blood cell distribution width).

COAGULATION

Platelet numbers can be estimated from a blood smear. A dog should have 8 to 30 platelets per oil immersion field; finding 1 platelet per field suggests a platelet count of approximately 15,000 to 20,000/µL. Coagulation panels may detect unsuspected coagulopathies (e.g., disseminated intravascular coagulation). Activated clotting times are crude estimates of the intrinsic clotting pathway; partial thromboplastin times are more sensitive. Mucosal bleeding time is an excellent screening test for coagulopathies severe enough to cause clinical bleeding.

SERUM BIOCHEMISTRY PROFILE

Serum alanine transaminase, alkaline phosphatase, blood urea nitrogen, creatinine, total protein, albumin, sodium, potassium, chloride, total CO_2, cholesterol, calcium, phosphorus, bilirubin, and glucose concentrations are important to evaluate in animals with severe vomiting, diarrhea, ascites, unexplained weight loss, or hyporexia. Clinicians cannot predict changes that will occur or the magnitude of changes in a particular animal, even when the cause of the disease is known. The total CO_2 concentration is not as definitive as blood gas analysis for defining acid-base, but it typically suffices.

The serum albumin concentration is more useful than serum total protein concentration. Hyperglobulinemia has many causes (e.g., heartworms, chronic dermatitis, ehrlichiosis) and can cause the serum total protein concentration to be normal in hypoalbuminemic patients. Severe hypoalbuminemia (i.e., <2.0 g/dL) is important diagnostically; it is more commonly found in animals with intestinal

lymphangiectasia, gastrointestinal (GI) blood loss, severe infiltrative alimentary tract disease, parvoviral diarrhea, or ascites. It is important to measure the serum albumin using technology designed for canine and feline albumin; some techniques used for measuring human albumin produce falsely low measurements of canine albumin. It is important to use the same lab when repeating the serum albumin concentration; different labs often have slightly different normal ranges, which causes confusion when monitoring hypoalbuminemic patients.

Ill animals (especially those receiving multiple drugs) are at risk for secondary renal or hepatic failure. Very young and very small animals easily become hypoglycemic if they cannot eat or absorb ingested nutrients. Finding hypercalcemia or hypoalbuminemia may provide a clue to the underlying problem in animals with weight loss or hyporexia.

SERUM CORTISOL

Atypical hypoadrenocorticism is more common in dogs than many clinicians realize. Measuring resting serum cortisol as a screening test to decide whether or not to perform an ACTH-stimulation test has become standard practice in patients with difficult to diagnose/control vomiting, diarrhea, or hyporexia.

URINALYSIS

Urinalysis is required to accurately evaluate renal function and, in conjunction with the urine protein/creatinine ratio, to help determine the cause of hypoalbuminemia. Urine should always be obtained before fluid therapy is begun.

FECAL PARASITIC EVALUATION

Fecal flotation is indicated in most animals with alimentary tract disease or weight loss, especially puppies and kittens. Even if parasitism is not the primary problem, it may cause additional debilitation. Concentrated salt or sugar solutions are typically used for fecal flotation. The former are usually superior, although incorrectly made solutions may not force heavier ova (e.g., whipworms) to float. Moreover, concentrated salt solutions can distort *Giardia* cysts, making identification difficult. Zinc sulfate flotation solution is preferred for detecting nematode ova and *Giardia* cysts. Centrifugation promotes separation of cysts from the fecal matter and results in a more sensitive fecal examination. Some parasites intermittently shed small numbers of ova or cysts, necessitating repeated fecal analyses for diagnosis. Whipworm and *Giardia* infections can be especially difficult to diagnose with fecal flotation.

The ova of the most common tapeworm species are contained in segments and are not found by flotation techniques. *Nanophyetus salmincola* (the fluke that transmits salmon poisoning) is detected by many flotation solutions, although sedimentation examinations are required to detect most other fluke ova. Cryptosporidiosis is difficult to detect by routine flotation techniques. The clinician should send the feces to a laboratory familiar with this coccidium and is able to perform special procedures to detect it. Enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and indirect fluorescent antibody (IFA) methodologies are more sensitive than fecal flotation for finding cryptosporidia (see later).

Direct fecal examination, although convenient, is not sensitive for nematodes and should not replace flotation techniques. However, occasionally amebiasis, strongyloidiasis, and whipworm infections missed by flotation procedures can be detected by direct examination. Motile *Giardia* and *Tritrichomonas* trophozoites may be found if the feces are very fresh and the smear is adequately diluted with saline solution. Direct examination is much less sensitive than zinc sulfate flotation, IFA, PCR, and ELISA techniques in detecting giardiasis (see later).

Fecal sedimentation is time consuming and offers no advantage in detecting common GI tract parasites. However, it does detect fluke ova missed by other techniques, especially the ova of *Eurytrema* spp., *Platynosomum* spp., *Amphimerus* spp., and *Heterobilharzia* spp.

Feces may be preserved by mixing equal volumes of feces and 10% neutral buffered formalin or by using commercially available kits. Polyvinyl alcohol is used in the latter, and feces preserved in this manner can be examined weeks to months later. These techniques are especially useful if one cannot immediately examine feces for protozoal cysts.

PCR analysis on feces can detect *Heterobilharzia* spp. (GI Lab, Texas A&M University, College Station, TX). It appears to be at least as sensitive as fecal sedimentation.

FECAL DIGESTION TESTS

Examining feces for undigested food particles by staining thin fecal smears with the Sudan stain (for fat) or iodine (for starch and muscle fibers) is discouraged. Finding excessive amounts of undigested fecal fat is supposedly suggestive of exocrine pancreatic insufficiency (EPI), but this test has many false-positive and false-negative results. If EPI is a differential diagnosis, a species-specific serum trypsin-like immunoreactivity (TLI) is the recommended test (see the section on digestion and absorption tests).

Fecal analysis for proteolytic activity (i.e., the fecal trypsin content) also tests for EPI. Qualitative estimates (e.g., fecal film digestion, fecal gelatin digestion) are unreliable. Quantitative analysis is seldom needed because the TLI test is easier to perform. It is rarely necessary to quantitate fecal proteolytic activity to diagnose EPI caused by pancreatic duct obstruction (exceedingly rare), something TLI does not detect. In this test, feces are collected for 3 consecutive days and stored frozen until sent to the laboratory. Quantitated fecal fat analysis is almost never indicated.

Fecal occult blood analyses are seldom useful because most pets eat meat by-products that cause a positive reaction. False-positive reactions may also be produced by cimetidine, oral iron preparations, and some vegetables. The

sensitivity of different techniques varies, making it difficult to accurately compare results. Finally, blood is often not distributed homogeneously throughout the feces, and a negative result could stem from a sampling error (especially in animals with lower intestinal tract problems).

If fecal occult blood analysis is desired, one should feed the animal a meat-free diet for 3 to 4 days before performing the test. Tests using the reagents benzidine or orthotoluidine to detect hemoglobin tend to be very sensitive (and hence less specific), whereas those using guaiac are less sensitive (and thus more specific). A sensitive and specific fluorometric method has been validated in dogs. Repeated testing may be necessary to demonstrate intermittent bleeding.

BACTERIAL FECAL CULTURE

Fecal culture is seldom indicated in small animals unless a contagious bacterial disease is strongly suspected, and even then simply finding a "pathogenic" bacteria in an animal's feces does not confirm that it is causing disease. Culture results must be correlated with clinical signs and the results of other laboratory tests. The clinician should always contact the laboratory before collecting/submitting feces, informing them specifically what bacteria to attempt to grow; there are specific techniques for collection, submission, and culture for most fecal pathogens. Fecal culture cannot be used to diagnose small intestinal antibiotic-responsive enteropathy (ARE), also called *dysbiosis*.

Potential pathogens most commonly cultured from feces from small animals include *Clostridium perfringens, Salmonella* spp., *E. coli,* and *Campylobacter jejuni.* Confirmation of toxin production by specific bacteria can be performed using PCR techniques or bioassay. *Salmonella* spp. are best cultured by inoculating at least 1 g of fresh feces into an enrichment medium and subsequently a selective medium specific for *Salmonella* spp. *Salmonella* can also be grown from colonic mucosa. To culture *C. jejuni,* very fresh feces must be inoculated onto selective media and incubated at approximately 40° C instead of 37° C. If inoculation is to be delayed, special transport media should be used, not routine commercial transport devices (e.g., culturette swabs). *Candida* spp. are occasionally cultured from feces. Growing *Candida* is often hard to interpret, but the organisms might cause problems in some animals (e.g., those receiving chemotherapy).

There is a culture technique (InPouch TF, BioMed Diagnostics) for *Tritrichomonas blagburni* in feline feces. The culture technique can be done in the practice and appears to be more sensitive than direct fecal examination but less sensitive than PCR.

ELISA, IFA, AND PCR FECAL ANALYSES

ELISA can be used to detect antibodies or antigens. The test for canine parvovirus is very specific. However, parvovirus may not be excreted in the feces for the first 24 to 48 hours after onset of clinical signs; therefore, it may be necessary to repeat the test in 2 to 3 days if initial results are negative in a dog strongly suspected of having parvoviral infection. Additionally, although dogs with parvoviral diarrhea initially shed large amounts of virus, fecal shedding decreases substantially during the ensuing 7 to 14 days. A repeatedly negative test result therefore does not rule out parvoviral infection, but it does necessitate a consideration of other acute, febrile gastroenteritides (e.g., salmonellosis). This test is particularly valuable if there are epidemiologic considerations (e.g., breeding kennel).

ELISAs for detecting a *Giardia*-specific antigen in human (ProSpecT/Microplate ELISA assay for Giardia, Alexon, Inc.) and canine/feline feces (SNAP Giardia Test, Idexx Laboratories) are available. The SNAP *Giardia* test appears to be sensitive with good negative predictive value, but it has poor positive predictive value at typical low prevalence rates when compared with IFA testing of feces. It has the advantage of being able to be performed in the practice. An IFA test (MERIFLUOR *Cryptosporidium/Giardia* direct immunofluorescent kit, Meridian Bioscience, Inc.) is probably the most sensitive and specific test for giardiasis but requires that feces be sent to a commercial laboratory.

ELISAs for detecting cryptosporidial antigens in feces (ProSpecT Cryptosporidium Microplate Assay, Meridian Diagnostics, Inc. and ProSpecT Cryptosporidium Microplate Assay, Remel, Inc.) are more sensitive than routine fecal examinations. Special staining of fecal smears with a modified Ziehl-Neelsen acid-fast technique is also sensitive, albeit more labor intensive. An IFA test (MERIFLUOR *Cryptosporidium/Giardia* direct immunofluorescent kit, Meridian Bioscience, Inc.) is not as sensitive as ELISA when looking for cryptosporidia.

Assays for bacterial toxins in feces are typically valuable for implicating specific bacteria as causing diarrhea in people, but a positive test in a dog or cat is not *prima facia* evidence it is causing disease. *C. difficile* in particular is of uncertain pathogenic significance in dogs and cats. ELISA tests (*C. perfringens* Enterotoxin Test, TechLab) and reverse passive latex agglutination tests (Oxoid PET-RPLA, Unipath Co.) for *C. perfringens* enterotoxin are available, but the results do not clearly correlate with clinical disease.

PCR testing for antigens in feces has become popular because of its sensitivity and specificity, but finding any of numerous agents in feces does not guarantee that the agent is responsible for disease. There are fecal PCR panels that can detect *Giardia, Cryptosporidium, Salmonella, C. perfringens* enterotoxin A, enteric coronavirus, parvovirus, and/or distemper virus in canine feces. Likewise there are fecal PCR panels that detect *Tritrichomonas blagburni, Giardia, Cryptosporidium, Toxoplasma gondii, Salmonella, C. perfringens* enterotoxin A, coronavirus, and/or panleukopenia virus in feline feces. The GI Lab (Texas A&M University) also offers PCR testing for *C. jejuni* and *C. coli*. In all cases, a positive PCR does not guarantee that the agent is producing clinical disease.

CYTOLOGIC EVALUATION OF FECES

Fecal cytologic evaluations may identify etiologic agents or inflammatory cells. In this method a thin, air-dried smear is stained with Gram or a Romanowsky-type stain (e.g., Diff-Quik). The latter identifies cells better than Gram stain does.

Finding excessive numbers of spore-forming bacteria (e.g., >3-4 per 1000× field) was once thought to strongly suggest clostridial colitis (see Fig. 31.1). However, the presence of spores is neither specific nor sensitive for clostridial colitis. Finding that the bacterial population is relatively uniform morphologically is of uncertain value, other than to show that the normal bacterial flora is disrupted. However, no comments can be made relative to cause or effect.

Short, curved, gram-negative rods (i.e., "commas" or "seagull wings") are supposedly suggestive of campylobacteriosis, but the value of this test in dogs and cats is doubtful. The larger spirochetes, which are often plentiful in diarrheic feces, are not *C. jejuni* and are of uncertain pathogenicity. Fungal organisms (e.g., *Histoplasma capsulatum, Cyniclomyces guttulatus, Candida* spp.) are rarely found by fecal examination; cytologic examination of mucosal scrapings or histologic examination of biopsy specimens is usually necessary to diagnose histoplasmosis.

Leukocytes in feces indicate a transmural colonic inflammation instead of just superficial mucosal inflammation. However, a definitive diagnosis of a particular cause is not possible.

ELECTRON MICROSCOPY

Electron microscopy can be used to find various viral particles (e.g., coronavirus, parvovirus, astrovirus) in feces. Because ELISA is usually adequate for detecting parvovirus, electron microscopy is rarely necessary. However, it is reasonable to choose this technique if other test results are not diagnostic and there are epidemiologic considerations. Fecal samples for electron microscopy analysis should be obtained early in the disease because fecal viral concentrations may decrease dramatically within 7 to 14 days after the onset of signs. Furthermore, some delicate viruses (e.g., coronavirus) degenerate quickly, and the feces from animals suspected of having such an infection must be handled appropriately if meaningful results are to be obtained. It is important that clinicians contact their laboratory for instructions on sample handling.

RADIOGRAPHY OF THE ALIMENTARY TRACT

Radiography allows evaluation of structures that cannot be adequately assessed during physical examination (e.g., esophagus, stomach) and may detect abnormalities missed by abdominal palpation (e.g., gastric mass, foreign object, splenic parenchymal mass). Plain radiographs should always be obtained before contrast-enhanced radiographs because (1) the former may be diagnostic and eliminate the need for contrast studies, (2) contrast-enhanced radiographs may be found to be contraindicated (e.g., evidence of GI tract leakage), and (3) plain radiographs are needed to ensure a correct radiographic technique during the contrast procedure. Contrast-enhanced radiographs may be able to detect abnormalities (e.g., a gastric outflow tract obstruction) that plain radiographs cannot.

Radiographs are generally useful in the diagnostic workup of animals with dysphagia, regurgitation, vomiting, abdominal mass or distention, abdominal pain, or acute abdomen. They are occasionally helpful in animals with constipation, weight loss, or hyporexia of unknown cause, but other tests are usually indicated first in such animals and often render radiographs unnecessary. Radiographic findings are rarely diagnostic in dogs or cats with diarrhea or copious abdominal effusion.

ULTRASONOGRAPHY OF THE ALIMENTARY TRACT

Ultrasonography may be done in combination with or instead of radiography. It is extremely operator dependent. It is often useful in animals with an acute abdomen, abdominal effusion, vomiting, chronic diarrhea, weight loss, or hyporexia of unknown cause and also in those with an abdominal mass, distention, or pain. Ultrasonography often identifies pancreatitis, infiltrations in various organs, and intussusceptions that radiography misses. Furthermore, while effusions render radiographs useless, they enhance ultrasonographic contrast. Ultrasonography is often more informative than radiography for determining whether an animal with an acute abdomen requires surgery. Finally, ultrasonography can be used to guide percutaneous aspiration and biopsy of intraabdominal lesions that would otherwise necessitate surgery or laparoscopy.

Techniques

A 5-MHz probe is probably the most utilitarian. Hair is often clipped so that there is no trapped air that could compromise image quality.

Findings

The thickness, echodensity, and homogeneity of organs (e.g., liver, spleen, intestine, stomach, mesenteric lymph nodes, masses) may be assessed. Intraparenchymal infiltrates that cannot be detected radiographically may also be found. The particular ultrasonographic findings seen in specific disorders of the alimentary tract are discussed in subsequent chapters dealing with the disorders.

IMAGING OF THE ORAL CAVITY, PHARYNX, AND ESOPHAGUS

INDICATIONS

Animals with dysphagia, oral pain, halitosis of unknown cause, or a swelling or mass should generally undergo imaging. If dysphagia of neuromuscular origin is suspected, dynamic contrast studies (i.e., fluoroscopy) are recommended. Ultrasonography can be useful for evaluating infiltrates or masses, but magnetic resonance imaging (MRI) offers even more detail.

Techniques

Anesthesia is necessary so that animals can be properly positioned for cranial radiographs. Lateral, dorsoventral (DV), and oblique radiographs are used to detect foreign objects or fractures. Open-mouth ventrodorsal (VD) views and end-on views of the nose may also be helpful. Computed tomography (CT) is superior to radiographs (and easier) for finding fractures, and a helical CT can perform the examination so quickly that deep sedation may be all that is needed. MRI is superior to CT for detecting soft tissue lesions. Dynamic studies (i.e., fluoroscopy, cinefluoroscopy) are necessary to evaluate for dysphagia of neuromuscular origin. Dynamic studies are performed by feeding conscious animals various forms of barium (i.e., liquid, paste, and mixed with food). Performing dynamic studies in sternal recumbency is preferred because lateral recumbency might increase transit time and change the type of peristaltic waves.

Findings

Foreign objects, fractures, bone lysis, soft tissue masses or densities, and emphysema are the most common findings. Bone surrounding the tooth roots should be examined for lysis and the temporomandibular joints for arthritis. It is important to consider the bilateral symmetry of the skull; one side should be compared with the other when evaluating the VD projection. When performing contrast-enhanced or dynamic studies, the clinician should watch for aspiration of barium, the strength with which the bolus is propelled into the esophagus, and synchronization of the opening of the cricopharyngeal muscle with the pharyngeal phase of swallowing.

INDICATIONS FOR IMAGING OF THE ESOPHAGUS

Indications for evaluating the esophagus include any type of neuromuscular dysphagia, regurgitation, pain when swallowing, unexplained recurrent pneumonia or cough, radiographic thoracic "masses" of undetermined origin, and before surgical lateralization of arytenoids for laryngeal paralysis. A barium contrast esophagram is often necessary to define esophageal pathology unless plain films reveal obvious megaesophagus, a foreign object, evidence of esophageal perforation (e.g., a pleural effusion, pneumothorax, pneumomediastinum), or an obvious hiatal hernia. Be sure to include the cervical esophagus. Finding obvious megaesophagus on plain radiographs is usually sufficient, but rare dogs with apparent megaesophagus on plain radiographs demonstrate normal function when barium is administered. Ultrasonography, CT, and MRI are seldom helpful for dogs and cats with esophageal disease, unless there is a thoracic mass.

Techniques

Liquid barium is the best contrast agent for esophageal studies. It provides excellent detail and is not problematic if aspirated unless there is preexisting pneumonia. The clinician must not administer drugs that affect esophageal motility (e.g., xylazine, ketamine, anesthesia). The animal should take several swallows of dilute barium from a syringe, shortly after which right lateral and VD radiographs are obtained. Barium paste does not offer any substantive advantages over liquid barium. Hypertonic iodine contrast agents do not achieve as good a contrast as barium and cause severe problems if aspirated; isotonic water-soluble iodine contrast agents are better but still provide mediocre contrast. If radiographic studies performed with liquid contrast agents do not detect an abnormality in an animal in which esophageal disease is strongly suspected, the study should be repeated using a mixture of barium and food (both canned food and dry kibble). Such studies may detect partial strictures or muscular weakness not found with previous studies.

If barium is retained in the esophagus but little or none enters the stomach, the animal should be held in a vertical position so that gravity facilitates migration of barium into the stomach. If barium readily enters the stomach, this indicates that there is no lower esophageal sphincter obstruction. If a hiatal hernia is suspected but not seen, a lateral radiograph of the caudal thorax may be taken while the abdomen is manually compressed. This is done in an attempt to force the contrast-filled stomach to herniate into the thorax, allowing diagnosis.

If esophageal disease seems likely but is not found by static radiographs, fluoroscopic studies are indicated next. If possible, the clinician should perform fluoroscopy as the animal swallows the barium to assess esophageal motility and look for partial esophageal obstruction, segmental esophageal weakness, gastroesophageal reflux, and esophageal-pharyngeal reflux (i.e., cricopharyngeal incompetence). Having the patient in sternal recumbency is preferred for dynamic studies. It may be necessary to observe the esophagus for several minutes (or longer) before some abnormalities (e.g., gastroesophageal or esophageal-pharyngeal reflux) occur. In animals with marginal esophageal disease, fluoroscopy may be necessary to document that primary or secondary esophageal waves are present but are either weak or not readily stimulated. If fluoroscopy is unavailable, multiple radiographs (usually lateral projections) taken in rapid succession beginning very shortly (i.e., 5-10 seconds) after swallowing are sometimes adequate.

If an esophageal perforation is suspected (e.g., septic pleuritis or mediastinitis, pneumomediastinum, or

pneumothorax), an isotonic iodine contrast medium should be used. However, the only purpose of such a study is to localize the perforation. If the clinician already knows where the leakage is likely to be (e.g., there is a bone foreign body in the esophagus), contrast radiographs are of dubious value. Perforations may not be obvious if the foreign body that caused them is filling and occluding the defect.

Findings

Esophageal dilation, foreign objects, soft tissue densities, spondylosis suggestive of spirocercosis, and hiatal hernia may often be identified on plain films. An air-filled esophagus is not always diagnostic of pathologic esophageal weakness. Although it is tempting to use plain radiograph findings as the basis for the diagnosis of esophageal disease when there is an "obvious" abnormality, it is possible to misinterpret plain films or miss abnormalities that a barium contrast–enhanced study would reveal. Rarely, animals with a dilated, air-filled esophagus on plain films have normal esophageal function when evaluated with a barium contrast esophagram (Fig. 27.1, *A*). In contrast, many animals with relatively minor changes on plain radiographs have substantial esophageal dysfunction (see Fig. 27.1, *B*). Occasionally, accumulation of food in the classic location for a vascular ring anomaly may be caused by localized esophageal weakness or a thymic cyst.

Almost all esophageal foreign objects can be seen on plain radiographs. However, excellent radiographic technique is necessary because some foreign objects (e.g., poultry bones, rawhide treats) are relatively radiolucent (Fig. 27.2). An esophageal perforation sometimes causes pneumothorax, pneumomediastinum, or a pleural/mediastinal effusion.

Contrast-enhanced esophagrams should be considered in animals with unidentified thoracic masses because many esophageal tumors radiographically resemble pulmonary parenchymal masses (see Fig. 29.8). Contrast-enhanced esophagrams may also show that structures that seemingly involve the esophagus actually do not. An obstruction is suggested on contrast-enhanced esophagrams if the barium column terminates abruptly as it travels caudally; weakness usually causes contrast to be retained throughout the esophagus or the weakened segment of the esophagus (Fig. 27.3). A partial obstruction is suggested by retention of barium-impregnated food but not liquid barium (see Fig. 29.7).

A barium contrast study will not always reveal a hiatal hernia (Fig. 29.4). Some hiatal hernias slide in and out of the diaphragm and may be normally positioned when the radiograph is taken. Gastroesophageal reflux and esophagitis also may be difficult to diagnose radiographically. Barium may adhere to a severely diseased mucosa, but less severe esophagitis may not be detected. Normal dogs may have an episode of gastroesophageal reflux during a contrast study, whereas dogs with pathologic gastroesophageal reflux may not have reflux during a short examination.

If the animal is believed to be regurgitating but the barium contrast–enhanced radiographs are unrevealing, either the assessment of regurgitation is wrong or there is occult disease

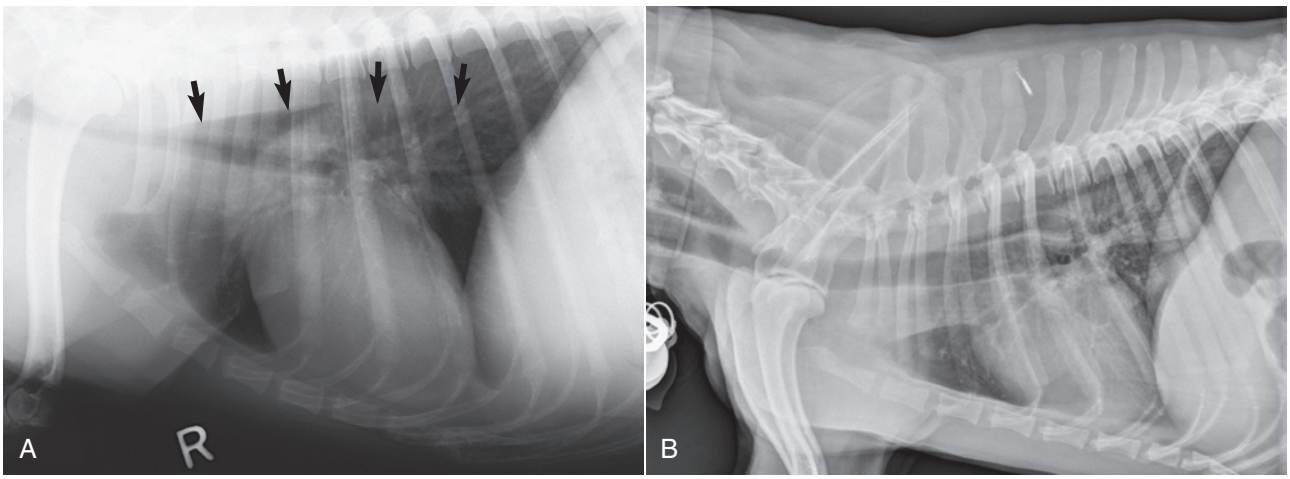


FIG 27.1
(A) Lateral thoracic radiograph from a dog that was seen because of coughing. Note the dilated, air-filled esophagus *(arrows)*. Contrast-enhanced esophagram (with fluoroscopy) obtained 2 days later documented normal esophageal size and function. **(B)** Lateral thoracic radiograph from a dog that is coughing and spitting up food occasionally. There is minimal air accumulation in the thoracic esophagus, but there is substantial air accumulation in the cervical esophagus immediately behind the cricopharyngeous sphincter. The dog has major esophageal dysfunction, primarily in the cervical esophagus. This image shows how easy it is to miss segmental esophageal weakness of the cervical esophagus on plain radiographs.

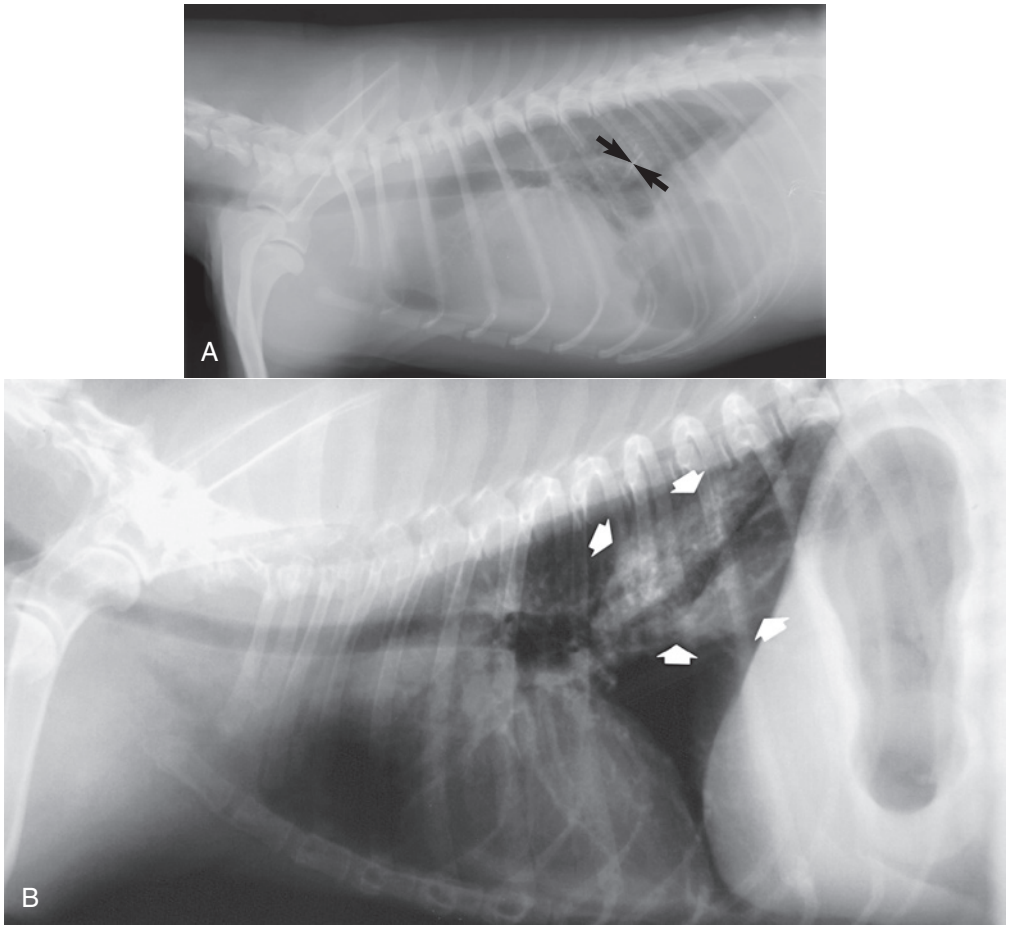


FIG 27.2
(A) Lateral thoracic radiograph from a dog with a foreign object in the esophagus *(arrows)*. Note the concomitant pleural effusion. A chicken bone had perforated the esophagus, and septic pleuritis was present. **(B)** Lateral thoracic radiograph from a dog with a rawhide treat in the esophagus. The density representing the bone *(arrows)* is more diffuse than was seen in **(A)** and looks more like a pulmonary parenchymal density than a bone. (**A** from Allen D, ed.: *Small animal medicine,* Philadelphia, 1991, JB Lippincott.)

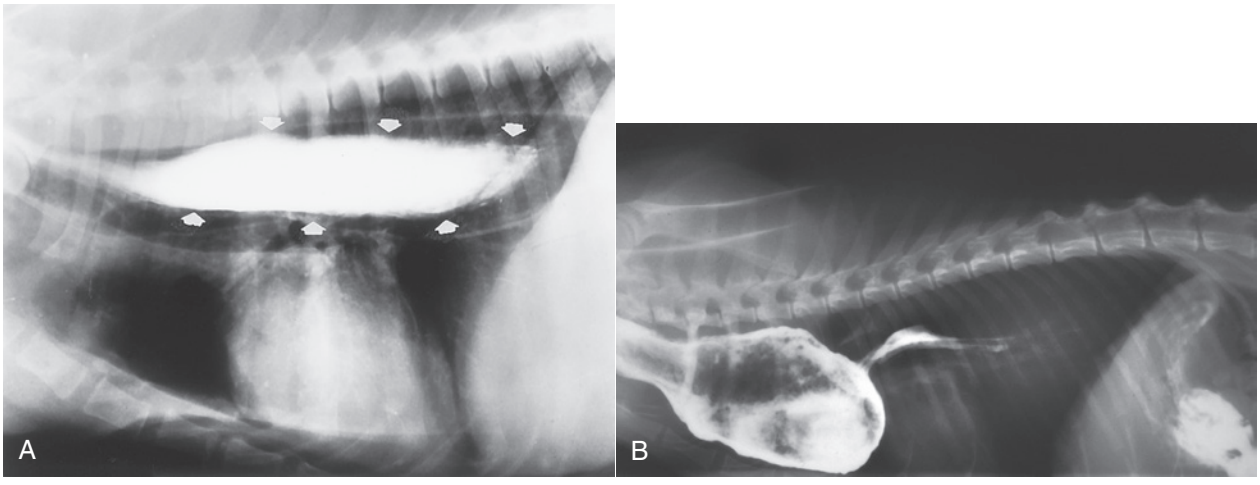


FIG 27.3
(A) Lateral thoracic contrast-enhanced esophagram from a dog with generalized esophageal weakness. Note that barium is retained throughout the length of the esophagus *(arrows)*. **(B)** Lateral thoracic contrast-enhanced radiograph of a cat with an esophageal obstruction caused by a vascular ring anomaly.

in which case reexamination of the esophagus with endoscopy or fluoroscopy or both are required.

IMAGING OF THE STOMACH AND SMALL INTESTINE

INDICATIONS FOR RADIOGRAPHIC IMAGING OF THE ABDOMEN WITHOUT CONTRAST MEDIA

Common indications for plain abdominal radiography include vomiting, acute abdomen, constipation, hyporexia, abdominal pain, abdominal enlargement, abdominal distention, or a mass. Plain radiographs are rarely beneficial in animals with a marked abdominal effusion (the fluid obliterates serosal detail) or with chronic diarrhea. Plain abdominal radiographs can be especially helpful in detecting radiodense foreign objects and alimentary tract dilation caused by obstruction.

Techniques

The clinician always should obtain at least two radiographic views, usually right lateral and VD projections. Cleansing enemas may improve the diagnostic usefulness of radiographs in patients with a great deal of feces; however, a critically ill animal or one with an acute abdomen generally should not have an enema unless plain radiographs show it is necessary.

Findings

Plain abdominal radiographs may detect masses, foreign objects, a gas- or fluid-distended hollow viscus, misshapen or emphysematous parenchymal organs, pneumoperitoneum, abdominal effusions, and displaced organs suggestive of a mass or adhesion.

Gastric outflow tract obstruction is easy to diagnose when there is marked gastric distention (Fig. 27.4). However, if the patient has recently vomited, the stomach may be empty and contracted. Gastric dilation, especially with volvulus, is easily recognized (see Fig. 30.3). Radiodense foreign objects are easily seen, but radiolucent foreign objects are seen only if they are outlined by swallowed air.

Intestinal obstructions are typically easier to diagnose with plain radiographs than are gastric obstructions. Obstructed intestines distended with air, fluid, or ingesta are not readily emptied when the patient vomits (unless it is a high duodenal obstruction) in contrast to an obstructed stomach, which is relatively easy to empty. Intestinal distention (i.e., ileus) may be caused by inflammation (i.e., adynamic or physiologic ileus) as well as obstruction (i.e., mechanical, occlusive, or anatomic ileus). Anatomic ileus (i.e., obstruction) typically produces a non-uniform intestinal distention with a greater degree of distention than is seen with physiologic ileus (Fig. 27.5). If "stacking" of the distended intestines or sharp bends and turns in the dilated intestines are seen, this also suggests anatomic ileus. Standing lateral radiographs rarely aid in differentiating anatomic from physiologic ileus. Even experienced radiologists occasionally confuse physiologic ileus with obstruction. Thus diseases producing severe inflammation (e.g., parvoviral enteritis) may closely mimic intestinal obstruction.

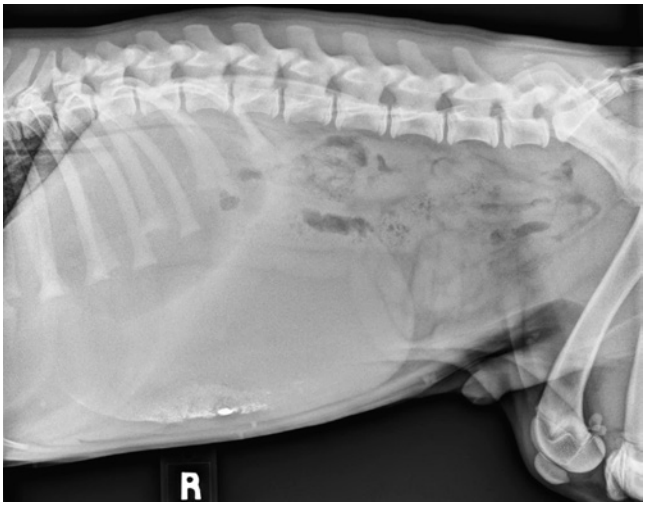


FIG 27.4
Plain lateral radiograph from a dog with gastric outflow obstruction. Note the dilated stomach protruding past the costal arch. This radiographic pattern is not sensitive for outflow obstruction, but it is relatively specific.

Special types of intestinal obstructions are associated with unique radiographic findings. If the entire intestinal tract is uniformly distended with gas (Fig. 27.6) and the clinical signs fit, mesenteric volvulus may be diagnosed. If marked intestinal distention is very localized and seems out of place (e.g., has herniated), a strangulated or incarcerated intestinal obstruction (see Fig. 31.11) should be considered.

Linear foreign bodies rarely produce gas-distended bowel loops. Instead, they tend to cause the intestines to bunch together; sometimes small gas bubbles are present (see Fig. 31.12). This occurs because the intestines "gather" around the linear foreign object as they try to propel it aborad. This "gathering" or "bunching" plus the fact that linear foreign bodies tend primarily to affect the upper small intestines (i.e., duodenum) mean that it is rare that they cause severely gas-distended loops of bowel. Sometimes pleated (i.e., "accordion-like") intestines can be seen on plain radiographs (see Fig. 31.12).

It is difficult to determine the thickness of intestines on plain radiographs. Animals with diarrhea and an increased amount of intestinal fluid are often misdiagnosed as having thickened intestinal walls.

Decreased serosal contrast is due to either lack of fat or excessive abdominal fluid (see Chapter 34). Displacement of an organ (Fig. 27.7) often means there is a mass present. Pneumoperitoneum is diagnosed if both the thoracic and abdominal surfaces of the diaphragm or if the serosal surfaces of the liver, stomach, or kidneys are easily seen (see Fig. 32.1, *A*). However, perforation sometimes causes only

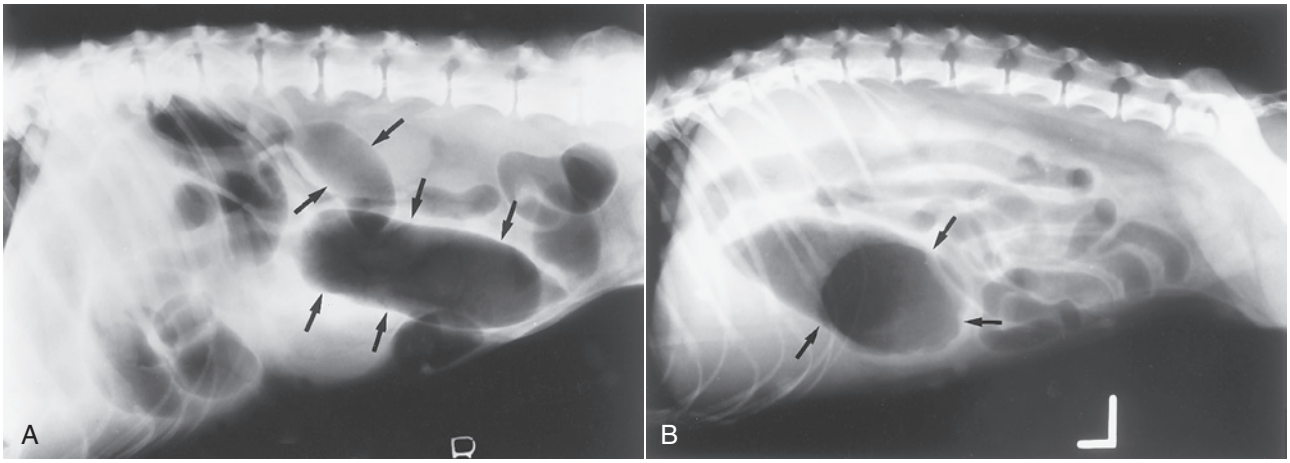


FIG 27.5
(A) Plain lateral abdominal radiograph from a dog with an intestinal obstruction causing intestinal distention. Note the markedly increased diameter of the small intestinal lumen *(arrows)*. **(B)** Plain lateral abdominal radiograph from a dog with peritonitis causing physiologic ileus. Note the lesser degree of small intestinal distention compared with that in **A.** The large gas-filled structure is the gastric pylorus *(arrows)*. (Courtesy Dr. Kenita Rogers, Texas A&M University, College Station, TX.)

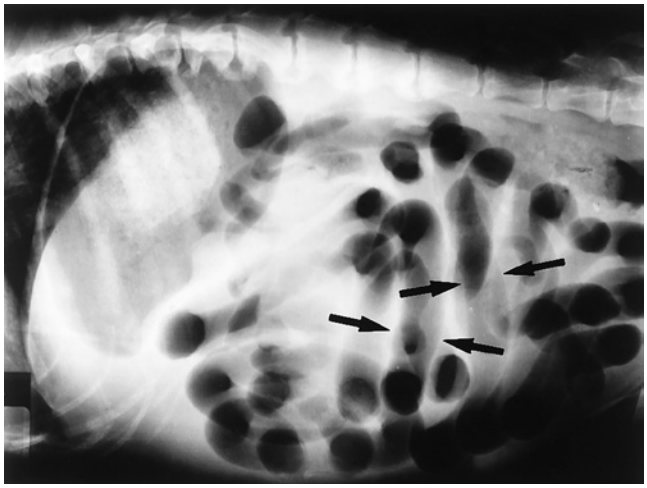


FIG 27.6
Lateral abdominal radiograph from a dog that had an acute onset of vomiting, abdominal pain, and shock. There is a uniform intestinal distention that is not as great as that in Fig. 27.5, *A*. However, distention is more than that seen in Fig. 27.5, *B*. Some intestinal loops have assumed a vertical orientation *(arrows)*, which suggests the existence of an obstruction. This dog had a mesenteric volvulus. (Courtesy Dr. Susan Yanoff, U.S. Military.)

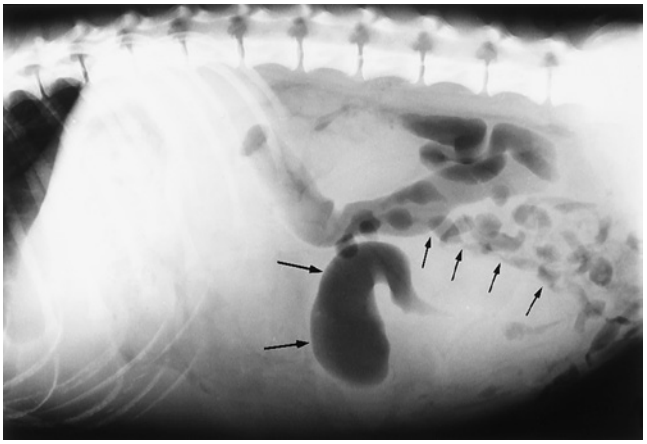


FIG 27.7
Lateral abdominal radiograph from a dog with a large granuloma caused by pythiosis. Small intestinal loops are displaced dorsally and caudally *(small arrows)*. The border of the mass is not discernible except where it displaces small intestinal loops. The finding of a dilated intestinal loop *(long arrows)* is consistent with obstruction.

there to be a few gas bubbles in the peritoneal cavity (see Fig. 32.1, *B*).

INDICATIONS FOR ULTRASONOGRAPHY OF THE STOMACH AND SMALL INTESTINES

Ultrasonography is particularly useful for detecting intussusceptions, pancreatitis, abdominal infiltrative disease, and small amounts of effusion not seen radiographically; evaluating the hepatic parenchyma; and identifying abdominal neoplasia in animals with abdominal effusion. Ultrasonography is much more revealing than radiography in animals with minimal body fat that have little or no radiographic contrast in the abdomen. However, very dehydrated animals may be difficult to image with ultrasound, and it is easy to miss small foreign objects (especially in the stomach/intestines if food and gas are present). Ultrasonography will not detect bony changes and modest microhepatica that are

detected by radiographs. The skill of the ultrasonographer determines the usefulness of the technique.

Technique

Before ultrasonography is performed, the abdominal hair is usually clipped to improve the quality of the examination. This is not necessary in animals with minimal hair. Because air in the stomach or intestines limits the usefulness of ultrasonography, exercise, drugs (e.g., some narcotics) that cause hyperventilation, and enemas should be avoided before the examination. The clinician should not hesitate to sedate the dog if it is hyperactive or hyperventilating.

Findings

Ultrasonography detects almost any soft tissue change that plain radiographs detect, plus gastric and intestinal infiltrates (Fig. 27.8, *A*), intussusceptions (see Fig. 27.8, *B*), enlarged lymph nodes (see Fig. 27.8, *C*), masses (see Fig. 27.8, *D*), some radiolucent foreign objects, and small amounts of free peritoneal fluid that radiographs cannot detect. If

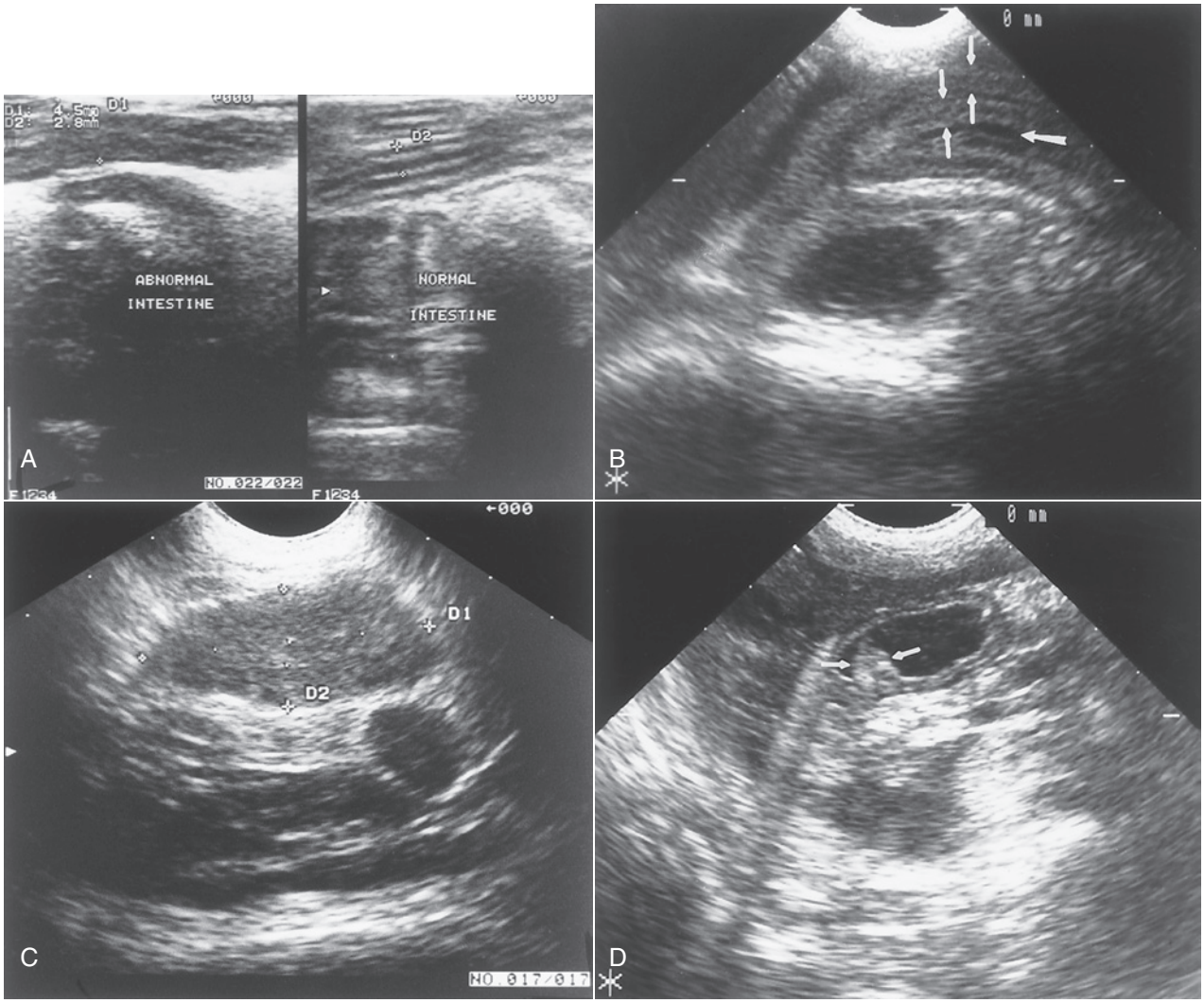


FIG 27.8
(A) Ultrasonographic image of two sections of small intestine from a cat with an alimentary tract lymphoma. The normal intestine on the right is 2.8 mm thick (see the two "+'s" noted as D2), whereas the abnormal intestine on the left is 4.5 mm thick (D1) because of neoplastic infiltrates. **(B)** Ultrasonographic image of an ileocolic intussusception that was not obvious on plain abdominal radiographs. There are two intestinal walls *(small arrows)* seen on each side of the lumen *(large arrow)*. **(C)** An enlarged mesenteric lymph node in a dog caused by lymphoma, seen by ultrasonography. The lymph node was not detected on radiographs or by abdominal palpation. **(D)** Ultrasound image of the gastric antrum from a dog with benign gastric polyps. One polyp can be seen *(arrows)* protruding into the gastric lumen. (Courtesy Dr. Linda Homco, Cornell University, Ithaca, NY.)

tissue infiltrates are found, they can sometimes be aspirated by the fine-needle technique.

INDICATIONS FOR CONTRAST-ENHANCED GASTROGRAMS

Since the advent of ultrasonography, contrast gastrograms are seldom required. However, they may be considered in vomiting animals when ultrasound studies and plain abdominal radiographs are unrevealing. It is primarily useful to detect gastric masses/foreign bodies and gastric motility problems. Endoscopy is usually a better choice to examine the stomach unless there is a primary motility problem (rare).

Technique

The animal should not be allowed to eat for at least 12 hours (preferably 24 hours) before the procedure, and feces should be removed with enemas. Plain radiographs should be obtained immediately before the contrast-enhanced films to verify that the abdomen has been properly prepared, that the radiographic technique is correct, and that the diagnosis cannot be made on the basis of the plain radiographic findings alone. Liquid barium sulfate is then administered orally (8-10 mL/kg in small dogs and cats and 5-8 mL/kg in large dogs). Iohexol can be administered orally (i.e., 700-875 mg I/kg, which is usually about 1¼ to 1½ mL/kg). The agent should be administered via a stomach tube to ensure adequate gastric filling and optimal evaluation of the stomach. The animal should not receive motility-altering drugs (e.g., xylazine, ketamine, parasympatholytics) that delay outflow.

Immediately after barium administration, radiographs are taken in left and right lateral plus DV and VD projections. Lateral and DV projections should be obtained again at 15 and 30 minutes and perhaps hourly from 1 to 3 hours. The right lateral view causes barium to pool in the pylorus, the left lateral view causes it to pool in the gastric body, the DV view causes it to pool along the greater curvature, and the VD view allows better evaluation of the pylorus and antrum. Double-contrast gastrograms provide more detail than single-contrast gastrograms. They are performed by administering and immediately removing barium via a stomach tube and then insufflating the stomach with gas until it is mildly distended.

If available, fluoroscopy is best performed immediately after administration of the barium. It can be used to evaluate gastric motility, gastric outflow, and the maximal opening size of the pylorus. If the animal is fed barium mixed with food (recommended only if gastric outflow tract obstruction is suspected despite normal liquid barium study findings), gastric emptying will be markedly delayed compared with that seen when the animal is fed liquid barium.

Findings

Gastric emptying is considered delayed if liquid barium does not enter the duodenum within 15 to 30 minutes after administration or if the stomach fails to almost completely empty the liquid barium within 3 hours. Luminal filling defects (e.g., growths and radiolucent foreign objects), pyloric lesions preventing gastric emptying, and infiltrative lesions may be seen using this method. However, normal peristalsis, ingesta, or gas bubbles may resemble an abnormality, so a change must be seen on *at least* two separate films before the clinician can diagnose disease.

Contrast-enhanced gastrograms are very insensitive for detecting ulcers and useless for erosions. Ulcers are documented radiographically if barium is seen to enter the gastric or duodenal wall or if a persistent spot of barium is identified in the stomach long after the organ has emptied itself of the contrast agent. The duodenum should be scrutinized in a search for constrictions and infiltrative lesions because many vomiting animals have disease there (e.g., inflammatory bowel disease, tumors) rather than in the stomach (see Chapter 31).

INDICATIONS FOR CONTRAST-ENHANCED STUDIES OF THE SMALL INTESTINE

Vomiting is the principal albeit rare reason for performing contrast studies of the upper small intestine. Contrast-enhanced radiographs can typically distinguish anatomic from physiologic ileus but are almost never needed for that purpose. Orad obstructions are easier to demonstrate than aborad ones. If a very aborad obstruction is suspected (e.g., ileocolic intussusception), a barium enema (or preferably ultrasonography) is often better than an upper GI contrast series. Although linear foreign objects usually produce subtle findings on plain radiographs, they often cause a classic "pleating" or "bunching" of the intestines on contrast films (see Fig. 31.12, *C*).

Animals with diarrhea seldom benefit from contrast studies of the intestines because normal radiographic findings do not exclude severe intestinal disease. Even if radiographic findings indicate infiltrative disease, it is still necessary to obtain a biopsy specimen to determine the cause. It is usually more cost-effective to skip contrast-enhanced radiographs and perform endoscopy or surgery.

Use of iodinated contrast agents (preferably iohexol) is reasonable if an alimentary tract perforation is suspected. However, if spontaneous septic peritonitis is strongly suspected, it can usually be definitively diagnosed by ultrasound-guided abdominocentesis and fluid analysis, which reveals septic peritonitis. If ultrasound is unavailable and blind abdominocentesis is unrevealing in such a patient, it is often better to perform a thorough exploratory laparotomy than contrast-enhanced radiography.

Contrast CT of the GI tract is possible but is seldom needed and can be difficult to critically evaluate.

Technique

Liquid barium sulfate is administered as described for contrast-enhanced gastrography. Lateral and VD radiographs should be obtained immediately and then 30, 60, and 120 minutes after barium administration. Additional films are obtained as necessary. The study is completed once

contrast has reached the colon. If chemical restraint is absolutely necessary, acetylpromazine may be used. Fluoroscopy is rarely needed for these studies.

Hypertonic iodinated contrast agents are inferior to barium for small intestinal studies because they decrease the intestinal transit time and can cause considerable fluid shifts by osmotically drawing fluid into the GI tract. Their potential advantages rarely outweigh their disadvantages. Isotonic iodinated contrast agents are safer and produce better detail than the hypertonic iodinated compounds but are still less diagnostic than barium.

Findings

In a complete intestinal obstruction, the barium column cannot advance beyond a certain point, and the intestines orad to this point are typically dilated. A partial obstruction may be denoted by delayed passage past a certain point (there may or may not be dilation of the intestines orad to this point) or constriction of the lumen. Because it is easy to overinterpret contrast-enhanced radiographs of the intestines, changes must be seen on *at least* two different films taken at different times before a disease is diagnosed.

"Enteritis" is often incorrectly diagnosed if a fine "brush border" in the lumen is found. However, this finding actually results from the barium normally distributing itself among villi, not from enteritis. Infiltration from neoplasia or inflammatory infiltrates classically causes scalloped margins (sometimes called *thumb-printing*). However, its absence does not rule out infiltrative disease. Focal dilations not caused by obstruction (i.e., diverticula) are rare and usually represent a localized neoplastic infiltrate. In rare instances, unsuspected intestinal blind loops or short-bowel syndromes may be detected. Motility problems may cause slowed passage of the contrast through the alimentary tract, but hypomotility is usually due to obstruction or abdominal inflammation.

INDICATIONS FOR BARIUM CONTRAST ENEMAS

This is a largely outdated procedure that is almost never done anymore. It might be useful if there is a severe colonic lesion and ultrasound and colonoscopy are not available. The reader is referred to earlier editions of this text for more information on barium contrast enhanced enemas.

PERITONEAL FLUID ANALYSIS

Fluid analysis is discussed in detail in Chapter 34. The fluid is obtained by performing abdominocentesis with a syringe and needle. If this technique fails, a multifenestrated catheter (e.g., dialysis catheter) may be successful. It is sometimes best to allow fluid to spontaneously drain out of the catheter without applying negative pressure.

If peritoneal inflammation is suspected but abdominal fluid cannot be retrieved, a diagnostic peritoneal lavage may be performed. In this method a sterile catheter (preferably with multiple fenestrations) is inserted into the abdomen and warm, sterile physiologic saline solution (20 mL/kg) is administered rapidly. The abdomen is massaged vigorously for 1 to 2 minutes, and then some of the fluid is aspirated. The aspirate is evaluated cytologically.

DIGESTION AND ABSORPTION TESTS

Exocrine pancreatic function may be tested by measuring fecal proteolytic activity (not recommended), fat absorption with and without pancreatic enzymes (not recommended), or serum TLI (recommended).

Serum TLI is the most sensitive and specific test for EPI and is convenient (i.e., submit 1 mL of refrigerated serum obtained after an overnight fast) and readily available. The TLI assay detects circulating proteins produced by a normally functioning exocrine pancreas and is even valid in animals receiving pancreatic enzyme supplements orally. It is important to use an assay that is specifically designed for the species being tested. Pancreatitis, renal failure, and severe malnutrition may increase the serum TLI concentrations, but this rarely causes results to be misinterpreted. However, if EPI is caused by obstruction of the pancreatic ducts (rare) as opposed to acinar cell atrophy or destruction (common), the serum TLI test may not detect maldigestion. In such cases, a quantitative fecal proteolytic assay is required.

Normal dogs have serum TLI activities of 5.2 to 35 µg/L. Values of less than 2.5 µg/L confirm a diagnosis of EPI. Values between 2.5 to 5.2 ug/L should be rechecked later. Normal cats have higher values (28-115 µg/L). The serum TLI assay is primarily indicated in patients with chronic small intestinal diarrhea or chronic weight loss of unknown origin. Feline EPI is less common than canine EPI, but the test is still a good idea in cats. Although principally used to detect EPI, serum TLI values substantially greater than normal are suggestive of pancreatitis.

SERUM CONCENTRATIONS OF VITAMINS

Serum concentrations of cobalamin and folate are sometimes helpful in animals with chronic small intestinal diarrhea or chronic weight loss. These tests may provide evidence of severe small intestinal mucosal disease; however, they are insensitive for small intestinal disease and not specific for any particular intestinal disease. Dietary cobalamin is absorbed in the intestine, principally the ileum; hence, ileal disease is thought to be particularly likely to cause hypocobalaminemia ostensibly because of malabsorption of the vitamin. Cobalamin concentrations are usually decreased in dogs with EPI, possibly because of the abnormalities in small intestinal bacterial populations in such animals. Severe mucosal disease, especially in the region of the ileum, may also cause serum cobalamin concentrations to be decreased. Perhaps the major indications for measuring serum cobalamin are to look for evidence of intestinal disease in patients

with weight loss of uncertain cause and to better define cats with known small intestinal disease (cobalamin-deficient cats can experience metabolic complications). If the serum cobalamin is low in a patient with weight loss of unknown cause, small intestinal disease may be responsible. B-complex vitamin supplementation may cause an increased serum cobalamin concentration.

Dietary folate is absorbed in the small intestine. Excessive numbers of bacteria in the upper small intestine sometimes synthesize and release folate, causing the serum concentrations to be increased. Likewise, severe intestinal mucosal disease may decrease absorption, causing lower serum concentrations. B-complex vitamin supplementation may increase serum folate concentrations. Like cobalamin, folate concentrations are insensitive for intestinal disease and not specific for any particular intestinal disease. Because bright light degrades cobalamin, samples should be frozen and kept in the dark during storage and transport.

OTHER SPECIAL TESTS FOR ALIMENTARY TRACT DISEASE

Antibodies to acetylcholine receptors should be measured if the clinician is looking for localized myasthenia, which is a potential cause of dysphagia or esophageal weakness (see p. 454). Increased titers to such antibodies are strongly suggestive of myasthenia gravis, even if there are no systemic signs. False-positive results are rare. Serum can be sent to Dr. Diane Shelton (Comparative Neuromuscular Laboratory, Basic Science Building, University of California at San Diego, La Jolla, CA 92093-0612) for this analysis.

Measurement of antibodies to 2M muscle fibers can be helpful in dogs with suspected masticatory muscle myositis (see p. 451). These antibodies are typically not found in dogs with polymyositis, whereas most dogs with masticatory myositis do have them. Serum is required for the test and can be sent to Dr. Diane Shelton for testing.

Serum gastrin concentrations are measured in animals with signs suggestive of gastrinoma (i.e., chronic vomiting, weight loss, and diarrhea in older animals, especially if there is concurrent esophagitis or duodenal ulceration). Gastrin stimulates gastric acid secretion and is trophic for gastric mucosa. Serum for assay of gastrin is harvested from an animal after an overnight fast and rapidly frozen. The serum gastrin concentration may be increased in animals with gastrinoma, a gastric outflow tract obstruction, renal failure, short-bowel syndrome, or atrophic gastritis and those receiving proton pump inhibitors (histamine-2 [H_2] receptor antagonists cause a lesser increase). Resting serum gastrin concentrations may vary, with occasional values in the normal range in animals with gastrinoma. Provocative testing should be considered in dogs strongly suspected of having gastrinoma but with normal baseline serum gastrin concentrations (see Chapter 49).

Testing for urease activity in gastric mucosa for *Helicobacter* spp. is rarely done anymore. *Helicobacter* spp. can usually be found easily by histology. For more information on urease activity, please see prior editions of this textbook.

Fecal α_1-protease inhibitor can be measured in feces and is a marker for GI protein loss. Clinically this test is rarely indicated but could be helpful when trying to distinguish whether hypoalbuminemia is at least partly due to a protein-losing enteropathy in a patient with known renal protein loss or hepatic insufficiency. The test is performed by the GI Lab at Texas A&M University.

Tests for *Pythium insidiosum* are available. ELISA tests for antibodies and PCR testing for antigen can be done at the College of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803.

ENDOSCOPY

Endoscopy can be cost effective in animals with chronic vomiting, diarrhea, or weight loss if cases are selected carefully and the endoscopist is accomplished. It permits rapid exploration of selected sections of the alimentary tract and mucosal biopsy without the need for a thoracotomy or laparotomy. Although excellent for detecting morphologic changes (e.g., masses, ulcers, obstruction), it is insensitive for revealing abnormal function (e.g., esophageal weakness).

Rigid endoscopy of the colon is easier to perform and less expensive than flexible endoscopy, and it provides excellent biopsy samples. Flexible endoscopes allow one to examine the ileocolic and cecocolic valve areas as well as the ascending and transverse colons, areas that cannot be inspected with a rigid endoscope. Flexible instruments are expensive and require time and commitment to become proficient in their use. One is limited by how far the instrument can be advanced. Expertise is required to obtain diagnostic tissue samples without excessive artifacts.

Esophagoscopy is useful in looking for esophageal tumors (Fig. 27.9), foreign objects (Fig. 27.10), inflammation (Fig. 27.11), and obstruction (Fig. 27.12). Foreign objects and cicatrix are preferentially treated endoscopically. It is important to enter the stomach and retroflex the scope's

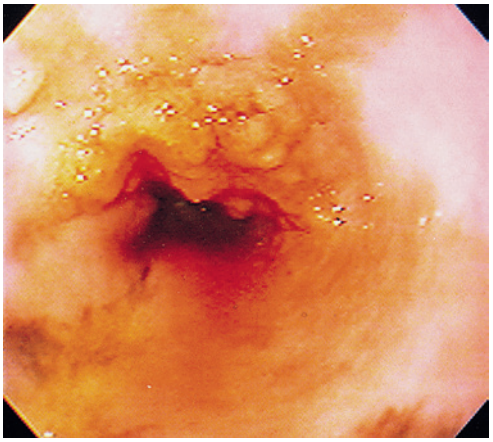


FIG 27.9
Endoscopic view of a polypoid mass in the esophagus of a Chow. This represents an adenocarcinoma.

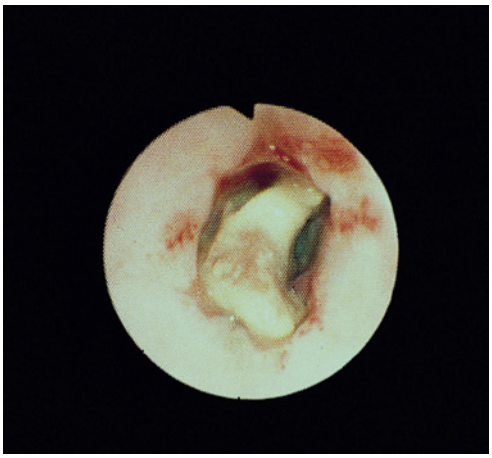


FIG 27.10
Endoscopic view of the esophagus of a dog with a chicken neck bone lodged in it. The bone was ultimately removed with a rigid scope and alligator forceps.

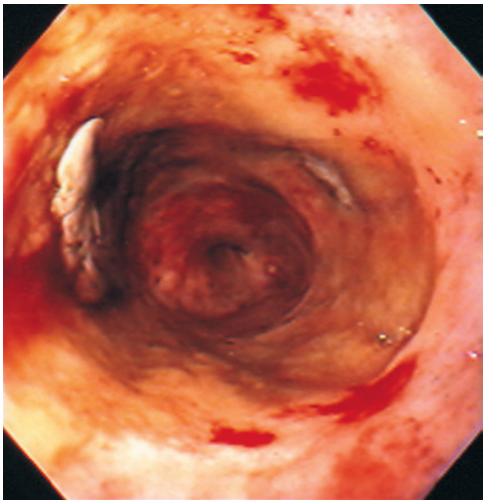


FIG 27.11
Endoscopic view of the distal esophagus of a dog with severe esophagitis secondary to a bone foreign body. Note the white plaque in the 9 o'clock position that is due to pressure necrosis from the foreign body.

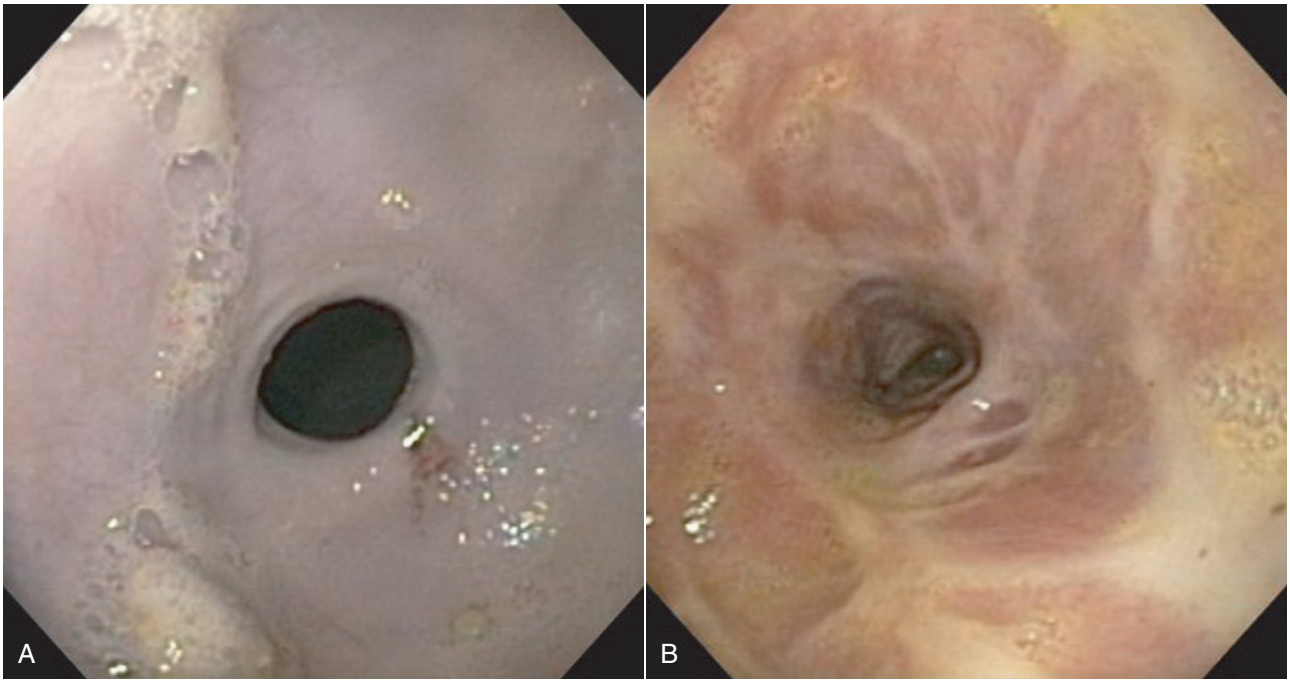


FIG 27.12
(A) Endoscopic view of a dog with an esophageal stricture. Note the obvious, circumferential narrowing. **(B)** Another endoscopic view of a dog's esophagus with an obvious narrowing. In this case, there are numerous, pale scars demonstrating that severe esophagitis was present at one time.

tip to view the lower esophageal sphincter area to detect leiomyomas (Fig. 27.13). The esophageal lumen is covered with squamous epithelium that cannot readily be pulled off with typical flexible endoscopic forceps. Therefore if esophageal mucosal biopsy specimens are desired, flexible endoscopes are typically inadequate unless the distal feline esophagus is being biopsied or there is a tumor or severe inflammation.

Although esophagoscopy may occasionally detect esophageal weakness, it is insensitive. Not all foreign objects can be safely removed endoscopically, and the clinician must guard against rupturing a diseased esophagus while trying



FIG 27.13
View of the lower esophageal sphincter (as seen from the stomach) of a dog with a leiomyoma (mass covered with normal-appearing mucosa). This tumor was causing vomiting and regurgitation.

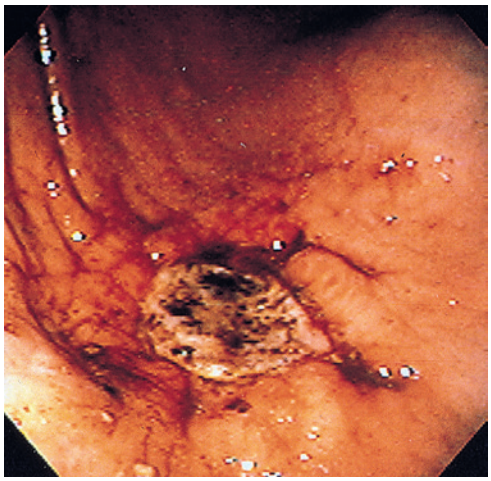


FIG 27.14
Endoscopic view of a gastric ulcer on the greater curvature in a Chow. Note that it is obvious that the mucosa is eroded to the level of the submucosa.

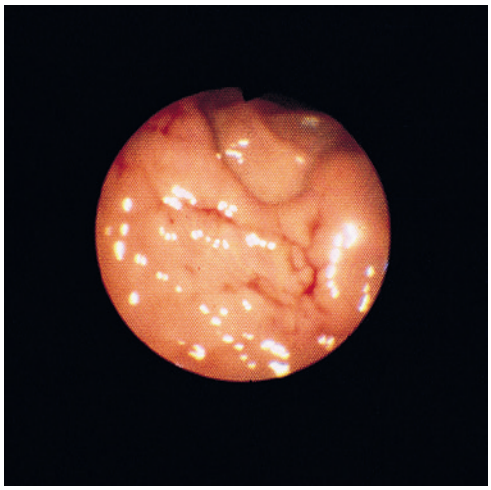


FIG 27.15
Endoscopic view of the gastric mucosa of a dog's stomach that has obvious bleeding. This dog had received nonsteroidal drugs, and the bleeding represented erosions that could not be detected with radiographs or ultrasonography. (From Fossum T, ed.: *Small animal surgery,* St Louis, 1997, Mosby.)

to extract a foreign object. Finally, care must be taken to avoid creating gastric distention in patients with esophageal strictures or tension pneumothorax in animals with an esophageal perforation.

Rigid endoscopy is often more useful than flexible endoscopy in removing esophageal foreign objects. Rigid endoscopes can protect the esophagus during extraction of the object and allow use of rigid forceps that permit the endoscopist greater control. Care must be taken to maintain the animal's esophagus as straight as possible when using a rigid endoscope. If a flexible endoscope is used to remove a foreign body, it is sometimes helpful to pass it through a rigid scope or tube that has been passed through the cricopharyngeal sphincter; this may facilitate retrieval of the foreign object through the sphincter.

Gastroduodenoscopy and biopsy are indicated in selected animals with vomiting, apparent upper GI blood loss, suspected gastroduodenal reflux, or small intestinal disease. It is more sensitive and specific than radiography for detecting mucosal ulcers (Fig. 27.14), erosions (Fig. 27.15), tumors (Fig. 27.16), and inflammatory lesions (Figs. 27.17 to 27.19). Endoscopy is also quicker and less stressful to the animal than exploratory laparotomy. Many foreign objects in the upper GI tract (Fig. 27.20) can be removed endoscopically, and multiple biopsy specimens can be obtained. Occasionally, unexpected diagnoses (e.g., *Physaloptera* infection; Fig. 27.21) may be found. It may be necessary to use endoscopes with outer diameters of 9 mm or less in dogs and cats weighing less than 4 to 5 kg. Whenever possible, a scope with a 2.8-mm biopsy channel should be used to obtain larger tissue specimens and allow the use of better foreign object retrieval devices.

The stomach must be as empty as possible when gastroduodenoscopy is performed, which usually necessitates at least a 24-hour fast; many animals undergoing gastroscopy may not empty their stomachs as rapidly as would a dog without abdominal disease. During the procedure the stomach must be adequately inflated with air to allow thorough evaluation of its mucosa. Suction must be available to remove secretions or air. The endoscopist must inspect the mucosa methodically. It is particularly easy to miss lesions (e.g., ulcers or *Physaloptera*) just inside the pylorus. Biopsy

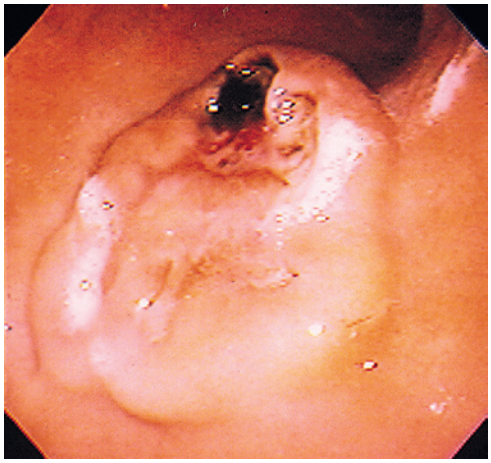


FIG 27.16
Endoscopic view of the stomach of a dog with an obvious mass in the greater curvature. This is an ulcerated leiomyosarcoma that was successfully removed.

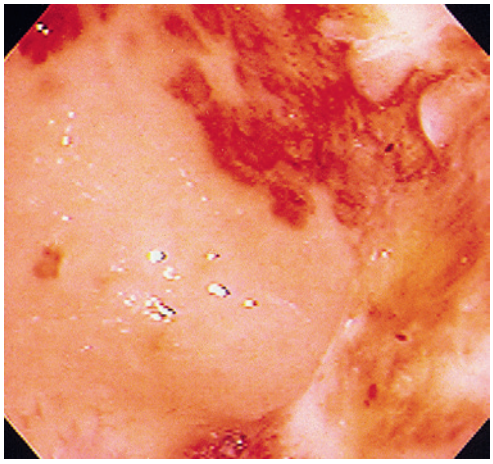


FIG 27.17
Endoscopic view of the stomach of a cat with diffuse inflammation, erosion, and ulceration of unknown cause.

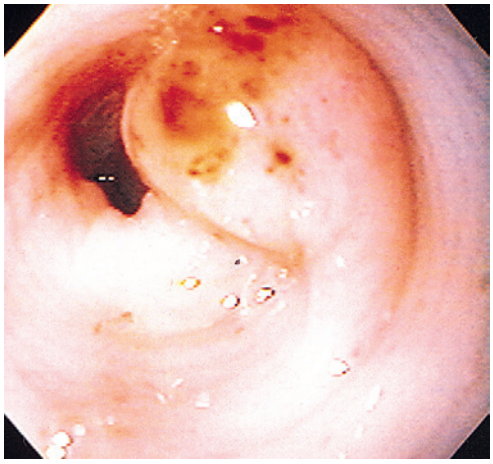


FIG 27.18
A focal gastritis near the pylorus of a dog. Note the reddened spots on the lesion, which were responsible for intermittent hematemesis.

specimens of the gastric and duodenal mucosa should always be obtained because normal gross findings do not rule out severe mucosal disease. Like esophagoscopy, gastroduodenoscopy is not sensitive in identifying functional problems (i.e., gastric hypomotility).

Proctoscopy or colonoscopy is indicated in dogs and cats with chronic large bowel disease unresponsive to appropriate dietary, antibacterial, or anthelmintic therapies as well as those that are losing weight, are hypoalbuminemic, or are at increased risk for specific diseases (e.g., histiocytic ulcerative colitis in Boxers). Colonoscopy plus biopsy is more sensitive and definitive for infiltrative diseases than imaging. Proctoscopy is used in animals with obvious rectal abnormalities (e.g., mass or stricture felt on digital rectal examination). Rigid biopsy forceps obtain excellent tissue samples that allow identification of most lesions, including submucosal ones. Biopsy instruments used with flexible endoscopes do not obtain as deep a tissue specimen but are adequate for sampling mucosal lesions.

Proctoscopy and colonoscopy are easier to perform, require less restraint, and do not always require the more expensive flexible equipment demanded by other endoscopic procedures. The colon must be clean to allow proper inspection of the mucosa. All food should be withheld for at least 36 and preferably 48 hours before the procedure, a mild laxative (e.g., bisacodyl) should be administered the night before the procedure, and several copious warm water enemas should be given the night before and the morning of the procedure. Proctoscopy requires less cleaning than colonoscopy. Commercial intestinal lavage solutions (e.g., GoLytely, CoLyte) clean the colon better than enemas and are particularly useful in larger dogs, those that will be undergoing ileoscopy (which necessitates a very clean ileocolic area), and animals in pain that resist enemas. The lavage solution is usually given to the animal twice the night before the procedure and perhaps once the morning of the procedure. In rare cases, it can cause gastric dilation or volvulus, and inadvertent aspiration can be devastating.

Occasional dogs with substantial colonic irritation strain so much that they essentially clean themselves out, and colonoscopy can be performed without cleansing enemas or lavage solutions. These same patients can sometimes be scoped with just manual restraint or mild sedation (Video 27.1). However, many animals undergoing colonoscopy have colonic or rectal irritation, and anesthesia is usually preferred.

Normal colonic mucosa is smooth and glistening, and submucosal blood vessels should be seen (Fig. 27.22). Enema tubes may cause linear artifacts. The colon should distend to a uniform diameter, but it may have bends. If a flexible scope is used, the clinician should identify and inspect the ileocolic valve and the cecum (Figs. 27.23 and 27.24). The clinician should always biopsy the mucosa. While some patients with neoplastic or inflammatory infiltrative diseases have obvious bruising (Video 27.2), normal gross findings do not rule out significant infiltrative disease. Strictured areas with relatively normal-appearing mucosa are usually caused by a

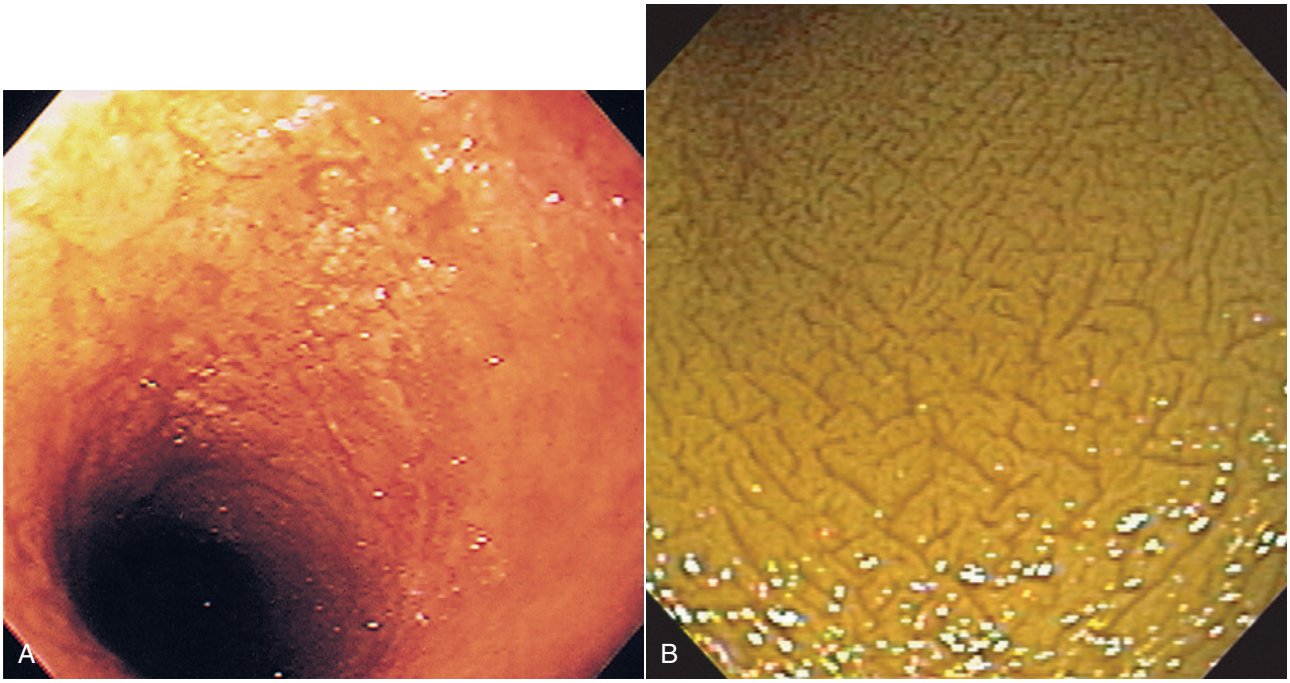


FIG 27.19
(A) The duodenum of a dog with marked inflammatory bowel disease. Note the pseudomembrane-like appearance, which suggests severe disease. **(B)** The duodenum of a cat with severe inflammatory bowel disease. Note the distinctive appearance (i.e., "flat" with long "cracks," much like drying mud).

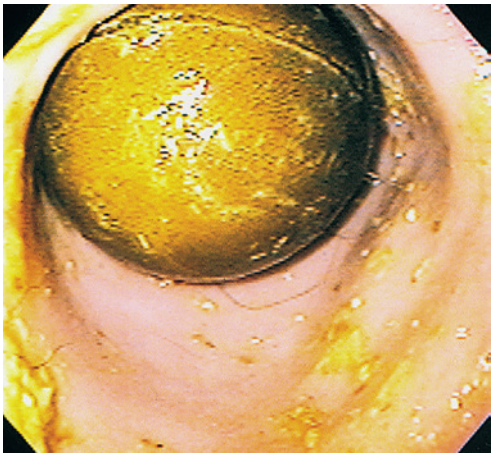


FIG 27.20
Endoscopic view of the antrum of a dog with a ball foreign object that has been present for months and was not detected on plain radiographs or by ultrasonography.

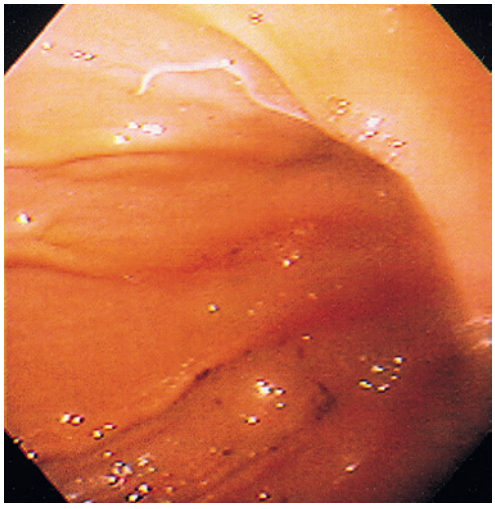


FIG 27.21
Endoscopic view of the greater curvature of the stomach of a dog with a *Physaloptera* attached.

submucosal lesion, in which case biopsying must be aggressive enough to ensure that submucosal tissue is included in the specimen. Cytology can often detect histoplasmosis, protothecosis, some neoplasms, and eosinophilic colitis.

An adult or a pediatric human sigmoidoscope is usually adequate for rigid colonoscopy. The tip of the rigid biopsy forceps should have a shearing action (i.e., one part of the tip should fit into the other when it is closed, thus acting like a pair of scissors) instead of a clamshell (also called "double spoon") action in which the edges of the top and bottom jaws simply meet.

Ileoscopy is principally indicated in dogs with diarrhea and in cats with vomiting or diarrhea. It is performed during flexible colonoscopy and requires thorough colonic cleansing so that the ileocolic valve can be visualized. It is difficult or impossible to enter the ileum of most cats (because of size), but one can often pass biopsy forceps through the ileocolic valve and blindly biopsy the ileal mucosa



FIG 27.22
Endoscopic view of a normal colon in a dog, showing typical submucosal blood vessels. Inability to see such blood vessels may suggest inflammatory infiltrates.

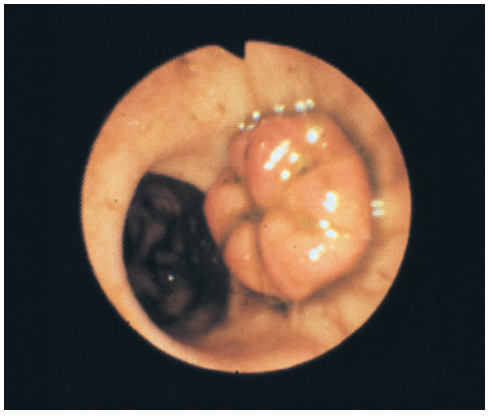


FIG 27.23
Normal ileocolic valve region in a dog. The ileocolic valve is the mushroom-like structure, and the opening below it is the cecocolic valve.

(Fig. 27.25; Video 27.3). Ileoscopy can be particularly valuable in diagnosing lymphoma in cats when the duodenal biopsies are nondiagnostic.

CAPSULE ENDOSCOPY

Recently capsule endoscopy has been introduced into veterinary medicine. It has primarily been used for looking for bleeding GI lesions but may be useful for diagnosing intestinal lymphangiectasia.

BIOPSY TECHNIQUES AND SUBMISSION

FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration or core biopsy of enlarged lymph nodes, abdominal masses, and infiltrated abdominal organs

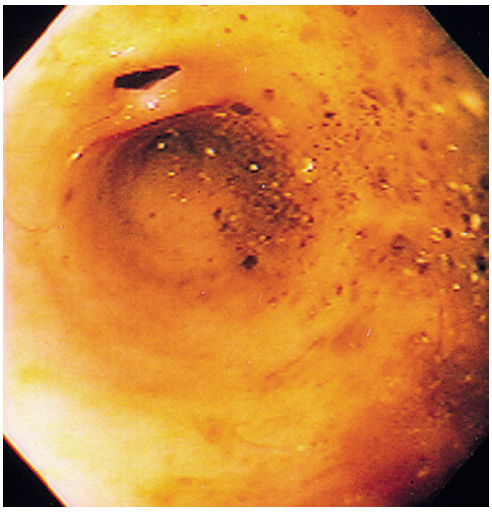


FIG 27.24
Endoscopic view of a normal ileocolic valve region from a cat. The blind pouch is the cecum, and the small opening above it is the ileocolic valve.

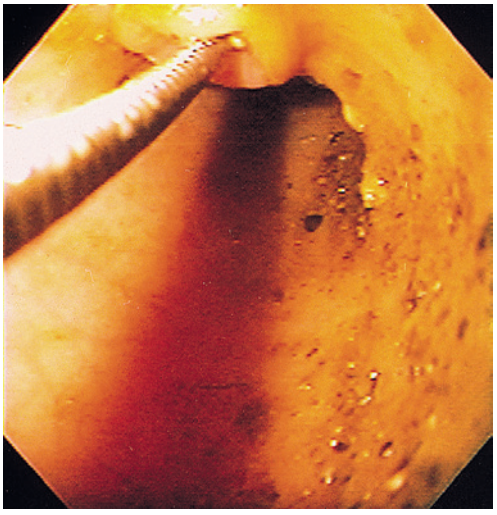


FIG 27.25
Same site as in Fig. 27.24. A biopsy instrument has been blindly passed into the ileum because the scope cannot be advanced through the narrow orifice.

may be guided by abdominal palpation or ultrasonography. A 23- to 25-gauge needle is typically used so that any inadvertent intestinal or vascular perforation is not harmful (see Chapter 74).

ENDOSCOPIC BIOPSY

Rigid endoscopy usually provides excellent biopsy samples of the descending colon (i.e., large specimens that include the full thickness of the mucosa, including some muscularis mucosa), but the stomach and small intestine cannot be biopsied with this equipment. Flexible endoscopes can reach more of the alimentary tract, but the tissue samples obtained with these scopes may not always be deep enough to allow submucosal lesions to be diagnosed. Ideally, the tissue to be

biopsied is visualized, but the clinician may blindly pass the biopsy forceps through the ileocolic valve to biopsy the ileum if the tip of the endoscope cannot be advanced into these areas.

Not all laboratories are adept at processing and interpreting endoscopic samples of intestinal tissue. Endoscopes with 2.8-mm biopsy channels are generally preferred to those with a 2.0- or a 2.2-mm channel because the larger forceps allow retrieval of substantially larger and deeper tissue samples.

When intestinal or gastric mucosa is biopsied, the tissue sample must be handled carefully to minimize artifacts and distortion. The tissue should be carefully removed from the biopsy forceps with a 25-gauge needle. A squash preparation of one tissue specimen can be evaluated cytologically, and the remaining samples are fixed in formalin and evaluated histologically. The cytology slides should be evaluated by a pathologist familiar with GI cytology. Cytologic preparations of the gastric mucosa may show adenocarcinoma, lymphoma, various inflammatory cells, or spirochetes (see Fig. 30.1). Cytologic studies of the intestinal mucosa may show eosinophilic enteritis, lymphoma, histoplasmosis, or protothecosis, and occasionally giardiasis, bacteria, or *Heterobilharzia* ova. Cytology is specific but insensitive (i.e., failing to find something does not allow the clinician to eliminate it).

The laboratory should be consulted regarding the proper way to submit endoscopic tissue samples. To simply submit intestinal tissues floating freely in formalin almost guarantees that few if any pieces will be optimally oriented on the histopathology slide. The clinician should place tissues from different locations in different vials of formalin; each vial should be properly labeled. Small tissue samples should not be allowed to dry out or be damaged before placement in formalin.

Two common problems with endoscopically obtained tissue samples are that the sample is too small or there is excessive artifact. Lymphomas are sometimes relatively deep in the mucosa (or are submucosal), and a superficial biopsy specimen may then show only a tissue reaction above the tumor, resulting in a misdiagnosis of inflammation. Multiple biopsy specimens should be obtained until there are at least six to eight samples of excellent size and depth (i.e., the full thickness of mucosa). It is important for the pathologist to inform the clinician whether or not the quality of the tissue samples was adequate for evaluation and if the severity of the histologic lesions found is consistent with the severity of clinical signs.

FULL-THICKNESS BIOPSY

If endoscopy is not available, abdominal surgery may be needed to perform gastric and intestinal biopsies. Full-thickness biopsy specimens obtained surgically can have fewer artifacts than those obtained endoscopically; however, the clinician must consider the pros and cons of surgery in a potentially debilitated or ill animal. Endoscopy allows the clinician to direct the biopsy forceps to lesions that cannot be seen from the serosal surface. If surgery is performed, the entire abdomen should be examined (i.e., literally from the beginning of the stomach to the end of the colon along with all parenchymal organs). Biopsy specimens of the stomach, duodenum, jejunum, ileum, mesenteric lymph nodes, and liver (and the pancreas in cats) should be obtained, regardless of how normal these organs appear, unless an obvious lesion (e.g., a large tumor) is found. The colon is more likely to dehisce than the small intestine, and full thickness colonic biopsies should be avoided unless there is an overriding reason to do them. It is wise not to assume that a grossly impressive lesion is responsible for the clinical signs; rather, the clinician usually should perform a biopsy even when the diagnosis seems obvious. Dehiscence is a major risk if biopsy is occurring in an abdomen that already has septic peritonitis present. It is a concern if the serum albumin concentration is less than 1.5 g/dL, but excellent technique minimizes the risk. The clinician should consider whether esophagostomy, gastrostomy, or enterostomy feeding tubes should be placed in emaciated animals before exiting the abdomen.

Suggested Readings

Allenspach K. Diseases of the large intestine. In: Ettinger SJ, et al., eds. *Textbook of veterinary internal medicine*. 7th ed. St Louis: WB Saunders; 2010.

Bonadio CM, et al. Effects of body positioning on swallowing on esophageal transit in healthy dogs. *J Vet Intern Med*. 2009;23:801.

Bonfanti U, et al. Diagnostic value of cytologic examination of gastrointestinal tract tumors in dogs and cats: 83 cases (2001-2004). *J Am Vet Med Assoc*. 2006;229:1130.

Cartwright JA, et al. Evaluating quality and adequacy of gastrointestinal samples collected using reusable or disposable forceps. *J Vet Intern Med*. 2016;30:1002.

Davignon DL, et al. Evaluation of capsule endoscopy to detect mucosal lesions associated with gastrointestinal bleeding in dogs. *J Small Anim Pract*. 2016;57:148.

Dryden M, et al. Accurate diagnosis of *Giardia* spp. and proper fecal examination procedures. *Vet Ther*. 2006;7:4.

Gaschen L, et al. Comparison of ultrasonographic findings with clinical activity index (CIBDAI) and diagnosis in dogs with chronic enteropathies. *Vet Radiol Ultrasound*. 2009;49:56.

Gould E, et al. A prospective, placebo-controlled pilot evaluation of the effects of omeprazole on serum calcium, magnesium, cobalamin, gastrin concentrations, and bone in cats. *J Vet Intern Med*. 2016;30:779.

Grooters AM, et al. Development of a nested polymerase chain reaction assay for the detection and identification of *Pythium insidiosum*. *J Vet Intern Med*. 2002;16:147.

Gualtieri M. Esophagoscopy. *Vet Clin North Am*. 2001;31:605.

Hall EJ, et al. Diseases of the small intestine. In: Ettinger SJ, et al., eds. *Textbook of veterinary internal medicine*. 7th ed. St Louis: WB Saunders Elsevier; 2010.

Hardy BT, et al. Multiple gastric erosions diagnosed by means of capsule endoscopy in a dog. *J Am Vet Med Assoc*. 2016;8:926.

Jergens A, et al. Endoscopic biopsy specimen collection and histopathologic considerations. In: Tams TR, et al., eds. *Small animal endoscopy*. 3d ed. St Louis: Elsevier; 2011.

Jergens AE, et al. Maximizing the diagnostic utility of endoscopic biopsy in dogs and cats with gastrointestinal disease. *Vet J*. 2016;214:50.

Keh S, et al. Evaluation of computed tomographic enterography with an orally administered lactulose solution in clinically normal dogs.

Larsen M, et al. Diagnostic utility of abdominal ultrasonography in dogs with chronic vomiting. *J Vet Intern Med*. 2010;24:803.

Leib MS. Diagnostic utility of abdominal ultrasonography in dogs with chronic vomiting. *J Vet Intern Med*. 2010;24:803.

Leib MS. Colonoscopy. In: Tams TR, et al., eds. *Small animal endoscopy*. 3d ed. St Louis: Elsevier/Mosby; 2011.

McLeland SM, et al. Relationship among serum creatinine, serum gastrin, calcium phosphorous product, and uremic gastropathy in cats with chronic kidney disease. *J Vet Intern Med*. 2014;28:827.

Marks SL, et al. Diarrhea in kittens. In: August JR, eds. *Consultations in feline internal medicine*. 5th ed. St Louis: Elsevier/Saunders; 2006.

Mansell J, et al. Biopsy of the gastrointestinal tract. *Vet Clin N Am*. 2003;33:1099.

Mekaru S, et al. Comparison of direct immunofluorescence, immunoassays, and fecal flotation for detection of *Cryptosporidium* spp and *Giardia* spp in naturally exposed cats in 4 northern California animal shelters. *J Vet Intern Med*. 2007;21:959.

Parente NL, et al. Serum concentrations of gastrin after famotidine and omeprazole administration to dogs. *J Vet Intern Med*. 2014;28:1465.

Patsikas MN, et al. Ultrasonographic signs of intestinal intussusception associated with acute enteritis or gastroenteritis in 19 young dogs. *J Am Anim Hosp Assoc*. 2003;39:57.

Radhakrishnan A. Advances in flexible endoscopy. *Vet Clin North Am Small Anim Pract*. 2016;46:85.

Rishniw M, et al. Comparison of 4 *Giardia* diagnostic tests in diagnosis of naturally acquired canine chronic subclinical giardiasis. *J Vet Intern Med*. 2010;24:293.

Rudorf H, et al. Ultrasonographic evaluation of the thickness of the small intestinal wall in dogs with inflammatory bowel disease. *J Small Anim Pract*. 2005;46:322.

Ruiz GC, et al. Comparison of 3 handling techniques for endoscopically obtained gastric and duodenal biopsy specimens: a prospective study in dogs and cats. *J Vet Intern Med*. 2016;30:1014.

Ruiz G, et al. Diagnostic contribution of cytological specimens obtained from biopsies during gastrointestinal endoscopy in dogs and cats. *J Small Anim Pract*. 2017;58:17.

Schmitz S, et al. Comparison of three rapid commercial canine parvovirus antigen tests with electron microscopy and polymerase chain reaction. *J Vet Diagn Invest*. 2009;21:344.

Steiner JM. Canine pancreatic disease. In: Ettinger SJ, et al., eds. *Textbook of veterinary internal medicine*. 7th ed. Philadelphia: WB Saunders Elsevier; 2010.

Tams TR, et al. Endoscopic examination of the small intestine. In: Tams TR, et al., eds. *Small animal endoscopy*. 3d ed. St Louis: Elsevier/Mosby; 2011.

Willard MD, et al. Bacterial causes of enteritis and colitis. In: August JR, eds. *Consultations in feline internal medicine*. 5th ed. St Louis: Elsevier/Saunders; 2006.

Willard MD, et al. Effect of sample quality on the sensitivity of endoscopic biopsy for detecting gastric and duodenal lesions in dogs and cats. *J Vet Intern Med*. 2008;22:1084.

Willard MD, et al. Gastrointestinal, pancreatic, and hepatic disorders. In: Willard MD, et al., eds. *Small animal clinical diagnosis by laboratory methods*. 5th ed. St Louis: WB Saunders Elsevier; 2011.

Zwingenberger A, et al. Ultrasonographic evaluation of the muscularis propria in cats with diffuse small intestinal lymphoma or inflammatory bowel disease. *J Vet Intern Med*. 2010;24:289.

CHAPTER 28

General Therapeutic Principles



FLUID THERAPY

Fluid therapy is primarily used to treat shock, dehydration, and electrolyte and acid-base disturbances. Accurately predicting electrolyte and acid-base changes on the basis of clinical parameters is impossible, hence serum electrolyte concentrations typically must be measured in significantly ill patients. Vomiting gastric contents classically but inconsistently produces hypokalemic, hypochloremic, metabolic alkalosis. Loss of intestinal contents classically produces hypokalemia with or without acidosis, but hypokalemic metabolic alkalosis may occur. Vomiting animals are often hypokalemic, but patients with hypoadrenocorticism or severe renal failure may be hyperkalemic. Electrolyte concentrations can quickly be determined by point-of-care methodology. If fluid therapy must be started in a severely ill vomiting patient before electrolyte concentrations are known, physiologic saline solution plus 20 mEq potassium chloride per liter is typically a reasonable choice (Table 28.1), assuming the fluids are administered at one to two times maintenance requirement. If point-care-methodology is unavailable, a lead II electrocardiographic (ECG) tracing may be evaluated to look for evidence of hyperkalemia (see Chapter 53).

Reexpanding the vascular compartment and improving peripheral perfusion alleviates lactic acidosis. Hence, bicarbonate administration is almost never needed, and may in fact be detrimental. Bicarbonate is primarily administered to patients with extreme acidosis (e.g., pH < 7.05 or bicarbonate < 10 mEq/L) that are in imminent danger of dying. Bicarbonate, lactated Ringer's solution, and Normosol-R should not be used if alkalosis seems likely (e.g., vomiting of gastric origin).

Parenteral fluid administration is indicated if the animal is significantly hypovolemic or if absorption of enteral fluids is questionable (e.g., severe intestinal disease, obstruction, vomiting, or ileus). Subcutaneous (SC) fluid administration is acceptable if the animal is not severely dehydrated or in shock, absorbs the fluids, and tolerates repeated SC administration. Multiple SC depots of 10 to 50 mL each are given, depending on the animal's size. Dependent areas should be checked for unabsorbed fluids before administering more fluid SC. Severely dehydrated animals often absorb SC fluids very slowly, making initial intravenous (IV) administration preferred. IV fluid administration is required in patients that are severely dehydrated or are in shock, even if a venous cutdown is necessary. Intramedullary administration may be used if an IV catheter cannot be established. To do this, a large-bore hypodermic needle or a bone marrow aspiration needle (preferable) can be inserted into the femur (trochanteric fossa), tibia, wing of the ilium, or humerus. Fluids can be administered by the intramedullary route at a maintenance rate or faster. Intraperitoneal administration repletes the intravascular compartment more slowly than IV or intramedullary techniques and is not recommended.

Dogs in hypovolemic shock typically have tachycardia, poor peripheral perfusion, cool extremities, prolonged capillary refill time, weak femoral pulse, and/or tachypnea, while dogs in early systemic inflammatory response syndrome (SIRS) initially have red oral mucous membranes, warm extremities, and a strong, bounding femoral pulse before classic signs of shock occur. Treatment of severe shock does not consist of giving a fixed amount of fluids; rather, the clinician gives fluids to effect. This often consists of an initial IV bolus of 10 to 20 mL/kg of an isotonic crystalloid (e.g., lactated Ringer's, Normosol R or Physiologic saline, all typically without supplemental potassium) over 15 to 30 minutes. Next, instead of "blindly" giving a fixed, calculated amount, fluids are administered until the patient is hemodynamically stable, remembering that it is easy to overhydrate cats. Ultimately, one blood volume (i.e., 90 mL/kg for the dog; 50 mL/kg for the cat) is usually administered over the first 1 to 2 hours. However, additional fluids are typically needed 30 to 60 minutes later because the initial crystalloids quickly redistribute into the interstitial compartment. Large dogs in severe shock (e.g., gastric dilation/volvulus) may require two simultaneous 16- to 18-gauge cephalic catheters and IV bags placed in pneumatic compression devices to achieve an adequate flow rate.

Hypertonic saline and/or colloids allow small volume resuscitation, which is easier than administering large

TABLE 28.1

General Guidelines for Initial Potassium Supplementation of Intravenous Fluids

PLASMA POTASSIUM CONCENTRATION (mEq/L)	AMOUNT OF POTASSIUM CHLORIDE (KCl) TO ADD TO FLUIDS GIVEN AT MAINTENANCE RATES* (mEq/L)
3.7-5.0	10-20
3.0-3.7	20-30
2.5-3.0	30-40
2.0-2.5	40-60
≤2.0	60-70

*Do not exceed 0.5 mEq/kg/h potassium except in animals in hypokalemic emergencies, and then only with constant close electrocardiographic monitoring. Be sure to routinely monitor plasma potassium concentrations whenever administering fluids with more than 30 to 40 mEq of potassium per liter.

volumes of crystalloids to large animals. Four to five mL/kg of hypertonic saline solution (i.e., 7%) given IV over 10 to 20 minutes (do not exceed 1 mL/kg/min) is effective for approximately 30 minutes. Hypertonic solutions generally should not be used in animals with hypernatremic dehydration, cardiogenic shock, or renal failure and probably in those with uncontrolled hemorrhage. If necessary, hypertonic saline may be readministered in 2 mL/kg aliquots until a total of 10 mL/kg has been given or until the serum sodium concentration is 160 mEq/L. However, because the volume expansive effects of hypertonic saline last only for approximately 30 minutes, the clinician needs to administer other fluids (usually at a reduced rate until shock is controlled). A mixture of 23.4% saline solution plus 6% hetastarch or pentastarch in a 1:2 ratio administered at 3 to 5 mL/kg gives a longer duration of action than hypertonic saline solution alone.

Colloids (e.g., hetastarch or pentastarch) also draw water from the interstitial compartment into the vascular compartment, but their effects last longer than hypertonic saline and do not increase the total body sodium load. Relatively small volumes can be administered quickly (i.e., in dogs, 5-10 mL/kg slow IV bolus with a maximum of 20 mL/kg/day; in cats, 5-10 mL/kg/day), and the clinician must reduce the subsequent rate of IV fluid administration to prevent hypertension. Colloids should be used with caution in animals with bleeding tendencies. In rare cases, the colloid may go into extravascular compartments, drawing fluid out of the vascular compartment complicating the shock; therefore, close monitoring is required.

Maintenance fluid requirements for dogs weighing between 10 and 50 kg are 44 to 66 mL/kg/day with larger dogs needing less per kilogram than smaller dogs. Dogs weighing less than 5 kg may need 80 mL/kg/day. Cats weighing more than 3 kg need 53 to 61 mL/kg/day. It is important to choose the correct fluid to prevent electrolyte imbalances, especially hypokalemia. In general, potassium should be supplemented if the animal is hyporexic or vomiting, has diarrhea, or is receiving prolonged or intense fluid therapy (see guidelines for administration in Table 28.1). The animal should be monitored for iatrogenic hyperkalemia. Generally, no more than 0.5 mEq K/kg/h should be administered IV. If the animal is not vomiting, oral (PO) potassium supplementation is often more effective than parenteral supplementation. Cats receiving IV fluids often show an initial decrease in their serum potassium concentrations, even if the fluids contain 40 mEq or more of potassium chloride per liter; therefore, severely hypokalemic cats should initially receive oral potassium gluconate, if possible.

Dehydrated animals not in shock are treated by replacing the estimated fluid deficit. First, the degree of dehydration must be estimated. Prolonged skin tenting is usually first noted at 5% to 6% dehydration, but any patient with substantial weight loss may show skin tenting. Obese animals and those with peracute dehydration often do not show skin tenting even with severe dehydration. Dry, tacky oral mucous membranes usually indicate 6% to 7% dehydration. However, well-hydrated, panting, or dyspneic animals can have dry mouths. Multiplying the estimated percentage of dehydration by the animal's weight (in kilograms) determines the liters required to replace deficit. This amount is typically replaced over 2 to 8 hours, depending on the animal's condition. Fluid delivery rate should generally not exceed 88 mL/kg/h. In general, it is better to slightly (not grossly) overestimate rather than underestimate the fluid deficit, unless the animal has congestive heart failure, anuric/oliguric renal failure, severe hypoproteinemia, or pulmonary edema. In general, cats are more easily harmed by excessive fluid administration than are dogs.

Ongoing losses are typically estimated from observations of vomiting, diarrhea, and urination, but it is common to underestimate losses. Weighing the animal or the cage pads that soak up the urine/feces is another way to estimate ongoing losses because acute weight loss is due to fluid loss.

Development of inspiratory pulmonary crackles, a gallop rhythm, or edema (especially cervical) probably indicates overhydration. A new heart murmur is not always a sign of overhydration; severely dehydrated dogs with valvular insufficiency may not have an audible murmur until they are volume replete. Central venous pressure (CVP) is excellent for detecting excessive fluid administration, but it is rarely necessary except in animals with severe cardiac or renal failure and those receiving very aggressive fluid therapy. CVP is normally less than 4 cm H_2O and generally should not exceed 10 to 12 cm H_2O even during aggressive fluid therapy. Poor technique will often produce falsely high CVP readings.

Oral rehydration therapy makes use of the facilitated intestinal absorption of sodium. Co-administration of a monosaccharide (e.g., dextrose) or amino acid with sodium speeds up sodium absorption and subsequent water uptake. This approach works if the animal can ingest oral fluids (i.e.,

is not vomiting) and the intestinal mucosa has reasonable villus function. Absorption primarily occurs in the mature epithelium near the villus tip. Various products for use in people are commercially available, and there are also recipes for making these solutions. Failure to monitor the patient or follow instructions may lead to severe hypernatremia.

The type of fluid therapy used in hypoproteinemic animals depends on the degree of hypoalbuminemia. Excessive fluids can dilute the serum albumin concentration, causing ascites, edema, diminished peripheral perfusion, or a combination of these. Careful calculation of the fluid needs and ongoing losses is therefore necessary. In animals with severe hypoalbuminemia (e.g., serum albumin of 1.5 g/dL or less), it may be desirable to increase plasma oncotic pressure. Administering plasma is not generally recommended because large volumes of plasma are needed to substantially increase serum albumin concentration, making it very expensive. Further, animals with severe protein-losing enteropathies (PLEs) and protein-losing nephropathies rapidly excrete the administered protein, making repeated transfusions necessary. Human albumin has been administered and appears efficacious; however, some animals can die acutely from anaphylaxis. Canine albumin (5-6 mL/kg) is safer but is not readily available. Hetastarch and pentastarch may be used in place of plasma or albumin. These colloids are larger than albumin and persist in the intravascular space longer than albumin, thereby helping maintain plasma oncotic pressure in animals with severe PLE. After administering these colloids, the clinician should decrease the rate of fluid administration to prevent hypertension. Sometimes, administering hetastarch causes fluids to shift to the extravascular compartment with subsequent decrease in peripheral perfusion or worsening of ascites.

DIETARY MANAGEMENT

Dietary therapy is often important in animals with gastrointestinal tract problems. Symptomatic therapy for acute problems usually involves easily digested diets (i.e., "bland"), whereas specific therapy typically involves elimination (i.e., hypoallergenic) diets, ultra–low fat diets, fiber-supplemented diets, or a combination of these.

"Bland" (i.e., easily digested) diets are low in fat and fiber (both delay gastric emptying) and high in complex carbohydrates. Extremely hyperosmolar diets (e.g., concentrated sugar solutions or honey) should be avoided because they also may delay gastric emptying. These diets are indicated in animals with acute gastritis or enteritis. Such diets are available commercially (Box 28.1). Homemade versions usually consist of boiled poultry or lean hamburger, low-fat cottage cheese, boiled rice, and/or boiled potatoes in some combination. Boiled chicken, turkey, or fish and green beans may be useful in cats. A typical mixture is one part boiled chicken or cottage cheese and two parts boiled potato. These diets also tend to be low in lactose, which helps prevent maldigestion. Frequent, small amounts of these foods are fed until diarrhea resolves, and then the diet is gradually changed back to the routine one. This diet may be continued after the event is over, but a homemade diet should be nutritionally balanced if it is used long term, especially in puppies or kittens.

Elimination diets are indicated if a dietary allergy (i.e., an immune-mediated hypersensitivity) or intolerance (i.e., a non–immune-mediated problem) is suspected. These diets contain either dietary ingredients unlikely to provoke allergy or intolerance (i.e., hydrolyzed diets that contain relatively small particles that are less antigenic) or food stuffs the patient has not been exposed to before (i.e., a novel protein diet). Excellent commercial elimination diets are available, or the clinician may suggest a homemade diet. Examples of homemade elimination diets are described in Box 28.2.

BOX 28.1

Examples of Commercial "Bland" (Highly Digestible)* Diets

Hill's Prescription Diet i/d
Iams Intestinal Plus Low-Residue
Purina CNM EN-Formula
Royal Canin Gastrointestinal High Energy
Royal Canin Canine Low Fat

This is a partial list for the purpose of showing examples; it is not an all-inclusive list of such diets.

*"Bland" refers to easily digestible diets that often contain less fat and less fiber than is found in many pet foods.

BOX 28.2

Examples of Homemade Hypoallergenic* Diets

1 part boiled white chicken or turkey meat without the skin; 2 parts boiled or baked potato (without the skin)
1 part boiled or broiled white fish without the skin; 2 parts boiled or baked potato (without the skin)
1 part boiled mutton, venison, or rabbit without the skin; 2 parts boiled or baked potato (without the skin)
1 part drained low-fat cottage cheese; 2 parts boiled or baked potato (without the skin)
A nonflavored vitamin supplement may be given three times per week.
Rice can be substituted for potato, but many dogs and cats seem to digest potato more easily than rice.

These diets are not balanced but are usually adequate for 3 to 4 months of use in sexually mature animals. If growing animals are being fed such a diet, then a nutritionist must be consulted to balance calcium and phosphorus.

**Hypoallergenic* refers to a diet specially formulated for a given animal, one that does not expose the animal to potential allergens that it has eaten in the past. Therefore the clinician must obtain a careful dietary history to determine what will or will not constitute a hypoallergenic diet for a particular animal.

When elimination diets are effective, improvement is typically evident within 3 weeks, although rare patients require 6+ weeks. It is critical that no other foods or treats (e.g., flavored pills, toys, medications) be given to the animal during this time. If signs resolve during this time, the diet should be continued for at least 4 to 6 more weeks to ensure cause and effect as opposed to a spontaneous, fortuitous fluctuation of the disease.

Partially hydrolyzed diets (Purina HA, Nestle Purina; Hill's z/d, Hill's Pet Products; Hypoallergenic Hydrolyzed Protein HP diets and Ultamino Royal Canin) have been formulated in an attempt to eliminate proteins large enough to cause immunologic reactions. Although these diets are not uniformly effective, many dogs and cats with dietary allergy or intolerance will experience clinical improvement when eating these diets exclusively. The partially hydrolyzed proteins may also make such diets easier to digest and absorb.

Ultra–low-fat diets are indicated in dogs with PLE due to intestinal lymphangiectasia. Because long-chain fatty acids enter and accumulate in lacteals, removing them from the diet helps prevent dilation and rupture of lacteals and subsequent intestinal lymphatic loss. Medium-chain triglycerides (MCTs) were once recommended as supplements to low fat, reducing diets; however, MCT oil has an unpleasant taste and is not as effective as was once thought, so it is no longer recommended.

Fiber-enriched diets may ameliorate diarrhea in many patients with large bowel disease (especially those with minimal inflammation). Although once considered important, distinguishing soluble from insoluble fiber is no longer thought critical because many fibers have characteristics of both. A commercial high-fiber diet may be used, or fiber may be added to the current diet. Psyllium hydrocolloid (e.g., Metamucil) or coarse, unprocessed wheat bran may be added to the pet's diet (i.e., 1-2 teaspoons or 1-4 tablespoons per can of food, respectively). Supplementing too much soluble fiber can produce diarrheic stools. If the patient is fiber-responsive, clinical improvement is generally seen within 4 to 5 days of beginning the diet.

Fiber-supplemented diets might also lessen constipation not due to obstruction, rectal pain, or megacolon due to colonic inertia. Such a diet should be fed for at least 2 weeks before assessing efficacy, although most animals that respond do so within the first week. Some cats will not eat these diets or fiber supplements. Canned pumpkin pie filling is effective as a fiber and usually palatable; 1 to 3 tablespoons may be given daily. It is important that the animal maintain adequate water intake, lest the increased dietary fiber produce obstipation.

SPECIAL NUTRITIONAL SUPPLEMENTATION

If the animal refuses to ingest adequate calories, special nutritional supplementation is necessary. Daily nutritional requirements should be calculated to avoid underfeeding. Approximately 60 kcal/kg/day is reasonable for the maintenance needs of mature dogs and cats that are not lactating or losing a significant amount of energy or protein.

In some cases, simply sending the animal home, warming the food, or feeding the animal a more palatable diet (e.g., chicken baby food for dogs) will result in adequate caloric intake. Force-feeding by manually placing food in the animal's mouth seldom works in hyporexic animals. Mirtazapine is usually an effective appetite stimulant for dogs and cats. It is administered once daily in dogs and once every three days in cats. Maropitant (an antiemetic) is often helpful if nausea is the cause of hyporexia. Cyproheptadine stimulates some cats to eat, but seldom induces a severely anorectic cat to ingest adequate calories. Diazepam rarely causes acute feline hepatic failure and is not recommended. Megestrol acetate is an excellent appetite stimulant but occasionally causes diabetes mellitus, reproductive problems, or tumors. Cobalamin injections have been noted to increase appetite in some patients. Appetite stimulants are usually less effective in dogs than in cats.

Feeding tubes are a reliable way to ensure adequate caloric intake. Intermittent orogastric tube feeding is useful for animals that need nutritional support for a relatively short time, although it may be used for longer periods in orphaned puppies and kittens. It is typically done two or three times daily, using manual restraint and a mouth gag. A tube is measured and marked to correspond to the length from the tip of the nose to the midthoracic region. The tube is then carefully inserted through a mouth gag to the premarked point. If the animal coughs or is dyspneic, the tube may have entered the trachea and should be repositioned. To ensure safety, the tube should be flushed with water before warmed gruel is administered. Gruel should be given over several seconds to 1 minute. Because relatively large-diameter tubes can be used, homemade gruels may be administered. The major disadvantage is the need to physically restrain the animal. Indwelling tubes circumvent this problem.

Nasoesophageal tubes are useful in animals with a functional esophagus, stomach, and intestines. They are easy to place but difficult to maintain in vomiting animals. The clinician first anesthetizes the nose by instilling a few drops of lidocaine solution in one nostril. Then a sterile polyvinyl chloride, polyurethane, or silicone tube (diameter depends on the animal's size, but 5F-12F is typical) lubricated with sterile water-soluble jelly is inserted into the ventromedial nostril. The animal's head is restrained in its normal position, and the tube is inserted until the tip is just beyond the thoracic inlet. If the clinician encounters difficulty in passing the tube, the tip should be withdrawn, redirected, and advanced again. If the clinician is unsure whether the tube is in the esophagus, thoracic radiographs should be obtained.

Tape is applied to the tube, and then the tape is glued or sutured to the skin along the dorsal aspect of the nose. If the tube touches sensory vibrissae, the animal will not tolerate it. It may be necessary to place an Elizabethan collar on some animals to prevent them from pulling out the tube. Only small-diameter tubes (e.g., 5F) can be used in small dogs and cats, which limits the rate of administration and

necessitates the use of commercial liquid diets (Table 28.2) instead of homemade gruels. The clinician should flush the tube with water after each feeding to prevent occlusion. Long-term acceptance is typical, but rhinitis occurs in some animals.

Some dogs and cats do not tolerate nasoesophageal tubes and repeatedly pull them out. However, they are usually effective for short-term therapy (e.g., 1-10 days), and some animals tolerate them for weeks.

Pharyngostomy and esophagostomy tubes are indicated in patients with functional esophagus, stomach, and intestines that require nutritional support but do not tolerate nasoesophageal or intermittent tube feeding. Vomiting may make it difficult to maintain these tubes, but they can typically be used for weeks to months.

Pharyngostomy tubes are hard to place correctly and are not recommended. Esophagostomy tubes are the primary long-term feeding tube now used. There are commercially available kits that have various nuances in how they are used. In general, the animal is placed in right lateral recumbency, the mouth is held open, and a long right-angle hemostat or other device is placed through the cricopharyngeal sphincter. The tip of the hemostat is then forced up to show where to make the incision in the left cervical region. The incision should be made midway between the cricopharyngeal sphincter and the thoracic inlet. The tip of the hemostat is forced up through the esophagus and the nick in the skin; the tip of a feeding tube is then grasped and pulled into the esophagus and out the mouth so that the flared end of the catheter (i.e., where the syringe will be attached) is left protruding from the neck. The distal end of the catheter is then redirected down the esophagus with a rigid colonoscope or long hemostat or other device. Esophagostomy tubes do not cause gagging, a problem common with pharyngostomy tubes.

Gastrostomy tubes bypass the mouth and esophagus in animals with a functional stomach and intestines. They can also be used when nasoesophageal, esophagostomy, or intermittent gastric tubing is unacceptable. Vomiting is not a contraindication. This technique requires surgery, endoscopy, or special devices for proper placement.

Endoscopy is the preferred and safest way to place gastrostomy tubes percutaneously. Use of dedicated devices for placing gastrostomy tubes has made the procedure easier and readily available for clinicians without endoscopes; however, it is easy to misplace the tube when using these "blind" techniques. It is recommended that novices use a flexible endoscope to inflate the stomach (which pushes organs out of the way) and to be sure of the tube placement. Gastrostomy tubes allow administration of thick gruels and are often tolerated for weeks to years. Either a homemade gruel or a commercial liquid diet (see Table 28.2) may be used. These tubes must be left in place for at least 7 to 10 days to allow an adhesion to form between the stomach and the abdominal wall, which prevents gastric leakage into the peritoneal cavity when the tube is removed. They are often used in cats that do not tolerate nasogastric or esophagostomy tubes. The tube should be flushed with water and air after each feeding. Although the entire caloric requirement may be administered as soon as the tube is placed, it is often safer to start with half the daily requirement and work up to complete nutritional needs over 1 to 3 days. If the tube becomes plugged, it can sometimes be unplugged by using flexible endoscopy forceps or by instilling a fresh carbonated beverage into the tube. When the tube is removed, sufficient traction is applied so that the umbrella tip collapses and passes through the stomach and skin incision. The fistula usually closes spontaneously in 1 to 2 days. The major risk of using such tubes is leakage and peritonitis, which are rare but potentially catastrophic. In dogs larger than 20 to 25 kg, gastrostomy tubes are best placed surgically or sutures are passed through the abdominal wall and into the gastric wall to ensure that the stomach and abdominal wall stay in apposition and form an adhesion that prevents leakage. Improper use of dedicated devices can result in malplacement of the tube and/or perforation of abdominal organs (e.g., spleen, omentum). Because of these potential complications, esophagostomy tubes are preferred whenever possible.

Low-profile gastrostomy tubes can be used if a stoma has been previously established by a routine gastrostomy tube. The major advantage of such tubes is that they may replace routine gastrostomy tubes that are disintegrating or have been inadvertently pulled out, and some can be placed without anesthesia or a surgical/endoscopic procedure. Typically, sedation is all that is needed. However, to use a preexisting stoma, the low-profile gastrostomy tube must usually be placed within hours of removing the old gastrostomy tube, or another tube (e.g., a red latex male urinary catheter) must be inserted into the stoma as quickly as possible to prevent the old stoma from closing.

TABLE 28.2

Selected Enteral Diets

DIET	COMMENTS
Osmolite*	Polymeric diet; contains taurine, carnitine, and MCT; gluten free; low lactose; isotonic, comes in different caloric density preparations
CliniCare†	Polymeric diet; contains taurine but no lactose
Peptamen‡	Oligomeric diet; contains taurine, carnitine, and MCT; gluten free; lactose free; low residue; isotonic
Vivonex T.E.N.‡	Elemental diet; high in carbohydrates, low in protein and fat¶; contains glutamine and arginine; gluten free; lactose free; low residue

MCT, Medium-chain triglyceride.
*Abbott Nutrition.
†Zoetis.
‡Nestle Health Science.
¶To increase protein content, reconstitute one packet of powder with 350 mL water plus 250 mL of 8.5% amino acids for injection.

Enterostomy tubes are indicated in animals with functional intestines when the stomach must be bypassed (e.g., recent gastric surgery). Laparotomy or endoscopy is typically used to place these tubes. When placing it surgically or laparoscopically, a 12-gauge needle punctures the antimesenteric border of the intestine, and a sterile 5F plastic catheter is advanced aborally through the needle until approximately 15 cm extends into the intestinal lumen. The 12-gauge needle is removed, and a purse-string suture is placed to prevent the catheter from moving freely. The needle is then used in the same manner to make a pathway for the catheter to exit through the abdominal wall. The antimesenteric border of the intestine is sutured to the abdominal wall so that the sites where the tube enters the intestine and exits the abdomen are opposed. Traction sutures are used to secure the catheter.

Another technique is to first place a percutaneous gastrostomy tube and then insert the jejunostomy tube through the gastrostomy tube (i.e., a Peg-J tube). The jejunostomy tube is then directed into the duodenum either by dragging it with a flexible endoscope, or by directing a guide wire into the duodenum and running the tube over the guidewire through the gastrostomy tube and into the duodenum. Alternatively, one may use a flexible endoscope to grasp a guide wire entering the esophagus from the nose into the jejunum, drag that wire into the jejunum, and then pass a tube over the guide wire (i.e., a nasojejunostomy tube).

The small diameter of enterostomy tubes often necessitates administration of commercial liquid diets (see Table 28.2), which are best infused at a constant rate. The rate necessary to administer daily caloric needs is calculated. Half-strength feeding solution is administered at one half the calculated rate on day 1. The next day the rate of administration is increased to the calculated rate, but half-strength solution is still used. On the third day a full-strength solution is administered at the calculated rate. If diarrhea occurs, the rate of administration can be decreased or fiber (e.g., psyllium) can be added to the liquid diet. If placed surgically or laparoscopically, the tube should be left in place for 10 to 12 days to allow adhesions to develop around the area and prevent leakage. When enteral feeding is no longer necessary, the clinician simply removes the sutures and pulls out the catheter.

DIETS FOR SPECIAL ENTERAL SUPPORT

If the feeding tube diameter is sufficiently large, a gruel made by blending one can of dog or cat food (e.g., feline p/d [Hill's Pet Products]) plus 0.35 L of water provides approximately 0.9 kcal/mL and is useful for dogs and cats. Elemental diets are rarely needed in animals with severe intestinal disease. Some elemental diets (e.g., Vivonex, Nestle Nutrition) do not have as much protein as desired for dogs and cats (see Table 28.2); therefore some of the water used in mixing the elemental diet is replaced with 8.5% amino acids for injection (e.g., 350 mL water + 250 mL 8.5% amino acids). When feeding cats, the clinician must be sure that sufficient taurine is present in the diet.

Nasoesophageal, esophagostomy, and gastrostomy tubes are typically used for bolus feeding. Animals that have been hyporexic for days to weeks should usually start by receiving small amounts (e.g., 3-5 mL/kg) every 2 to 4 hours. The amount is gradually increased and the frequency decreased until the animal is receiving its caloric needs in three or four daily feedings. The clinician should expect to ultimately administer 22 to 30 mL/kg at each feeding to most dogs and cats. Larger volumes may be given if they do not cause vomiting or distress.

Jejunostomy tubes are designed for constant-rate feeding using an enteral feeding pump. The clinician should begin by feeding the animal a half-strength diet at one half the rate that will ultimately be necessary to meet the animal's caloric needs. If diarrhea does not result after 24 to 36 hours, the clinician increases the flow rate to what will ultimately be needed. If diarrhea still does not occur, the diet may then be changed from half strength to full strength. Constant infusion of these same diets may be done through gastrostomy and esophagostomy tubes in animals that readily vomit when fed in boluses (e.g., some cats with severe hepatic lipidosis). Animals that are critically ill and vomit readily might benefit from "microalimentation," in which very small amounts of liquid diet (e.g., 1-2 mL/h in 30-40 kg dogs) are infused via nasoesophageal tubes in an effort to provide some nutrition to the intestinal mucosa and prevent bacterial translocation and sepsis.

PARENTERAL NUTRITION

Parenteral nutrition is indicated if the animal's intestines cannot reliably absorb nutrients. It is the most certain method of supplying nutrition to such animals but is expensive and can be associated with severe metabolic and infectious complications. If parenteral nutrition will be used, one should consult with a nutritionist. If parenteral nutrition is administered, the animal should also receive some oral feeding, if possible, to help prevent intestinal villous atrophy.

ANTIEMETICS

Antiemetics are indicated for symptomatic therapy in many animals with acute vomiting, those that are severely nauseated, and those in which vomiting is contributing to morbidity (e.g., discomfort or excessive fluid and electrolyte losses). Peripherally acting drugs (Table 28.3) are less effective than centrally acting ones but may suffice in animals with minimal disease. Oral administration is unreliable in nauseated animals. Parasympatholytics (e.g., atropine, aminopentamide) have some central activity, but are generally no longer recommended. Centrally acting antiemetics are more effective. Parenteral administration is often preferred to ensure blood levels in vomiting patients. Suppositories are convenient, but their absorption is erratic.

Maropitant (Cerenia) is a neurokinin-1 (NK-1) receptor antagonist that is effective in preventing vomiting in a wide range of conditions. Approved for use in dogs and cats, it has

TABLE 28.3

Selected Antiemetic Drugs

DRUG	DOSAGE*	COMMENTS
Centrally Acting Drugs		
Neurokinin-1 receptor antagonist		
Maropitant (Cerenia)	1 mg/kg SC q24h (dogs or cats) 2 mg/kg PO q24h (dogs) 1 mg/kg PO q24h (cats) 8 mg/kg PO q24h for up to 2 days for motion sickness in dogs 4 mg/cat PO q24 h for vomiting due to renal failure	Treat puppies 2-7 months old for 5 days; older animals can be treated indefinitely
Serotonin receptor antagonists		
Ondansetron (Zofran)	0.1-0.2 mg/kg IV q8-24h 0.5 mg/kg in resistant cases	Oral administration much less effective
Metoclopramide (Reglan)	0.25-0.5 mg/kg PO, IM, or IV q8-24h 0.4 mg/kg loading dose, then 0.3 mg/kg/h by CRI	Can see CNS adverse effects; poorly effective in cats Most useful when used as an "add on" to maropitant or ondansetron; protect from light when administering as CRI
Phenothiazine derivatives		
Chlorpromazine (Thorazine) Prochlorperazine (Compazine)	0.3-0.5 mg/kg IM, IV, or SC q6-8h 0.1-0.5 mg/kg IM q8-12h	Watch for hypovolemia

IM, Intramuscularly; *PO,* orally; *SC,* subcutaneously.
*Dosages are for both dogs and cats unless otherwise specified.

poor oral bioavailability (food does not affect absorption) but good absorption after SC administration. It is such an effective antiemetic that it will often prevent vomiting secondary to foreign body obstruction, so it is important to try to rule out such obstruction before administering this drug. Gastrointestinal perforations have occurred because success with maropitant delayed diagnosis and removal of foreign bodies. It has analgesic effects for visceral pain.

Ondansetron (Zofran) and dolasetron (Anzemet) are serotonin (5-hydroxytryptamine, 5-HT) receptor antagonists. They are good drugs but are typically less effective than maropitant. Mirtazapine (primarily used as an appetite stimulant) may also have some antiemetic effects due to its antagonism of 5-HT.

Metoclopramide (Reglan) is a less effective antiemetic than the NK-1 and serotonin receptor antagonists (especially in cats). It inhibits the chemoreceptor trigger zone and increases gastric tone and peristalsis. Rarely, animals show unusual behavior (e.g., excitation) after administration. The drug is excreted in the urine, and severe renal failure makes adverse effects more likely. It rarely worsens vomiting, perhaps because it causes excessive gastric contractions. The liquid form of metoclopramide given orally is often not palatable to cats. Because of its prokinetic activity, the drug is contraindicated in animals with gastric or duodenal obstruction. Metoclopramide may be more effective in animals with severe vomiting if given intravenously at a dosage of 0.3-1.0 mg/kg/hr by constant rate infusion. In particular, metoclopramide may be used as an "add on" in difficult-to-control patients not responding to NK-1 and/or serotonin receptor antagonists.

Phenothiazine derivatives (e.g., prochlorperazine [Compazine]) are often effective but are seldom used now. They inhibit the chemoreceptor trigger zone and, in higher doses, the medullary vomiting center. Antiemesis is usually achieved at doses that do not produce marked sedation. However, these drugs may cause vasodilation and can decrease peripheral perfusion in a dehydrated animal.

Many other drugs have antiemetic effects. Mu-antagonist narcotics (e.g., fentanyl, morphine, methadone) may cause vomiting initially, but vomiting is usually inhibited once the drug penetrates to the medullary vomiting center. Butorphanol has some efficacy as an antiemetic and is sometimes used in patients undergoing chemotherapy.

ANTACID DRUGS

Antacid drugs (Table 28.4) lessen gastric acidity. Although they are not antiemetics, they sometimes seemingly have an "antidyspeptic" effect due to diminishing gastric hyperacidity.

Antacids, which titrate gastric acidity, are over-the-counter preparations that are typically of limited efficacy. Compounds containing aluminum or magnesium tend to be

TABLE 28.4

Selected Antacid Drugs

DRUG	DOSAGE*
Acid Titrating Drugs	
Aluminum hydroxide (many names)	10-30 mg/kg PO q6-8h
Magnesium hydroxide (many names)	5-10 mL PO q4-6h (dogs), q8-12h (cats)
Gastric Acid Secretion Inhibitors	
H_2 receptor antagonists†	
Ranitidine (Zantac)	1-2 mg/kg, PO or IV, q8-12h (dogs) 2.5 mg/kg IV or 3.5 mg/kg PO q12h (cats)
Famotidine (Pepcid, Pepcid AC)	0.1-0.2 mg/kg, PO, SC, IM or IV, q12-24h
Proton Pump Inhibitors	
Omeprazole (Prilosec)	1-2 mg/kg PO q12
Pantoprazole (Protonix)	1 mg/kg IV q24h (dog)‡
Esomeprazole (Nexium)	1 mg/kg IV q24h (dogs)‡

IM, Intramuscularly; *IV,* intravenously; *PO,* orally; *SC,* subcutaneously.
*Dosages are for both dogs and cats unless otherwise specified.
†These drugs are competitive inhibitors of histamine. Higher doses have been tried, but have not been shown to be more effective.
‡Dosages are based upon anecdotal reports. These drugs have not been used extensively, and their safety and efficacy in dogs are not established. Twice daily administration of omeprazole PO is more effective then once daily administration of pantoprazole IV.

TABLE 28.5

Selected Gastrointestinal Protectants and Cytoprotective Agents

DRUG	DOSAGE*	COMMENT
Sucralfate (Carafate)	0.5-1 g (dogs) or 0.25 g (cats) PO q6-8h, depending on animal's size (suspension is preferred)	Potentially constipating, absorbs some other orally administered drugs, primarily used to treat existing ulcers
Misoprostol (Cytotec)	2-5 µg/kg PO q8-12h (dogs)	May cause diarrhea/abdominal cramps, primarily used to prevent ulcers, not for use in pregnant animals

PO, Orally.
*Dosages are for both dogs and cats unless otherwise specified.

more effective and do not cause the gastric acid rebound that sometimes occurs in response to calcium-containing antacids. Antacids should be administered orally every 4 to 6 hours to ensure continued control of gastric acidity; however, this may cause diarrhea, especially in animals receiving magnesium-containing compounds. Hypophosphatemia, although unlikely, is possible after extensive aluminum hydroxide administration. Hypermagnesemia, also unlikely, is possible in patients with renal failure that receive magnesium-containing compounds. These types of antacids may also interfere with the absorption of some other drugs (e.g., tetracycline, cimetidine).

Histamine-2 (H_2) receptor antagonists are competitive inhibitors of histamine. They prevent histamine from stimulating the gastric parietal cell. Cimetidine (Tagamet) must be given three or four times daily to achieve best results; it inhibits hepatic cytochrome P450 enzymes, thereby slowing the metabolism of some drugs. Famotidine (Pepcid) is more effective and has less effect on hepatic enzyme activity. The main indication for these drugs has been treatment of gastric and duodenal ulcers. However, tachyphylaxis occurs when administering famotidine for several days, making it progressively less effective over time.[1] Furthermore, these drugs are not effective when used prophylactically to prevent ulceration associated with steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). Nizatidine and ranitidine have some gastric prokinetic activity. Very rarely these drugs may cause bone marrow suppression, central nervous system problems, or diarrhea. Parenteral administration, especially the rapid IV injection of ranitidine, may cause nausea, vomiting, or bradycardia.

Proton pump inhibitors (PPIs) (i.e., omeprazole [Prilosec], lansoprazole [Prevacid], pantoprazole [Protonix], esomeprazole [Nexium]) noncompetitively block the final common pathway of gastric acid secretion. This is the most effective class of drugs for decreasing gastric acid secretion. Maximum suppression of acid secretion usually requires 2 to 5 days of therapy, but the acid suppression occurring on the first day is as good as or better than that caused by H_2 receptor antagonists. Omeprazole is superior to H_2 receptor antagonists as a prophylactic drug in patients receiving ulcerogenic drugs. There is no evidence that combining PPIs and H_2 receptor antagonists is beneficial.[2] In fact, the combination might make PPIs less effective.

GASTRIC AND CYTOPROTECTIVE DRUGS

Sucralfate (Carafate) (Table 28.5) is principally indicated for animals with gastroduodenal ulceration or erosion but is also a mild analgesic for those with esophagitis. It should be administered as a suspension instead of tablets. It is a mediocre prophylactic drug. Sucralfate is a nonabsorbable sulfated sucrose complex that tightly adheres to denuded mucosa,

thus protecting it. It also inhibits peptic activity and may alter prostaglandin synthesis and the actions of endogenous sulfhydryl compounds. There is no evidence that combining sucralfate with PPIs or H_2 receptor antagonists is beneficial. Because sucralfate may adsorb other drugs, slowing their absorption, other orally administered drugs ideally should be given 1 to 2 hours before or after sucralfate administration. Sucralfate can cause constipation.

Misoprostol (Cytotec) is a prostaglandin E_1 analog designed to prevent NSAID-induced gastroduodenal ulceration, but it can be used to treat ulcers. Misoprostol does not appear to be as effective in preventing NSAID-induced ulcers in dogs as it is in people, and PPIs appear to be as effective as misoprostol. The major adverse effects of misoprostol seem to be abdominal cramping and diarrhea, which usually disappear after 2 to 3 days of therapy. It is also an abortifacient.

INTESTINAL "PROTECTANTS"

Intestinal protectants include drugs and inert adsorbents such as kaolin, pectin, and barium sulfate contrast media. Many people believe that inert adsorbents hasten clinical relief in animals with minor inflammation, possibly because they coat the mucosa or adsorb toxins. They make loose stools more normal simply by increasing fecal particulate matter. Inert adsorbents do not have proven efficacy in the treatment of gastritis or enteritis. It is inappropriate to rely on these drugs alone in very sick animals.

DIGESTIVE ENZYME SUPPLEMENTATION

Pancreatic enzyme supplementation is indicated to treat exocrine pancreatic insufficiency (EPI). Empirical use as a therapeutic trial for presumptive EPI is a poor approach. There are many products that vary greatly in potency. Although pills may work, enteric-coated pills are particularly ineffective. Powdered preparations tend to be more effective; Viokase-V (A.H. Robins Co.) and Pancreazyme (Daniels Pharmaceuticals) seem to be particularly efficacious. The powder should be mixed with food (approximately 1-2 teaspoons per meal). Incubating the mixture before feeding is not beneficial. Fat is the main nutrient that must be digested in animals with exocrine pancreatic insufficiency, and feeding a low-fat diet may ameliorate diarrhea. Antacid and/or antibiotic therapy has anecdotally helped prevent gastric acidity or small intestinal bacteria from reducing enzyme supplementation effectiveness. Occasionally, stomatitis or diarrhea develops in dogs receiving excessive enzyme supplementation.

MOTILITY MODIFIERS

Drugs that prolong intestinal transit time are used to symptomatically treat diarrhea. Infrequently needed, they are reasonable if diarrhea causes excessive fluid or electrolyte losses or owners demand control of the diarrhea at home. Opiates (Table 28.6) increase resistance to flow by augmenting segmental contraction. They are more effective than parasympatholytics, which paralyze intestinal motility and create ileus. Both classes of drugs have antisecretory effects. Because cats do not tolerate narcotics as well as dogs, opiates should be avoided in cats although loperamide may be used carefully.

Loperamide (Imodium) theoretically increases risk for bacterial proliferation in the intestinal lumen; however, this is rarely clinically important. An overdose can cause narcotic intoxication (i.e., collapse, vomiting, ataxia, hypersalivation), which requires treatment with narcotic antagonists. Dogs deficient in P-glycoprotein (i.e., those with MDR gene mutation [Collies, Australian Shepherds, etc.]) are at greater risk for adverse central nervous system signs.

Diphenoxylate (Lomotil) is similar to loperamide but somewhat less effective. It has more potential for toxicity than loperamide. It may have some antitussive properties. Rarely a dog responds to it but not to loperamide. This drug should not be used in cats.

Drugs that shorten transit time (prokinetic drugs) empty the stomach or increase intestinal peristalsis or both. Metoclopramide causes gastric prokinesis, enhancing gastric emptying of fluids. It can be administered orally or parenterally. Adverse effects are mentioned under the section on antiemetics. Cisapride is a 5-HT_4 agonist that stimulates normal motility from the lower esophageal sphincter to the anus. It is usually effective unless the tissue has been irreparably damaged (e.g., megacolon in cats). Primarily used for the treatment of constipation, it may also be used for the

TABLE 28.6

Selected Drugs Used for Symptomatic Treatment of Diarrhea

DRUG	DOSAGE*
Intestinal Motility Modifiers (Opiates)	
Diphenoxylate (Lomotil)	0.05-0.2 mg/kg PO q8-12h (dogs)
Loperamide (Imodium)	0.12 mg/kg PO q8-12h (dogs) 0.08-0.16 mg/kg PO q12h (cats)
Antiinflammatory/Antisecretory Drug	
Bismuth subsalicylate† (Pepto-Bismol, Kaopectate)	1 mL/kg/day PO divided q8-12h (dogs) for 1-2 days

PO, Orally.
*Dosages are for both dogs and cats unless otherwise specified.
†This drug contains salicylate and can be nephrotoxic if combined with other nephrotoxic drugs.

management of gastroparesis (in which it is usually more effective than metoclopramide) and small intestinal ileus. It has rarely been reported to be beneficial in dogs with megaesophagus (perhaps because the dogs had gastroesophageal reflux). Cisapride is no longer available from human pharmacies but is generally available from veterinary pharmacies. It is typically available only as an oral preparation, but can be formulated for parenteral use. It has few significant adverse effects, although intoxication with large doses may cause diarrhea, muscular tremors, ataxia, fever, aggression, and other central nervous system signs. It should not be used concurrently with drugs that are hepatic P450 inhibitors or that inhibit P-glycoprotein. Erythromycin stimulates motilin receptors and enhances gastric motility at doses less than required for antibacterial activity (i.e., 0.5-1 mg/kg). It may also increase intestinal motility. Nizatidine and ranitidine are H_2 receptor antagonists that have some gastric prokinetic effects at routinely administered doses. Bethanechol (Urecholine) is an acetylcholine analog that stimulates intestinal motility and secretion. It produces strong contractions that can cause pain or injure the animal; hence, it is infrequently used except for increasing urinary bladder contractions. Obstruction of an outflow area can be a contraindication to the use of prokinetic drugs because vigorous contractions against such a lesion may cause pain or perforation. Obstruction of the urinary outflow tract is also a contraindication to the use of bethanechol.

Pyridostigmine (Mestinon) inhibits acetylcholinesterase and is used to treat myasthenia gravis. It is preferred over physostigmine and neostigmine. It is used for the treatment of acquired megaesophagus due to localized myasthenia. It must be used cautiously because overdose may cause toxicity accompanied by signs of parasympathetic overload (e.g., vomiting, miosis, diarrhea).

ANTIINFLAMMATORY AND ANTISECRETORY DRUGS

Intestinal antiinflammatory or antisecretory drugs (or both) are indicated for lessening fluid losses due to diarrhea or for controlling intestinal inflammation that is unresponsive to dietary or antibacterial therapy.

Bismuth subsalicylate (Pepto-Bismol, Kaopectate) is effective in many dogs with acute enteritis (see Table 28.6), probably because of the antiprostaglandin activity of the salicylate moiety. Its main disadvantages are that the salicylate is absorbed (warranting cautious use in cats or dogs receiving nephrotoxic drugs), it turns stools black (mimicking melena), and it must be administered orally (many animals dislike its taste). Bismuth is bactericidal for certain organisms (e.g., *Helicobacter* spp.).

Octreotide (Sandostatin) is a synthetic analog of somatostatin that inhibits alimentary tract motility and secretion of gastrointestinal hormones and fluids. It has had limited use in dogs and cats but might be helpful in selected animals with intractable diarrhea or lymphangiectasia. The dose in the dog is unknown but suggested to be 10-40 mg/kg SC q12-24h.

Salicylazosulfapyridine (sulfasalazine [Azulfidine]) is used in dogs with colonic inflammation. This drug is generally not beneficial in animals with small intestinal problems. It is a combination of sulfapyridine and 5-aminosalicylic acid. Colonic bacteria split the molecule, and 5-aminosalicylic acid (probably the active moiety) is subsequently "deposited" on diseased colonic mucosa. Dogs generally receive 50 to 60 mg/kg divided into three doses daily, but not to exceed 3 g daily. Sulfasalazine given orally may be effective at lower-than-expected doses if used in combination with glucocorticoids. Anecdotally, 15 to 20 mg/kg/day, sometimes divided into twice-daily doses, is often tolerated by cats, but they must be closely observed for salicylate intoxication (i.e., lethargy, anorexia, vomiting, hyperthermia, tachypnea). Some cats that vomit or become hyporexic may tolerate the medication if it is given in enteric-coated tablets. Many dogs with colitis respond to therapy in 3 to 5 days. However, the drug may have to be given for 2 weeks before one decides that it is ineffective. If signs of colitis resolve, the dose should be gradually reduced. If the patient cannot be weaned off the drug entirely, the lowest effective dose should be used and the animal monitored regularly for drug-induced adverse effects (especially those resulting from the sulfa moiety). Sulfasalazine may cause transient or permanent keratoconjunctivitis sicca. Other possible complications include cutaneous vasculitis, arthritis, bone marrow suppression, diarrhea, and any other problem reported with sulfa drugs or NSAIDs.

Olsalazine and mesalamine contain or are metabolized to 5-aminosalicylic acid but do not have the sulfa, which is responsible for most of sulfasalazine's adverse effects. In people they are as effective as sulfasalazine but safer. Olsalazine and mesalamine have been used effectively in dogs. They are given in a dose generally about half that of sulfasalazine. Keratoconjunctivitis sicca has also developed in dogs receiving mesalamine.

Glucocorticoids are potentially indicated in animals with chronic alimentary tract inflammation (e.g., moderate to marked inflammatory bowel diseases) that is unresponsive to well-designed elimination diets and/or antimicrobial therapy. Prednisolone is preferred over prednisone. Relatively high doses (i.e., prednisolone, 2.2 mg/kg/day PO) are often used initially, and the dose is tapered to find the lowest effective dose. Dexamethasone is sometimes effective when prednisolone is not, but dexamethasone is much more ulcerogenic than prednisolone. If oral administration is a problem in a cat, long-lasting steroid injections (e.g., methylprednisolone acetate) may be tried. Methylprednisolone appears to be a more effective antiinflammatory than prednisolone, requiring only 80% of the dose used when administering prednisolone. Budesonide (Entocort) is a steroid that is largely eliminated from the body by first-pass metabolism in the liver, thus diminishing (but not totally eliminating) systemic steroid side effects. It is primarily indicated in patients who are known to respond to prednisolone but cannot tolerate that steroid's side effects.

Glucocorticoids are often beneficial in cats with inflammatory bowel disease (IBD), but they may worsen intestinal disease in some dogs and cats. Iatrogenic Cushing syndrome primarily occurs in dogs but can develop in cats that are grossly overdosed. It is important to have a diagnosis before using high-dose prednisolone therapy because some diseases that mimic steroid-responsive lymphocytic colitis (e.g., histoplasmosis) are absolute contraindications to glucocorticoid therapy. Although more common in the southeastern United States and the Ohio River Valley, histoplasmosis has been diagnosed in patients residing in nonendemic areas.

Retention enemas of glucocorticoids or 5-aminosalicylic acid are rarely indicated in animals with severe distal colitis unresponsive to other medications. The dose is estimated from the human dose. These enemas place large doses of an antiinflammatory agent directly on the affected area while minimizing systemic effects. Contraindications to their use are the same as those for systemic administration of the active ingredient of the enema.

Immunosuppressive therapy (e.g., cyclosporine, chlorambucil, azathioprine) is indicated in animals with severe IBD that is unresponsive to glucocorticoid, dietary, antimicrobial, and cobalamin therapy. It is also used in animals with severe disease in which it is in the animal's best interest to use aggressive immunosuppressive therapy initially. These drugs should be used only in patients with a definitive diagnosis. Immunosuppressive therapy can be more efficacious than glucocorticoid therapy alone and allows glucocorticoids to be given at lower doses and for shorter periods, thereby decreasing their adverse effects. However, the possibility of adverse effects from these drugs usually limits their use to animals with severe disease. The reader is referred to Chapter 72 for additional information on immunosuppressive therapy.

Cyclosporine (Atopica) is a potent immunosuppressive drug sometimes used in dogs with IBD, lymphangiectasia, and perianal fistulas. The dose is 3 to 6 mg/kg PO every 12 hours, but erratic bioavailability requires therapeutic drug monitoring in nonresponding patients, usually after 8 to 10 days of therapy. There is considerable variation in the bioavailability of different preparations of cyclosporine. It may be administered intravenously in vomiting patients, but then the initial dose should probably be decreased by 50%. Because of its considerable expense, it is sometimes administered with low doses of ketoconazole (3-5 mg/kg PO q12h), which inhibits metabolism of cyclosporine and in turn allows the use of lower doses at less expense to the client. Animals receiving too much cyclosporine usually first show hyporexia, which can be confusing when dealing with patients with gastrointestinal disease that are hyporexic to begin with.

Oral chlorambucil is an alkylating agent used in dogs with severe alimentary tract inflammation and sometimes lymphangiectasia, and in cats with severe IBD. It is typically administered with glucocorticoids initially. Chlorambucil has fewer adverse effects than azathioprine. In dogs, 4 to 6 mg/m^2 is administered daily for up to three weeks, and then the dose is reduced. A reasonable starting dose in cats is 1 mg twice weekly for cats weighing less than 3.2 kg and 2 mg twice weekly for cats weighing more than that. Beneficial effects may not be seen for 4 to 5 weeks. If a response is seen, the dose should then be decreased very slowly over the next 2 to 3 months. The animal should be monitored for myelosuppression.

Azathioprine (Imuran) is used only in dogs (50 mg/m^2 PO, daily or every other day), never cats. For smaller dogs a 50-mg azathioprine tablet is typically crushed and suspended in a liquid (e.g., 15 mL of a vitamin supplement) to allow more accurate dosing. The suspension must be mixed well before each dosing. Every-other-day dosing is much safer but takes much longer (i.e., 2-5 weeks) than every-day dosing to see clinical effects. Side effects in dogs may include hepatic disease, pancreatitis, and bone marrow suppression.

ANTIBACTERIAL DRUGS

In dogs and cats with gastrointestinal problems, antibiotics are primarily indicated if aspiration pneumonia, fever, a leukogram suggestive of sepsis, severe neutropenia, antibiotic-responsive enteropathy (sometimes also called "dysbiosis"), clostridial colitis, or symptomatic *Helicobacter* gastritis is being treated. Animals with an acute abdomen may reasonably be treated with antibiotics while the nature of the disease is being defined. Colitis can be a reasonable indication for amoxicillin (22 mg/kg PO q12h) or tylosin (10-20 mg/kg PO per day) if clostridial colitis is strongly suspected, but most animals with acute gastroenterocolitis of unknown cause (including those with acute hemorrhagic diarrheal syndrome—previously called *hemorrhagic gastroenteritis*) do not benefit from antibiotic therapy. Routine use of antimicrobials in animals with alimentary tract disorders is discouraged unless the patient is at high risk for infection or is being treated for a specific disorder responsive to antibiotics.

Nonabsorbable aminoglycosides (e.g., neomycin) are generally not indicated unless an infection known to be sensitive to the drug (e.g., campylobacteriosis) is strongly suspected. Metronidazole (10-15 mg/kg PO q24h) has been commonly used for a variety of gastrointestinal diseases, most of which were probably inappropriate. Metronidazole is sometimes successful for suspected ARE, and some dogs and cats diagnosed with IBD respond better to metronidazole than to glucocorticoids supporting the hypothesis that the "IBD" was probably ARE. Adverse effects are uncommon but may include salivation (because of its taste), vomiting, central nervous system abnormalities (e.g., central vestibular signs), and perhaps neutropenia. These adverse effects usually resolve after withdrawing the drug. Cats sometimes accept oral suspensions better than the 250-mg tablets, which must be cut and have an unpleasant taste. Metronidazole is potentially carcinogenic in some species, but there is no evidence of risk in dogs and cats.

Tylosin (10-20 mg/kg PO q24h or divided q12h) is commonly used to treat ARE and clostridial colitis. Tetracycline (22 mg/kg PO q12h) has also been used for ARE. The clinician should be prepared to treat the patient for 3 weeks before deciding that therapy for ARE has been unsuccessful.

Pets occasionally have enteritis caused by a specific bacterium, but this is not necessarily an indication for antibiotics. Clinical signs resulting from some bacterial enteritides (e.g., salmonellosis, enterohemorrhagic *Escherichia coli*) generally do not resolve more quickly when the animal is treated with antibiotics, even those to which the bacteria are sensitive.

Dogs and cats with viral enteritis but without obvious systemic sepsis may reasonably be treated with antibiotics if secondary sepsis is likely to occur (e.g., those with or likely to develop neutropenia). First-generation cephalosporins (e.g., cefazolin) are often effective for such use.

If systemic or abdominal sepsis is suspected to have originated from the alimentary tract (e.g., septicemia caused by parvoviral enteritis, perforated intestine), broad-spectrum antimicrobial therapy is indicated. Antibiotics with an excellent aerobic gram-positive and anaerobic spectrum of action (e.g., ampicillin plus sulbactam [Unasyn] 20 mg/kg IV q8h or clindamycin, 11 mg/kg IV q8h) combined with antibiotics with excellent activity against most aerobic bacteria (e.g., amikacin, 25 mg/kg IV q24h; or enrofloxacin, 15 mg/kg IV q24h [use 5 mg/kg in cats]) are often effective. To improve the anaerobic spectrum, especially if a cephalosporin is used instead of ampicillin, the clinician may include metronidazole (10 mg/kg IV, q8-12h). Alternatively, a second-generation cephalosporin (e.g., cefoxitin, 30 mg/kg IV q6-8h) may be used. In general, it takes at least 48 hours before the clinician can ascertain whether the therapy is being effective.

Despite the clinical imperative to control life-threatening infection as quickly as possible, it is also important to be a responsible member of the medical community, in this case specifically in regard to antibiotics effective against multi–drug-resistant infections. Some antibiotics are referred to as "drugs of last resort" because there are bacteria for which only 1 or 2 antibiotics are still effective. Vancomycin, imipenem, meropenem, doripenem, the oxazolidinone linezolid (Zyvox), the streptogramin combination of dalfopristin and quinupristin (Synercid), tigecycline (Tygacil), the lipopeptide daptomycin (Cubicin), moxifloxacin (Avelox), the glycopeptide telavancin, the oxazolidinone telithromycin (Ketek®), and the fourth- and fifth-generation cephalosporins (cefepime, cefpirome, ceftaroline, ceftobiprole) should not be used unless bacteria resistant to all other antibiotics have been cultured and there is no other therapy that is expected to be effective.

Helicobacter gastritis may be treated with various combinations of drugs. Currently, the combination of amoxicillin, metronidazole, and bismuth seems effective in dogs and cats. Antacids (i.e., omeprazole; see Table 28.4) and macrolides (i.e., erythromycin or azithromycin; see pp. 515-516) have been used in people, but they do not appear necessary in dogs or cats. Sole-agent therapy of *Helicobacter pylori* in people is typically unsuccessful, but some dogs and cats seem to respond to erythromycin or amoxicillin as a sole agent. If high doses of erythromycin (22 mg/kg PO, twice daily) cause vomiting, the dose may be lowered to 10 to 15 mg/kg twice daily. A 10- to 14-day course of treatment appears adequate for most animals, although recurrence of infection is probable.

PROBIOTICS/PREBIOTICS

Administering live bacteria or yeast in the food with the intent to produce a beneficial effect is called *probiotic therapy*. Administering a specific dietary substance to specifically increase or decrease the numbers of specific bacteria is called *prebiotic therapy*. Concurrent use of probiotics and prebiotics is called *symbiotic therapy*. Currently there are only a few reports purporting a clear benefit in dogs or cats.

Lactobacillus, Bifidobacterium, and *Enterococcus* are bacteria typically administered to dogs. These bacteria are believed to stimulate Toll-like receptors on the intestinal epithelial cells and thereby affect cytokine production. The beneficial effect seems to last only as long as the bacteria are being administered. These bacteria rarely become permanently established in the gastrointestinal microflora. Not all probiotics sold in drug or grocery stores contain what the label states, which may be at least partially responsible for why efficacy has not be demonstrated. In general, large numbers of bacteria appear to be necessary, which explains why feeding yogurt (which contains relatively modest numbers of *Lactobacilli*) is typically ineffective.

FECAL TRANSPLANTATION

Much work is being done on fecal transplantation as a means of altering the intestinal bacterial flora and avoiding the need for antibiotics in dogs and cats with chronic intestinal diseases. Currently, there is no consensus as to the best technique(s) or the appropriate indications. However, this might become an important alternative to antibiotic therapy.

ANTHELMINTIC DRUGS

Anthelmintics are frequently prescribed for dogs and cats with alimentary tract disease, even if parasitism is not the primary problem. It is often reasonable to use these drugs empirically for the treatment of suspected parasitic infections in animals with acute or chronic diarrhea. Selected anthelmintics are listed in Table 28.7.

ENEMAS, LAXATIVES, AND CATHARTICS

Enemas are classified as either cleansing or retention.

TABLE 28.7

Selected Anthelmintics/Antiprotozoals

DRUG	DOSAGE* (PO)	USE	COMMENTS
Fenbendazole (Panacur; Safe-Guard)	50 mg/kg, once daily for 3-5 days	H/R/W/G	Not approved for cats but often used for 3-5 days in cats to eliminate *Giardia*. Give with food.
Metronidazole (Flagyl)	12-15 mg/kg PO q12h for 8 days (dogs) 17 mg/kg PO q24h for 7 days (cats)	G	Rarely see neurologic signs Use of metronidazole benzoate is 62% metronidazole and requires dose of 25 mg/kg
Ronidazole	30 mg/kg PO q24h for 12 days (cats) (not approved)	G	For *Tritrichomonas* infections in cats; drug is not approved for use in animals. Rarely causes neurologic signs.
Pyrantel (Nemex)	5 mg/kg (dogs) 20 mg/kg, once only (cats)	H/R/P H/R	Give after meal, repeat in 2 weeks
Pyrantel/febantel/praziquantel (Drontal Plus)	10 mg/kg febantel PO in food q24h for 3 days (adult dogs and cats) 15 mg/kg for puppies and kittens	T/H/R/W	Can treat *Giardia*: q24h for 3 days
Imidocloprid/moxidectin (Advantage multi)	Topical—follow manufacturers' recommendations	H/R/W	
Ivermectin/Pyrantel (Heartguard plus for dogs)	Pyrantel 5 mg/kg Ivermectin 6 µg/kg	H/R	
Milbemycin (Sentinel, Trifexis)	0.5 mg/kg monthly (dog)	H/R/W	Not approved for use in cats. Not safe to use in dogs with *D. immitis* microfilaremia.
Praziquantel (Droncit)	5 mg/kg PO for dogs > 6.8 kg 7.5 mg/kg PO for dogs < 6.8 kg 7.5 mg/kg IM or SC for dogs < 2.3 kg 6.3 mg/kg IM or SC for dogs 2.7-4.5 kg 5 mg/kg IM or SC for dogs > 5 kg 11.4 mg/cat PO for cats < 1.8 kg; or IM or SC for cats 1.8-2.2 kg 22.7 mg/cat PO, SC, or IM for cats 2.3-5 kg 34.5 mg/cat PO, IM or SC for cats > 5 kg For *Heterobilharzia,* 20 mg/kg SC q8h for 1 day (dogs only)	T	10 mg/kg for juvenile *Echinococcus* spp. or *Spirometra*
Epsiprantel (Cestex)	5.5 mg/kg PO, once, for dogs 2.75 mg/kg PO, once, for cats	T	—
Sulfadimethoxine (Albon)	50 mg/kg on day 1, then 27.5 mg/kg q12h for 9 days	C	May cause dry eyes, arthritis, various cytopenias, hepatic disease
Trimethoprim-sulfadiazine (Tribrissen)	30 mg/kg for 10 days	C	May cause dry eyes, arthritis, various cytopenias, hepatic disease

C, Coccidia; *G, Giardia; H,* hookworms; *P, Physaloptera; PO,* orally; *R,* roundworms; *SC,* subcutaneously; *T,* tapeworms; *W,* whipworms.
*Dosages are for both dogs and cats unless otherwise specified.

Retention enemas are given so that the material administered stays in the colon until it exerts its desired effects (e.g., antiinflammatory retention enemas in animals with IBD, water in obstipated animals). Obstipated animals may require frequent administrations of modest volumes of water (e.g., 20-200 mL, depending on the animal's size) so that the water stays in the colon and gradually softens the feces. The clinician should avoid overdistending the colon or administering drugs that may be absorbed and produce undesirable effects. Suspected or pending colonic rupture is a contraindication to the use of enemas, but this can be difficult to predict. Animals that have undergone neurosurgery (e.g., hemilaminectomy) and are receiving glucocorticoids, especially dexamethasone, may be at increased risk for colonic perforation. Animals with colonic tumors and those that have recently undergone colonic surgery or biopsy should not receive enemas unless there is an overriding reason.

Cleansing enemas are designed to remove fecal material. They involve repeated administration of relatively large volumes of warm water. In dogs the water is administered by gravity flow from a bucket or bag held above the animal. The enema tube is gently advanced as far as it will easily go into the colon (hopefully to the flexure between the descending and transverse colon). Between 50 and 100 mL is tolerated by most small dogs, 200 to 500 mL by medium-size dogs, and 1 to 2 L by large dogs. Care should be taken to avoid overdistending or perforating the colon. Enemas are usually administered to cats with a soft canine male urinary catheter and a 50-mL syringe. Cats typically vomit if rapid fluid administration causes colonic distention. A suspected or pending colonic perforation is a contraindication to a cleansing enema.

Hypertonic enemas are potentially dangerous and should not be used unless there is a clear-cut and imperative reason to do so. They can cause massive, fatal fluid and electrolyte shifts (i.e., hyperphosphatemia, hypocalcemia, hypokalemia, hyperkalemia), especially in cats and small dogs; but any animal that cannot quickly evacuate the enema is at risk.

Cathartics and laxatives (Table 28.8) should be used only to augment defecation in animals that are not obstructed. They are not routinely indicated in small animals except as part of lower bowel cleansing before colonoscopy or colonic surgery.

Irritative laxatives (e.g., bisacodyl) stimulate defecation rather than soften feces. They are often used before colonoscopic procedures and in animals that are reluctant to defecate because of an altered environment. They are probably inappropriate for long-term use because people who use them chronically develop dependence and other colonic problems. A glycerin suppository or a lubricated matchstick is often an effective substitute for an irritative laxative. These objects are carefully placed in the rectum to stimulate defecation.

Bulk and osmotic laxatives include a variety of preparations: various fibers (especially soluble ones), magnesium sulfate, lactulose, and, in milk-intolerant animals, ice cream or milk. They promote fecal retention of water and are indicated in animals that have overly hard stools not caused by ingestion of foreign objects. Fiber is a bulking agent that is incorporated into food and can be used indefinitely. Commercial diets relatively high in fiber may be used, or existing diets may be supplemented with fiber (see p. 434). It is important to supply adequate amounts of water so that the additional fiber does not cause harder-than-normal stools. Too much fiber may cause excessive stool or inappetence resulting from decreased palatability (a danger for fat cats at risk for hepatic lipidosis). Fiber should not be given to animals with a partial or complete alimentary tract obstruction, because impaction may occur.

Lactulose (Cephulac) was designed to control signs of hepatic encephalopathy, but it is also an effective osmotic laxative. It is a disaccharide that is split by colonic bacteria



TABLE 28.8

Selected Laxatives, Cathartics, Stool-Softening Agents, and Bulking Agents

DRUG	DOSAGE (PO)	COMMENTS
Bisacodyl (Dulcolax)	5 mg (small dogs and cats) 10-15 mg (larger dogs)	Do not break tablets.
Coarse wheat bran	1-3 tbsp/454 g of food	
Canned pumpkin pie filling	1-3 tbsp/day (cats only)	Principally for cats.
Dioctyl sodium sulfosuccinate (Colace)	10-200 mg q8-12h (dogs only) 10-25 mg q12-24h (cats only)	Be sure animal is not dehydrated when treating.
Lactulose (Cephulac)	1 mL/4.5 kg q8-12h, then adjust dose as needed (dogs only) 5 mL q8-12h, then adjust dose as needed (cats only)	Can cause severe osmotic diarrhea.
Psyllium (Metamucil)	1-2 tsp/454 g of food	Be sure animal has enough water, or constipation may develop.

PO, Orally.

into unabsorbed particles. Lactulose is particularly useful for animals that refuse to eat high-fiber diets. The dose necessary to soften feces must be determined in each animal, but an initial dose of 1 ml/4.5 kg may be given two or three times daily. This initial dose is then modified to achieve the desired fecal consistency. Cats often ultimately need relatively high dosages (e.g., 5 mL two to three times daily). If gross overdosing occurs, so much water can be lost in the feces that hypernatremic dehydration ensues. There are no obvious contraindications to the use of lactulose.

Suggested Readings

Allen HS. Therapeutic approach to cats with chronic diarrhea. In: August JR, eds. *Consultations in feline internal medicine*. ed 6. St Louis: Elsevier/Saunders; 2011.

Allenspach K, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med*. 2006;20:239.

Allenspach K, et al. Antiemetic therapy. In: August JR, eds. *Consultations in feline internal medicine*. ed 6. St Louis: Elsevier/Saunders; 2011.

Archer TM, et al. Oral cyclosporine treatment in dogs: a review of the literature. *J Vet Intern Med*. 2014;28:1.

Boothe DM. Gastrointestinal pharmacology. In: Boothe DM, ed. *Small animal clinical pharmacology and therapeutics*. ed 2. St Louis: Elsevier/WB Saunders; 2012.

Boscan P, et al. Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. *Am J Vet Res*. 2011;72:1576.

Bybee SN, et al. Effect of the probiotic *Enterococcus faecium* SF68 on presence of diarrhea in cats and dogs housed in an animal shelter. *J Vet Intern Med*. 2011;25:856.

Campbell S, et al. Endoscopically assisted nasojejunal feeding tube placement: technique and results in five dogs. *J Am Anim Hosp Assoc*. 2011;47:e50.

Cook EK, et al. Pharmacokinetics of esomeprazole following intravenous and oral administration in healthy dogs. *Vet Med (Auckl)*. 2016;7:123.

Galvao JFB, et al. Fluid and electrolyte disorders in gastrointestinal and pancreatic disease. In: DiBartola SP, ed. *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 4. St Louis: Elsevier/WB Saunders; 2012.

Hall EJ, et al. Diseases of the small intestine. In: Ettinger SJ, et al., eds. *Textbook of veterinary internal medicine*. ed 7. St Louis: Saunders/Elsevier; 2010.

Herstad H, et al. Effects of a probiotic intervention in acute canine gastroenteritis—a controlled clinical trial. *J Small Anim Pract*. 2010;51:34.

Holahan ML, et al. Enteral nutrition. In: DiBartola SP, ed. *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 4. St Louis: Elsevier/WB Saunders; 2012.

Hopper K, et al. Shock syndromes. In: DiBartola SP, ed. *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 4. St Louis: Elsevier/WB Saunders; 2012.

Hughes D, et al. Fluid therapy with macromolecular plasma volume expanders. In: DiBartola SP, ed. *Fluid, electrolyte, and acid-base disorders in small animal practice*. ed 4. St Louis: Elsevier/WB Saunders; 2012.

Kilpinen S, et al. Efficacy of two low-dose oral tylosin regimens in controlling the relapse of diarrhea in dogs with tylosin-responsive diarrhea: a prospective, single-blinded, two-arm parallel, clinical field trial. *Acta Vet Scand*. 2014;56:43.

Lesman SP, et al. The pharmacokinetics of maropitant citrate dosed orally to dogs at 2 mg/kg and 8 mg/kg once daily for 14 consecutive days. *J Vet Pharmacol Ther*. 2013;36:462.

Martin-Flores M, et al. Effects of maropitant in cats receiving dexmedetomidine and morphine. *J Am Vet Med Assoc*. 2016;2489:1257.

Parkinson S, et al. Evaluation of the effect of orally administered acid suppressants on intragastric pH in cats. *J Vet Intern Med*. 2015;29:104.

Reineke EL, et al. Evaluation of an oral electrolyte solution for treatment of mild to moderate dehydration in dogs with hemorrhagic diarrhea. *J Am Vet Med Assoc*. 2013;243:851.

Saker KE, et al. Critical care nutrition and enteral-assisted feeding. In: Hand MS, et al., eds. *Small animal clinical nutrition*. ed 5. Topeka, Kan: Mark Morris Institute; 2010.

Schmitz S, et al. A prospective, randomized, blinded, placebo-controlled pilot study on the effect of *Enterococcus faecium* on clinical activity and intestinal gene expression in canine food-responsive chronic enteropathy. *J Vet Intern Med*. 2015;29:533.

Unterer S, et al. Treatment of aseptic dogs with hemorrhagic gastroenteritis with amoxicillin/clavulanic acid: a prospective blinded study. *J Vet Intern Med*. 2011;25:973.

Williamson K, et al. Efficacy of omeprazole versus high-dose famotidine for prevention of exercise-induced gastritis in racing Alaskan sled dogs. *J Vet Intern Med*. 2010;24:285.

Wong C, et al. The colloid controversy: are colloids bad and what are the options. *Vet Clin North Am Small Anim Pract*. 2017;47:411.

References

1. Tolbert MK, et al. Repeated famotidine administration results in a diminished effect on intragastric pH in dogs. *J Vet Intern Med*. 2017;31:117.
2. Tolbert MK, et al. Efficacy of intravenous administration of combined acid suppressants in healthy dogs. *J Vet Intern Med*. 2015;29:556.

CHAPTER 29

Disorders of the Oral Cavity, Pharynx, and Esophagus



MASSES, PROLIFERATIONS, AND INFLAMMATION OF THE OROPHARYNX

SIALOCELE

Etiology

Sialoceles are accumulations of saliva in subcutaneous tissues caused by salivary duct obstruction and/or rupture, and subsequent leakage of secretions into subcutaneous tissues. Most cases are probably traumatic, but some are idiopathic.

Clinical Features

A large swelling is found under the jaw or tongue or occasionally in the pharynx. Acutely the swelling may be painful, but most are nonpainful. Oral cavity sialoceles may cause dysphagia, whereas those located in the pharynx often produce gagging or dyspnea. If traumatized, sialoceles may bleed or cause anorexia due to discomfort. Classically found in 2- to 4-year-old dogs; German Shepherds and Miniature Poodles seem to be predisposed.

Diagnosis

Aspiration with a large-bore needle reveals thick fluid with some neutrophils. The fluid usually resembles mucus, strongly suggesting its salivary gland origin. Contrast sialograms and/or contrast computed tomography (CT) sometimes define which gland is involved.

Treatment

The mass is opened and drained. The salivary gland responsible for the secretions must be excised.

Prognosis

The prognosis is excellent if the correct gland is removed.

SIALOADENITIS/SIALOADENOSIS/ SALIVARY GLAND NECROSIS

Etiology

The etiology is unknown, but the condition apparently has occurred as an idiopathic event as well as secondary to chronic vomiting/regurgitation.

Clinical Features

The condition may cause a painless enlargement of one or more salivary glands (usually the submandibular). If there is substantial inflammation, animals may be dysphagic. A syndrome has been reported in which noninflammatory swelling (sialoadenosis) is associated with vomiting only responsive to phenobarbital therapy. Cause and effect are unclear, but it is clear that chronic vomiting will cause sialoadenitis and even necrosis in some dogs.

Diagnosis

Cytology or histopathology confirms that the mass is salivary tissue and determines whether inflammation or necrosis is present.

Treatment

If there is substantial inflammation and pain, surgical removal seems most efficacious. If the patient is vomiting, a search should be made for an underlying cause. If a cause is found, it should be treated and the size of the salivary glands monitored. If no other cause for vomiting can be found, phenobarbital may be administered at anticonvulsant doses (see Chapter 62).

Prognosis

The prognosis is usually excellent.

NEOPLASMS OF THE ORAL CAVITY IN DOGS

Etiology

Most soft tissue masses of the oral cavity are neoplasms, and most of these are malignant (i.e., melanoma, squamous cell carcinoma, fibrosarcoma). However, acanthomatous ameloblastomas (previously called *epulides*), fibromatous epulides (classically in Boxers), oral papillomatosis, and eosinophilic granulomas (e.g., in Siberian Huskies and Cavalier King Charles Spaniels) also occur.

Clinical Features

The most common signs of tumors of the oral cavity are halitosis, dysphagia, bleeding, salivation, or a growth

protruding from the mouth. Papillomatosis and fibromatous periodontal hyperplasia are benign growths that may cause discomfort when eating and occasionally cause bleeding, mild halitosis, or tissue protrusion from the mouth. The biologic behaviors of the different tumors are presented in Table 29.1.

Diagnosis

A thorough examination of the oral cavity (which may require that the animal be under anesthesia) usually reveals a mass involving the gingiva, although the tonsillar area, hard palate, and tongue may be affected. Diagnosis requires cytologic or histopathologic analysis, although papillomatosis and melanomas may be strongly suspected based upon their gross appearance. The preferred diagnostic approach in a dog with a mass of the oral cavity is to image the area (e.g., CT) and perform a relatively deep incisional biopsy. A deep biopsy is necessary to avoid misdiagnosis that often occurs if only the superficial, ulcerated, necrotic surface is obtained. If malignancy is possible, thoracic radiographs or CT should be obtained to evaluate for metastases (uncommon but a very poor prognostic sign if present). Fine-needle aspiration of regional lymph nodes, even if they appear normal, is indicated to detect metastases. Melanomas may be amelanotic

TABLE 29.1

Some Characteristics of Selected Oral Tumors

TUMOR	TYPICAL APPEARANCE/ LOCATION	BIOLOGIC BEHAVIOR	PREFERRED THERAPY
Squamous Cell Carcinoma			
Gingiva	Fleshy or ulcerated/on rostral gingiva	Malignant, locally invasive	Wide surgical resection on rostral gingiva ± radiation; piroxicam may help palliate.
Tonsil	Fleshy or ulcerated/on one or rarely both tonsils	Malignant, commonly spreads to regional lymph nodes	None (chemotherapy may be of some benefit); piroxicam may be helpful for palliation.
Tongue margin (dog)	Ulcerated/on margin of tongue	Malignant, locally invasive	Surgical resection of tongue/radiotherapy; piroxicam may be helpful for palliation.
Base of tongue (cat)	Ulcerated/at base of tongue	Malignant, locally invasive	None (radiotherapy of tongue may be used palliatively).
Malignant Melanoma	Gray, black, or pink; can be smooth, usually fleshy/on gum, tongue, or palate	Very malignant, early metastases to lungs	Surgery and/or radiation therapy for local control. For systemic control, carboplatin chemotherapy has been used with limited success.
Fibrosarcoma	Pink and fleshy/on palate or gums	Malignant, very invasive locally	Wide surgical resection (radiation may be of some value in selected cases after surgical excision). Biologically high-grade, histologically low-grade tumors in young Labradors, Golden Retrievers, and German Shepherd Dogs may have higher metastatic potential).
Acanthomatous Ameloblastoma (Epulis)	Pink and fleshy/on gum or rostral mandible	Benign, locally invasive into bone	Surgical resection ± radiation for gross or microscopic disease. Must remove associated tooth and dental ligament.
Fibromatous Epulis	Pink, fleshy, solitary or multiple/on gums	Benign	Surgical resection, must remove associated tooth and dental ligament
Ossifying Epulis	Pink, fleshy, solitary or multiple/on gums	Benign	Surgical resection, must remove associated tooth and dental ligament
Papillomatosis	Pink or white, cauliflower-like, multiple/seen anywhere	Benign; malignant transformation to squamous cell carcinoma may occur rarely.	Nothing, surgical resection or cryotherapy
Plasmacytoma	Fleshy or ulcerated growth on gingiva	Malignant, locally invasive, rarely metastasizes	Surgical resection and/or radiation or melphalan chemotherapy

and can cytologically resemble fibrosarcomas, carcinomas, or undifferentiated round cell tumors. Biopsy and subsequent histopathologic analysis may be required for a definitive diagnosis.

Treatment and Prognosis

The preferred therapeutic approach in dogs with confirmed malignant neoplasms of the oral cavity and lack of clinically detectable metastases is wide, aggressive surgical excision of the mass and surrounding tissues (e.g., mandibulectomy, maxillectomy) and/or radiation. Enlarged regional lymph nodes should be excised and evaluated histopathologically, even if they are cytologically negative for neoplasia. Early complete excision (especially gingival or hard palate squamous cell carcinomas and acanthomatous epulides) may be curative. Sometimes, fibrosarcomas can be cured if diagnosed early and resected completely (i.e., 3 cm margins). However, young Labrador Retrievers and Golden Retrievers in particular tend to have a histologically low-grade but biologically high-grade subtype of fibrosarcoma, which has a very high metastatic rate. Melanomas have metastatic rates of 60% to 80%, making surgical cure extremely rare. Rostral tumors tend to have a better prognosis, probably because they are diagnosed earlier than more caudal tumors. Acanthomatous ameloblastomas may respond to radiation therapy alone (complete surgical excision is preferred), and squamous cell carcinomas or fibrosarcomas with residual postoperative disease may benefit from postoperative adjunctive radiation therapy. Lingual squamous cell carcinomas affecting the base of the tongue and tonsillar carcinomas have a very poor prognosis; complete excision or irradiation usually causes severe morbidity. Melanomas metastasize early and have a very guarded prognosis. Chemotherapy is usually not beneficial in dogs with squamous cell carcinoma, acanthomatous ameloblastomas, or melanoma. Piroxicam can palliate some patients with squamous cell carcinoma. Combination chemotherapy may palliate some dogs with fibrosarcomas (see Chapter 76). Radiotherapy plus hyperthermia has been successful in some dogs with oral fibrosarcoma. In all cases, an oncologist should be consulted.

Papillomatosis usually resolves spontaneously, although it may be necessary to resect some of the masses if they interfere with eating. Rarely there may be malignant transformation to squamous cell carcinoma. Fibromatous epulides may be resected if they cause problems.

NEOPLASMS OF THE ORAL CAVITY IN CATS

Etiology

Tumors of the oral cavity are less common in cats than in dogs, but they are almost all malignant and are usually squamous cell carcinomas that are diagnosed and treated as described for dogs. Cats are different from dogs in that they also have sublingual squamous cell carcinomas and eosinophilic granulomas (which mimic carcinoma but have a much better prognosis).

Clinical Features

Dysphagia, halitosis, anorexia, and/or bleeding are common features of these tumors.

Diagnosis

A large, deep biopsy specimen is needed because it is crucial to differentiate malignant tumors from eosinophilic granulomas. The superficial aspect of many oral cavity masses is ulcerated and necrotic because of proliferation of normal oral bacterial flora, making it difficult to accurately diagnose a mass when deep tissue samples are not obtained.

Treatment

Surgical excision is desirable, but cats often do not tolerate aggressive oral surgery as well as dogs do. Long-term or permanent feeding tubes may be required. Radiation therapy and/or chemotherapy may benefit cats with incompletely excised squamous cell carcinomas not involving the tongue or tonsil.

Prognosis

In general, the prognosis for cats with oral squamous cell carcinoma is poor (see Chapter 81).

FELINE EOSINOPHILIC GRANULOMA

Etiology

The cause of feline eosinophilic granuloma is uncertain. Hypersensitivity reactions are thought to be responsible, and a genetic predisposition has been suggested.

Clinical Features

Feline eosinophilic granuloma complex includes indolent ulcer, eosinophilic plaque, and linear granuloma, but it has not been established that these diseases are related. Indolent ulcers are classically found on the lip or oral mucosa (especially the maxillary canine teeth) of middle-aged cats. Eosinophilic plaque usually occurs on the skin of the medial thighs and abdomen. Linear granuloma is typically found on the posterior aspect of the rear legs of young cats but may also occur on the tongue, palate, and oral mucosa. Severe oral involvement of an eosinophilic ulcer or plaque typically produces dysphagia, halitosis, and/or anorexia. Eosinophilic granuloma may affect the chin and paw pads in addition to the mouth.

Diagnosis

An ulcerated mass may be found at the base of the tongue or on the hard palate, the glossopalatine arches, or anywhere else in the mouth. A deep biopsy specimen of the mass is necessary for accurate diagnosis. Peripheral eosinophilia is inconsistently present.

Treatment

Systemic antibiotics directed against *Staphylococcus* spp. (e.g., amoxicillin plus clavulanic acid, trimethoprim-sulfa combinations) are often effective in treating indolent

ulcers and eosinophilic plaque. If antibiotics are ineffective, then high-dose glucocorticoid therapy (oral prednisolone, 2.2-4.4 mg/kg/day) can be used, but cyclosporine seems to be the most effective treatment for indolent ulcers and plaque not responding to antibiotics. Some cats are best treated with methylprednisolone acetate injections (20 mg every 2-3 weeks as needed) instead of oral medications. Although effective, megestrol acetate may cause diabetes mellitus, mammary tumors, and uterine problems, and should not be used except under exceptional circumstances.

Prognosis

The prognosis is good, but the lesion can recur.

GINGIVITIS/PERIODONTITIS

Etiology

Bacterial proliferation and toxin production, usually associated with tartar buildup, destroy normal gingival structures and produce inflammation. Immunosuppression caused by feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and/or feline calicivirus might predispose to this disease.

Clinical Features

Dogs and cats may be affected. Many are asymptomatic, but halitosis, oral discomfort, refusal to eat, dysphagia, drooling, and tooth loss may occur.

Diagnosis

Visual examination of the gums reveals hyperemia around the tooth margins. Gingival recession may reveal tooth roots. Accurate diagnosis can be made through probing and oral radiographs. The stage of periodontal disease is defined by radiographs.

Treatment

Supragingival and subgingival tartar should be removed, and the crowns should be polished. Antimicrobial drugs effective against anaerobic bacteria (e.g., amoxicillin, clindamycin, metronidazole; see Drugs Used in Gastrointestinal Disorders table, pp. 515-517) may be used before and after cleaning teeth. Regular brushing of the teeth and/or oral rinsing with a veterinary chlorhexidine solution formulated for that purpose helps control the problem.

Prognosis

The prognosis is good with proper therapy.

STOMATITIS

Etiology

There are many causes of canine and feline stomatitis (Box 29.1). The clinician should always consider the possibility of immunosuppression with secondary stomatitis (e.g., FeLV, FIV, diabetes mellitus, hyperadrenocorticism).

BOX 29.1

Common Causes of Stomatitis

Renal failure (primarily with severe, acute renal injury)
Trauma
- Foreign objects
- Chewing or ingesting caustic agents
- Chewing on electrical cords

Immune-mediated disease
- Pemphigus

Chronic ulcerative paradental stomatitis (especially Maltese Terriers)
Upper respiratory viruses (feline viral rhinotracheitis, feline calicivirus)
Infection secondary to immunosuppression (feline leukemia virus, feline immunodeficiency virus)
Tooth root abscesses
Severe periodontitis
Osteomyelitis
Thallium intoxication (very rare)

Clinical Features

Most dogs and cats with stomatitis have thick ropey saliva, severe halitosis, and/or anorexia caused by pain. Some animals are febrile and lose weight.

Diagnosis

A thorough oral examination usually requires anesthesia. Stomatitis is diagnosed by gross observation of the lesions, but an underlying cause should be sought. Biopsy is routinely indicated, as are routine clinical pathology data and radiographs of the mandible and maxilla, including the tooth roots. Bacterial culture is not helpful.

Treatment

Therapy is both symptomatic (to control signs) and specific (i.e., directed at the underlying cause). Thorough teeth cleaning and aggressive antibacterial therapy (i.e., systemic antibiotics effective against aerobes and anaerobes, cleansing oral rinses with antibacterial solutions such as chlorhexidine) often help. In some animals extracting teeth associated with the most severely affected areas may help. Bovine lactoferrin has been suggested to ameliorate otherwise resistant lesions in cats.

Prognosis

The prognosis depends on the underlying cause.

FELINE LYMPHOCYTIC-PLASMACYTIC GINGIVITIS AND PHARYNGITIS/ CAUDAL STOMATITIS

Etiology

An idiopathic disorder, feline lymphocytic-plasmacytic gingivitis might be caused by feline calicivirus, *Bartonella henselae,* immunodeficiency from FeLV or FIV infection, or any

stimulus-producing sustained gingival inflammation. Cats might have an excessive oral inflammatory response that can produce marked gingival proliferation.

Clinical Features

Hyporexia and/or halitosis are the most common signs. Affected cats grossly have reddened gingiva around the teeth and/or posterior pillars of the pharynx (the latter is not seen with gingivitis). The gingiva may be obviously proliferative in severe cases and bleed easily. Dental neck lesions often accompany the gingivitis. Teeth chattering is also occasionally seen.

Diagnosis

Biopsy of affected (especially proliferative) gingiva is needed for diagnosis. Histologic evaluation reveals a lymphocytic-plasmacytic infiltration. Serum globulin concentrations may be increased. Checking for FeLV and FIV infection is important, and virus isolation from biopsied tissue may be helpful.

Treatment

There is currently no reliable therapy for this disorder. Proper cleaning and polishing of teeth and antibiotic therapy effective against anaerobic bacteria may help. High-dose glucocorticoid therapy (e.g., prednisolone, 2.2 mg/kg/day, methylprednisolone 10-20 mg subcutanenous (SC), triamcinolone 0.2 mg/kg orally [PO] daily) is often useful. In some severe cases, multiple tooth extractions (especially premolars and molars) may alleviate the source of the inflammation, in which case it is important that the root and periodontal ligament also be removed. Extraction of the canine teeth should be avoided if possible. Immunosuppressive drugs such as chlorambucil or cyclosporine (initially give 2-4 mg/kg PO bid, but then adjust based upon blood levels) may also be tried in obstinate cases.

Prognosis

The prognosis is guarded; severely affected animals often do not respond well to therapy.

DYSPHAGIAS

MASTICATORY MUSCLE MYOSITIS/ATROPHIC MYOSITIS

Etiology

Masticatory muscle myositis/atrophic myositis is an idiopathic immune-mediated disorder that affects muscles of mastication in dogs. The syndrome has not been reported in cats.

Clinical Features

In the acute stages, the temporalis and masseter muscles may be swollen and painful. However, many dogs are not presented until the muscles are severely atrophied and the mouth cannot be opened.

Diagnosis

Atrophy of temporalis and masseter muscles and inability to open the dog's mouth while anesthetized allow the clinician to establish a presumptive diagnosis. Histopathology (preferably with immunohistochemistry) of the temporalis and masseter muscles confirms the diagnosis. Finding antibodies to type 2M fibers strongly supports this diagnosis. Animals may have increased serum creatine kinase (CK) activity.

Treatment

High-dose prednisolone therapy (2.2 mg/kg/day) with or without azathioprine (50 mg/m^2 q48h) typically controls acute disease but is seldom helpful in patients with chronic disease that cannot open their mouths. Once control has been achieved, the prednisolone is administered every 48 hours and then the dose of prednisolone is tapered to avoid adverse effects. However, this tapering must be done slowly to prevent recurrence (see the section on immunosuppressive drugs in Chapter 72). If the mouth cannot be opened even under anesthesia, a gastrostomy tube may be used. Although some clinicians have used force to break the adhesions in chronic cases, this approach may cause mandibular fracture and is not recommended.

Prognosis

The prognosis is usually good for acute cases, but continued medication may be needed.

CRICOPHARYNGEAL ACHALASIA/DYSFUNCTION

Etiology

The cause of cricopharyngeal achalasia/dysfunction is unknown, but it is usually congenital. There is an incoordination between the cricopharyngeus muscle and the rest of the swallowing reflex, which produces obstruction at the cricopharyngeal sphincter during swallowing (i.e., the sphincter does not open at the proper time). The problem has a genetic basis in Golden Retrievers.

Clinical Features

Primarily seen in young dogs, cricopharyngeal achalasia rarely occurs as an acquired disorder. The major sign is regurgitation immediately after or concurrent with swallowing. Some animals become hyporexic, and severe weight loss occurs. Clinically this condition may closely mimic pharyngeal dysphagia.

Diagnosis

Definitive diagnosis requires fluoroscopy or cinefluoroscopy while the animal is swallowing barium or other contrast media. A young animal regurgitating food immediately on swallowing is suggestive of the disorder, but pharyngeal dysphagia with normal cricopharyngeal sphincter function must be differentiated from cricopharyngeal disease.

Treatment

Injection of the cricopharyngeal muscle with botulism toxin benefits some patients, and it is believed that these patients stand to improve the most from cricopharyngeal myotomy, whereas those that do not respond to botulinum toxin seem to respond poorly to surgery. If surgery is performed, be careful not to cause cicatrix at the surgery site. It is critical that this disorder is distinguished from pharyngeal dysphagia and that esophageal function in the cranial esophagus is evaluated before surgery is considered (see next section on pharyngeal dysphagia). Treatment with thyroxine might rarely help some patients.

Prognosis

The prognosis is usually good if cicatrix does not occur postoperatively.

PHARYNGEAL DYSPHAGIA

Etiology

Pharyngeal dysphagia is primarily an acquired disorder with neuropathies, myopathies, and junctionopathies (e.g., localized myasthenia gravis) seeming to be the main causes. Inability to form a normal bolus of food at the base of the tongue and/or propel the bolus into the esophagus is often associated with lesions of cranial nerves IX or X. Simultaneous dysfunction of the cranial esophagus may cause food retention just caudal to the cricopharyngeal sphincter.

Clinical Features

Although pharyngeal dysphagia principally is found in adults, younger animals occasionally have transient signs. Pharyngeal dysphagia often clinically mimics cricopharyngeal achalasia; regurgitation is associated with swallowing. Pharyngeal dysphagia sometimes causes more difficulty swallowing fluids than solids. Aspiration (especially associated with liquids) is common because the proximal esophagus is often flaccid and retains food and water, predisposing to later reflux into the pharynx.

Diagnosis

Fluoroscopic examination of the patient swallowing barium is typically required for diagnosis. An experienced radiologist is needed to reliably distinguish pharyngeal dysphagia from cricopharyngeal dysphagia. With the former condition the animal does not have adequate strength to push food boluses into the esophagus, whereas in the latter the animal has adequate strength but the cricopharyngeal sphincter stays shut or opens at the wrong time during swallowing, thereby preventing normal movement of food from the pharynx to the proximal esophagus. Serum CK may be increased in some patients with myopathies. Some causes may be detected by electromyography of laryngeal, pharyngeal, and esophageal muscles and/or muscle biopsy.

Treatment

Cricopharyngeal myotomy is often curative for animals with cricopharyngeal achalasia but can be disastrous for animals with pharyngeal dysphagias because it allows food retained in the proximal esophagus to more easily reenter the pharynx and be aspirated. The clinician must either bypass the pharynx (e.g., gastrostomy tube) or resolve the underlying cause (e.g., control the myopathy, junctionopathy, or neuropathy).

Prognosis

Prognosis is guarded because it is often difficult to characterize and treat the underlying cause, and the dog or cat is prone to progressive weight loss and recurring aspiration pneumonia.

ESOPHAGEAL WEAKNESS/ MEGAESOPHAGUS

CONGENITAL ESOPHAGEAL WEAKNESS

Etiology

The cause of congenital esophageal weakness (i.e., congenital megaesophagus) is uncertain, but a defect in vagal afferent innervation of the esophagus is suspected.

Clinical Features

Affected animals (primarily dogs) are usually presented because of "vomiting" (actually regurgitation) with or without weight loss, coughing, or fever from pneumonia. Occasionally, coughing and other signs of aspiration tracheitis and/or pneumonia may be the only signs reported by the owner. In particularly severe cases, one may see the cervical esophagus balloon in and out during respiration (Video 29.1).

Diagnosis

The clinician must first determine from the history that regurgitation is likely, instead of vomiting (see p. 391). Radiographs showing generalized esophageal dilation without evidence of obstruction (see Fig. 27.3, *A*) allow presumptive diagnosis of esophageal weakness. If plain thoracic radiographs are not revealing, then static or dynamic barium contrast radiographs are appropriate because many patients with esophageal weakness do not have abnormalities on plain radiographs. Fluoroscopic examination is required to distinguish idiopathic congenital esophageal weakness from lower esophageal achalasia; however, the latter is thought to be very uncommon. The esophageal deviation normally seen in brachycephalics (Fig. 29.1) must not be confused with esophageal pathology. Diverticula in the cranial thorax caused by esophageal weakness occur occasionally and can be confused with vascular ring obstruction (Fig. 29.2). Congenital rather than acquired disease is suspected if the regurgitation and/or aspiration began when the pet was young. If clinical features have

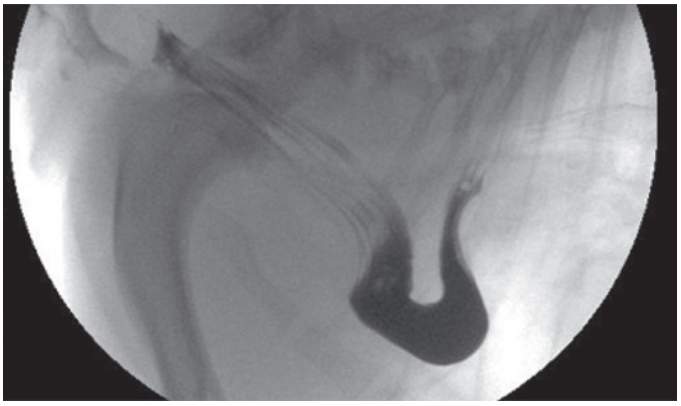


FIG 29.1
Lateral contrast radiograph of a Boston Terrier showing esophageal deviation, which is normal in brachycephalic breeds.

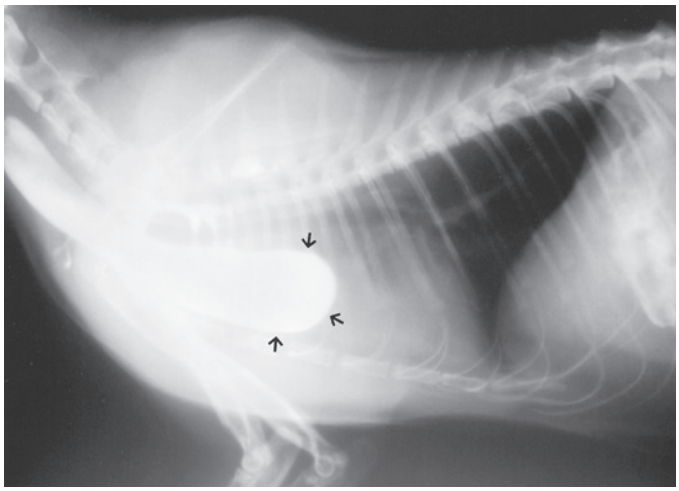


FIG 29.2
Lateral contrast thoracic radiograph of a cat. Note large diverticulum suggestive of obstruction *(arrows)*. This cat had generalized esophageal weakness without obstruction.

been relatively mild or intermittent, the diagnosis might not be made until the animal is older, but a careful history should suggest that disease has been present since the animal was young. Endoscopy is not as useful as contrast radiographs for diagnosing this disorder. In general, only very severe esophageal weakness may be diagnosed endoscopically (Video 29.1). Collies may have dermatomyositis, which also causes esophageal weakness. Some breeds (e.g., Miniature Schnauzer, Great Dane, Dalmatian, Chinese Shar-Pei, Irish Setter, Labrador Retriever) appear to be at increased risk.

Treatment

Congenital esophageal weakness currently cannot be cured or resolved by medical therapy, although cisapride (0.1-0.5 mg/kg) occasionally ameliorates signs (probably because it increases lower esophageal sphincter [LES] pressure in patients with substantial, concomitant gastroesophageal reflux). Dietary/feeding management is used to try to prevent further dilation and aspiration. The animal is fed from an elevated platform that requires the pet to stand on its rear legs making the cervical and thoracic esophagus nearly vertical so that gravity aids food passing through the esophagus and into the stomach. This position should be maintained for 5 to 10 minutes after the animal has finished eating and drinking. There are devices (e.g., "Bailey chair"; see http://petprojectblog.com/archives/dogs/megaesophagus-and-the-bailey-chair/) that aid the owner in keeping the patient vertical while feeding. Feeding several small meals a day also helps prevent esophageal retention.

Gruel is usually recommended, but some animals do better if fed dry or canned dog food. It is impossible to predict what consistency of food will be best for a given dog; therefore, trial and error are necessary. In some dogs the dilated esophagus may partially return to normal size and function. Even if the esophagus remains dilated, some dogs may be well managed by dietary/feeding modification and have a good quality of life.

In animals with severe aspiration, gastrostomy tubes can be used to bypass the esophagus, and some animals with gastrostomy tubes respond well for varying periods of time. These animals may still regurgitate saliva and also food if there is gastroesophageal reflux. Intermittent suctioning of the esophagus at home can be done in desperate situations.

Prognosis

The prognosis is hard to accurately predict. If the owners are aggressive about experimenting with different dietary consistencies and keeping the patient vertical after eating/drinking, some animals respond well. Others develop aspiration pneumonia despite all treatment efforts. Aspiration pneumonia is the major cause of death.

ACQUIRED ESOPHAGEAL WEAKNESS

Etiology

Acquired esophageal weakness in dogs is usually caused by a neuropathy, myopathy, or junctionopathy (e.g., myasthenia gravis; see Box 26.5). German Shepherds, Golden Retrievers, and Irish Setters might have increased risk. Dogs with idiopathic laryngeal paralysis often have cervical esophageal weakness, probably due to a generalized neuropathy. In cats, esophagitis may cause acquired esophageal weakness.

Clinical Features

Acquired esophageal weakness primarily occurs in dogs. Patients usually are presented because of "vomiting" (actually regurgitation), but some dogs present with respiratory signs (e.g., cough) and no history of regurgitation. Sometimes very small amounts of material are regurgitated into the pharynx where it is aspirated but never expelled. In other cases, material is expelled but re-swallowed or re-eaten by the animal (Fig. 29.3 *A,B*). Weight loss may occur if sufficient calories are lost by regurgitation.

Diagnosis

The initial diagnostic step is to document that regurgitation rather than vomiting is occurring (see p. 391). Acquired esophageal weakness is usually diagnosed by finding generalized esophageal dilation without evidence of obstruction on plain or contrast imaging (see Fig. 27.3, *A*). Severity of clinical signs does not always correlate with the magnitude of radiographic changes. It is important to note that plain thoracic radiographs may not reveal esophageal weakness; barium contrast esophagrams are indicated if esophageal regurgitation is suspected but the plain films appear normal (Fig. 29.3 *A,B*). Some symptomatic animals have segmental weakness primarily affecting the cervical esophagus, just behind the cricopharyngeus muscle (Video 29.2). Normal dogs often have minimal amounts of barium retained in this location, so it is important to distinguish insignificant from clinically important retention. Lower esophageal spasm and stricture very rarely radiographically mimic esophageal weakness. Ideally, fluoroscopy should be used to look for evidence of gastroesophageal reflux, which may benefit from prokinetic therapy (e.g., cisapride).

It is important to search for underlying causes of acquired esophageal weakness (see Box 26.5). The titer of antibodies to acetylcholine receptors (indicative of myasthenia gravis) should be measured in dogs. "Localized" myasthenia may affect only the esophagus and/or oropharyngeal muscles. Rare patients test negative initially but positive if retested months later. Resting serum cortisol measurements are indicated to screen for otherwise occult hypoadrenocorticism

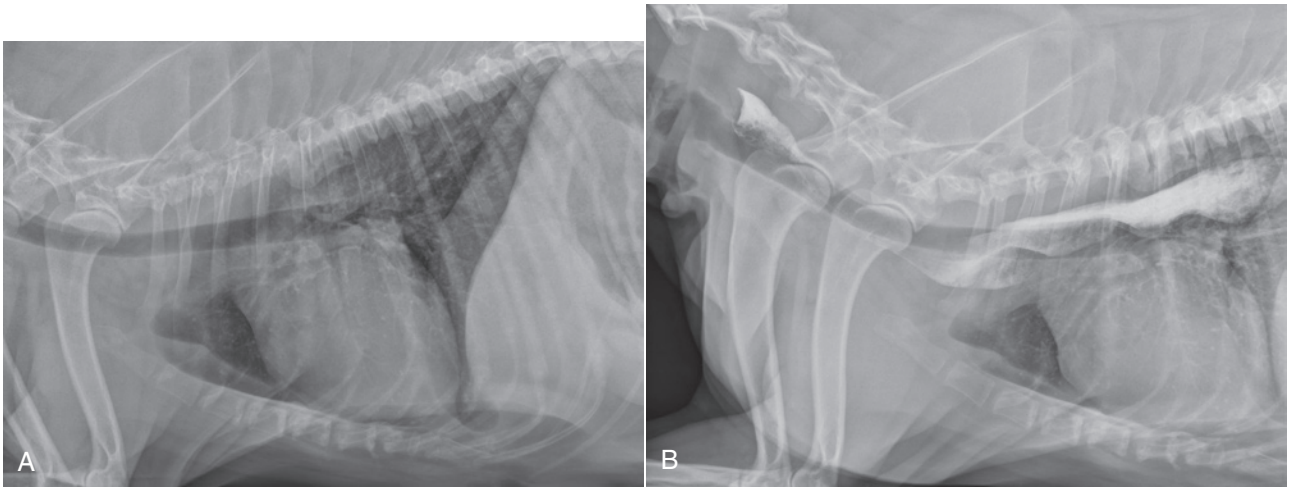


FIG 29.3
(A) Lateral radiograph of a dog with a severe cough but no history of regurgitation. There is no evidence of esophageal pathology. **(B)** A barium-contrast esophagram of the same dog showing major retention of the barium due to acquired esophageal weakness.

(even if serum electrolyte concentrations are normal; see Chapter 50). Electromyography may reveal generalized neuropathies or myopathies. Dysautonomia occurs occasionally and is suspected on the basis of clinical signs (i.e., dilated colon, dry nose, dilated pupils, keratoconjunctivitis sicca, and/or bradycardia that responds poorly to atropine). Gastric outflow obstruction in cats can cause intractable vomiting with secondary esophagitis producing megaesophagus. Other causes are rarely found (see Box 26.5). If an underlying cause cannot be found, the disease is termed *idiopathic acquired esophageal weakness* (i.e., idiopathic acquired megaesophagus).

Treatment

Dogs with acquired megaesophagus caused by hypoadrenocorticism typically respond well to glucocorticoid replacement (see Chapter 50). Localized myasthenia typically responds to pyridostigmine, which is preferred to physostigmine and neostigmine (see Chapter 66). Adjunctive immunosuppressive therapy with azathioprine may be helpful in some patients not responding well to pyridostigmine, but it is not clear that combination therapy is always superior to pyridostigmine alone. Glucocorticoid therapy is not recommended. Gastroesophageal reflux may respond to prokinetic and antacid therapy (cisapride at 0.1-0.5 mg/kg PO q8-12h and omeprazole at 1-2 mg/kg PO q12h are preferred). If the disease is idiopathic, conservative dietary therapy as described for congenital esophageal weakness is the only recourse. Some dogs with congenital esophageal weakness regain variable degrees of esophageal function, but this is less common with idiopathic acquired esophageal weakness. Severe esophagitis may cause secondary esophageal weakness, which resolves after appropriate therapy (discussed in more detail later in this chapter). In severely affected patients not responding adequately to dietary/feeding modifications, gastrostomy tubes may diminish the potential for aspiration, ensure positive nitrogen balance, and allow for administration of oral drugs. Some dogs benefit from the long-term use of a gastrostomy tube, but others continue to regurgitate and aspirate due to severe gastroesophageal reflux or accumulation of saliva in the esophagus.

Prognosis

All animals with acquired esophageal weakness are at risk for aspiration pneumonia and sudden death. If the underlying cause can be treated and the esophageal dilation and weakness can be resolved, the prognosis is often good because the risk of aspiration is eliminated. The prognosis is worse in patients with aspiration pneumonia and those with idiopathic megaesophagus that are older than 13 months of age at the time of onset of clinical signs because they are less likely to experience spontaneous remission. The prognosis is also poor for patients that fail to respond to dietary/feeding management. The size of the esophageal dilation on radiographs is not clearly associated with prognosis.

ESOPHAGITIS

Etiology

Esophagitis is principally caused by gastroesophageal reflux, persistent vomiting of gastric acid, esophageal foreign objects, and caustic agents. Medicines, especially tetracyclines, clindamycin, ciprofloxacin, and nonsteroidal antiinflammatory drugs (NSAIDs) may cause severe esophagitis if they are retained in the esophagus because they are not washed down with water or food (especially in cats).

Gastroesophageal reflux during anesthesia can produce severe esophagitis with subsequent stricture formation. It is impossible to predict which animals will reflux during anesthesia. Various factors have been suggested to place patients at increased risk for anesthesia-associated reflux, but none has consistently had a strong association that can be used clinically. An association between distal esophagitis (ostensibly caused by gastroesophageal reflux) and upper respiratory disease in brachycephalic dogs has been suggested. Eosinophilic esophagitis is rare and has uncertain causes in dogs. Pythiosis can cause severe esophagitis (see p. 484).

Clinical Features

Signs depend upon the severity of the inflammation. Regurgitation is expected, although anorexia and drooling due to refusal to swallow may predominate if swallowing is too painful. If a caustic agent (e.g., disinfectant) is ingested, the mouth and tongue are often hyperemic and/or ulcerated; hyporexia may be the primary sign.

Diagnosis

A history of vomiting followed by a change in character that sounds more like regurgitation suggests esophagitis secondary to excessive exposure to vomited gastric acid (e.g., dogs with parvoviral enteritis or foreign body obstruction). Regurgitation or hyporexia beginning shortly after an anesthetic procedure may indicate esophagitis caused by reflux. Plain and contrast radiographs may reveal hiatal hernias, gastroesophageal reflux, or esophageal foreign bodies. Contrast esophagrams do not reliably detect esophagitis (sometimes there is slight barium retention by the roughed, irregular mucosa), but contrast enhanced fluoroscopy can be definitive for gastroesophageal reflux in some cases (Video 29.3). Typically esophagoscopy is needed to diagnose esophagitis (Fig. 27.11).

Treatment

Decreasing gastric acidity, preventing reflux of gastric contents into the esophagus, and protecting the denuded esophagus are the hallmarks of treatment. Proton pump inhibitors (e.g., omeprazole) are far superior to histamine-2 (H_2) receptor antagonists for decreasing gastric acidity, a critical factor in these animals. Metoclopramide stimulates gastric emptying, resulting in less gastric volume to reflux into the esophagus; its main advantage is that it can be given intravenously. Cisapride (0.1-0.5 mg/kg) is a more effective prokinetic but must be given orally. Erythromycin and ranitidine also have

some prokinetic activity. Sucralfate (particularly suspensions) might protect denuded esophageal mucosa if there is gastroesophageal reflux (see Table 28.5), but its main value is to provide some analgesia for the discomfort of the esophagitis. For dogs in a lot of pain that will not even swallow their saliva, viscous lidocaine, which is available over the counter, may be administered orally. Antibiotics are of dubious value. In exceptional cases, a gastrostomy feeding tube protects the esophagus while the mucosa is healing and ensures a positive nitrogen balance. Glucocorticoids may be administered in an attempt to prevent cicatrix, but there is no evidence that they are effective Symptomatic hiatal hernias may have to be surgically repaired.

Proton pump inhibitors and prokinetics may be administered prophylactically to lessen anesthesia-associated reflux with subsequent esophagitis. Although such therapy lessens the frequency of acid reflux, it does not abolish it.

Prognosis

The prognosis depends on the severity of the esophagitis and whether an underlying cause can be identified and controlled. Early aggressive therapy helps prevent cicatrix formation.

HIATAL HERNIA

Etiology

Hiatal hernia is a diaphragmatic abnormality that allows part of the stomach (usually the cardia) to prolapse into the thoracic cavity. It may also allow gastroesophageal reflux.

Clinical Features

Brachycephalic breeds seem predisposed to this disorder. Regurgitation is the primary sign in symptomatic individuals, but some animals are asymptomatic.

Diagnosis

Plain radiographs or positive-contrast esophagrams may reveal gastric herniation into the thorax (Fig. 29.4); however, herniation may be intermittent and difficult to detect. Manually putting pressure on the abdomen while taking a radiograph may cause displacement of the stomach into the thorax during the study. Hiatal hernias are occasionally found endoscopically, but the endoscopic appearance can be subtle and is easily missed by novice endoscopists.

Treatment

If the hiatal hernia is symptomatic at an early age, surgery is more likely to be required to correct it. If clinical signs of hiatal hernia first appear later in life, aggressive medical management of gastroesophageal reflux (e.g., cisapride, omeprazole) is sometimes sufficient. If medical management is unsuccessful, surgery can be considered.

Prognosis

The prognosis is often good after surgical repair (congenital cases) or aggressive medical management (acquired cases).

DYSAUTONOMIA

Etiology

Dysautonomia in dogs and cats is an idiopathic condition that causes loss of autonomic nervous system function. In at least some circumstances (e.g., Key-Gaskell syndrome of cats), it might be due to a clostridial toxin.

Clinical Features

Clinical signs vary substantially. Megaesophagus and subsequent regurgitation are common but not invariable. Dysuria and a distended urinary bladder, mydriasis and lack of pupillary light response, dry mucous membranes, weight loss, constipation, vomiting, poor anal tone, and/or anorexia have all been reported.

Diagnosis

Dysautonomia is usually first suspected clinically by finding dysuria, dry mucous membranes, and abnormal pupillary light responses. Radiographs revealing distention of multiple areas of the alimentary tract (e.g., esophagus, stomach, small intestine) also are suggestive. A presumptive antemortem diagnosis is usually made by observing the effects of pilocarpine on pupil size after 1 to 2 drops of 0.05% pilocarpine are placed in one eye only. Finding that the treated eye rapidly constricts whereas the untreated eye does not is consistent with dysautonomia. Similarly, finding that a dysuric dog with a large urinary bladder can urinate after subcutaneous administration of 0.04 mg bethanechol/kg is also suggestive (although not all affected animals respond). Definitive diagnosis requires histopathology of autonomic ganglia obtained at necropsy.

Treatment

Treatment is palliative. Bethanechol can be given (2.5-15 mg once daily) to aid in urinary evacuation. The urinary bladder should be expressed as needed. Gastric prokinetics (e.g., cisapride) may help lessen vomiting. Antibiotics may be administered for aspiration pneumonia secondary to megaesophagus.

Prognosis

The prognosis is usually grim.

ESOPHAGEAL OBSTRUCTION

VASCULAR RING ANOMALIES

Etiology

Vascular ring anomalies are congenital defects. An embryonic aortic arch persists, trapping the esophagus in a ring of tissue. Persistent right fourth aortic arch (PRAA) is the most commonly recognized vascular anomaly (see Chapter 5).

Clinical Features

Vascular ring anomalies occur in dogs and cats. Regurgitation is the most common presenting complaint, although

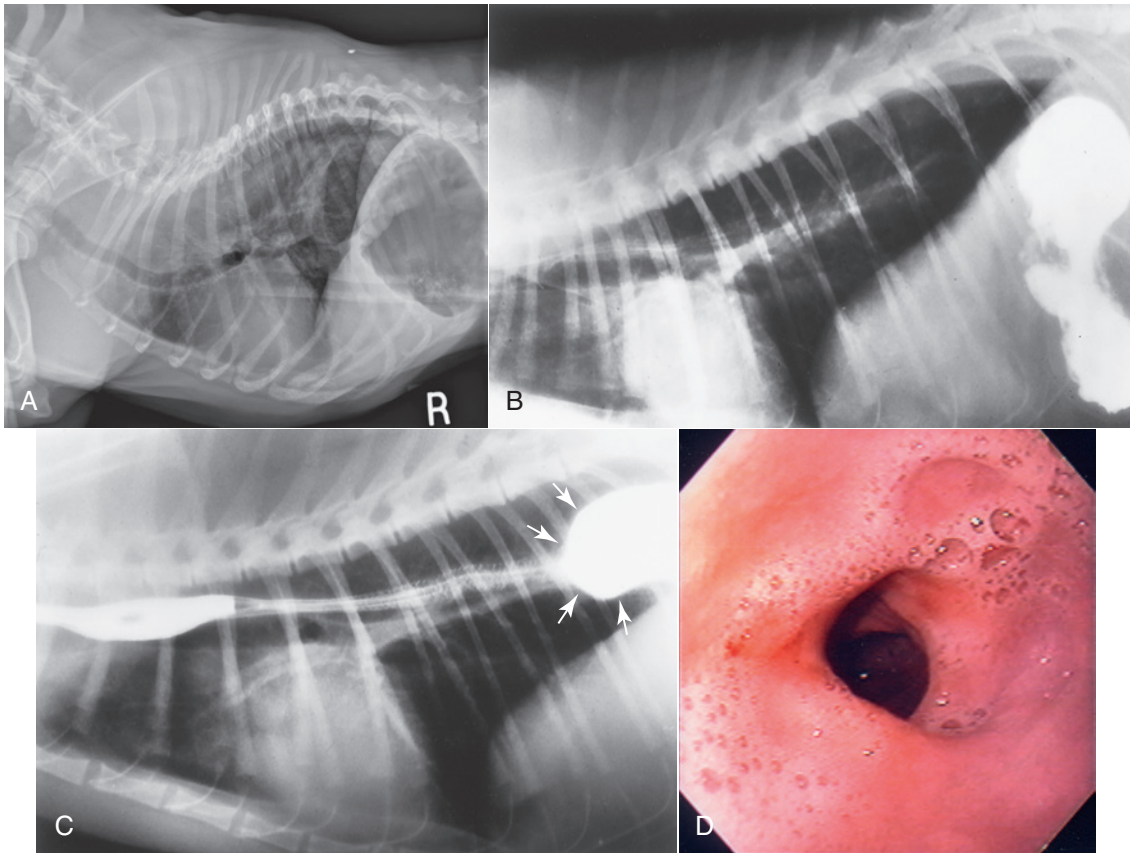


FIG 29.4
(A) Lateral radiograph of a dog with a hiatal hernia showing the gastric shadow extending cranial to the diaphragm. **(B)** Lateral view of contrast esophagram of a cat with hiatal hernia. There is no evidence of hernia on this radiograph because it has apparently slid back into the abdomen. **(C)** Lateral view of contrast esophagram of the cat in **B.** The body of the stomach has now slid into the thoracic cavity *(arrows),* confirming that a hiatal hernia is present. **(D)** An endoscopic image of the lower esophageal sphincter (LES) area of a dog with a hiatal hernia. Gastric rugal folds can be seen. (**A,** Courtesy Dr. Russ Stickle, Michigan State University, East Lansing, Mich. **B** and **C,** Courtesy Dr. Royce Roberts, University of Georgia, Athens, Ga.)

aspiration (i.e., coughing or dyspnea) may occur. Clinical features often begin shortly after the animal eats solid food for the first time. However, some animals have relatively minor clinical signs and are not diagnosed until they are several years old or only if they are obstructed by an esophageal foreign body.

Diagnosis

Definitive diagnosis is usually made by contrast esophagram (see Fig. 27.3, *B*). Typically the esophagus cranial to the heart is dilated, whereas the esophagus caudal to the heart is normal. In rare cases the entire esophagus is dilated (the result of concurrent megaesophagus) except for a narrowing at the base of the heart. It has been suggested that if focal leftward deviation of the trachea is seen at the cranial border of the heart in the ventrodorsal or dorsoventral projections, this is sufficient to diagnose PRAA in young dogs that are regurgitating food. However, it is easy to misdiagnose PRAA with radiographs; therefore, advanced imaging (e.g., contrast thoracic CT) is recommended before surgery. Endoscopically, the esophagus has an extramural narrowing (Fig. 29.5; i.e., not a mucosal proliferation or scar) near the base of the heart.

Treatment

Surgical resection of the anomalous vessel is necessary. Conservative dietary management (i.e., gruel diet) by itself is inappropriate because the dilation will probably progress. In particular, the animal will be at risk for foreign body occlusion at the site of the PRAA.

Prognosis

Most patients improve dramatically after surgery, but some have minimal to no improvement, probably because of concomitant esophageal weakness. A guarded prognosis is appropriate. If a postsurgical stricture occurs, esophageal ballooning or a second surgical procedure may be considered.

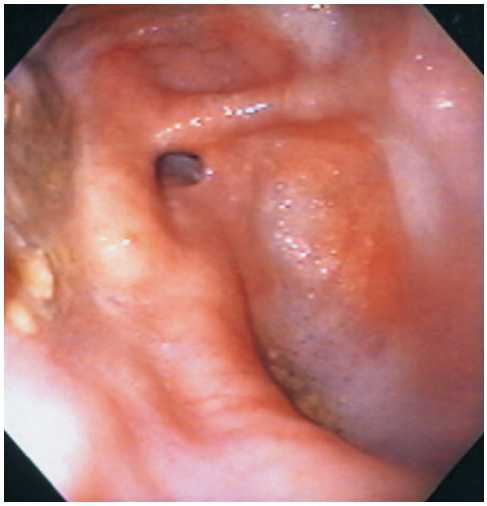


FIG 29.5
Endoscopic view of an esophageal lumen constricted by an extramural vascular ring anomaly. There is massive esophageal dilation cranial to the vascular ring, which "outlines" the trachea and the aorta. Not all vascular rings have such dilation allowing the endoscopist to see these structures so clearly.

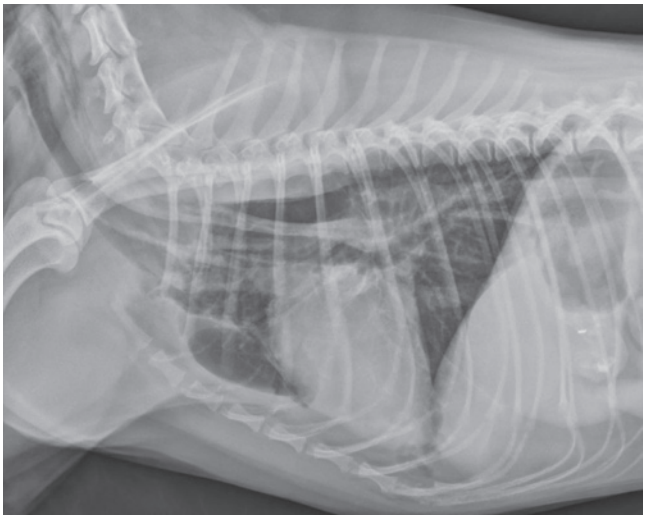


FIG 29.6
A lateral radiograph taken immediately after removing an esophageal foreign object, demonstrating pneumomediastinum and thus confirming that esophageal perforation has taken place.

ESOPHAGEAL FOREIGN OBJECTS

Etiology

Almost anything may lodge in the esophagus, but objects with sharp points (e.g., bones, fishhooks) are probably most common. Food boluses, hairballs, and chew toys can also be responsible. Most obstructions occur at the thoracic inlet, the base of the heart, or immediately in front of the diaphragm.

Clinical Features

Dogs are more commonly affected because of their less-discriminating eating habits. Regurgitation or hyporexia secondary to esophageal pain is common. Acute onset of regurgitation (as opposed to vomiting) is suggestive of esophageal foreign body. Clinical signs depend on where the obstruction occurs, whether it is complete or partial, how long the foreign body has been present, and whether esophageal perforation has occurred. Complete obstructions cause regurgitation of solids and liquids, whereas partial obstructions may allow retention of liquids. Acute dyspnea may indicate that the foreign object is impinging on airways at the base of the heart or that aspiration pneumonia has developed. Esophageal perforation usually causes fever, depression, and/or hyporexia; subsequent pleural effusion or pneumothorax/pneumomediastinum may cause dyspnea. Subcutaneous emphysema rarely occurs.

Diagnosis

Plain thoracic radiographs reveal most esophageal foreign bodies (see Fig. 27.2), although the clinician may have to search carefully to find poultry bones or other items that are relatively radiolucent. It is important to look for evidence of esophageal perforation (i.e., pneumomediastinum, pleural effusion, fluid in the mediastinum). Esophagrams are rarely necessary; esophagoscopy is diagnostic and typically therapeutic.

Treatment

Foreign objects are best removed endoscopically unless they are too firmly lodged to pull free or radiographs suggest perforation. Thoracotomy is generally indicated in these two situations. However, acute perforations due to a sharp foreign body (e.g., fish hook) may often be treated medically (see later). Objects that cannot be moved without substantial force should not be pulled vigorously because of the risk of creating or enlarging a perforation. During endoscopy, the esophagus should be insufflated carefully to avoid rupturing weakened areas, thereby causing tension pneumothorax. If the object is hard to retrieve and there are no sharp edges, the clinician may push it into the stomach where it can be retrieved via laparotomy or allowed to dissolve. Alternatively, one may pass a large Foley catheter past the foreign body, inflate the balloon so that it begins to distend the esophagus, and then pull the catheter (and the foreign body) out (Video 29.4). A lubricated Foley catheter can likewise be used to help open up the lower esophageal sphincter and make it easier to push a foreign object into the stomach.

After an object has been removed, the esophageal mucosa should be reexamined endoscopically to evaluate damage caused by the object. Thoracic radiographs should be repeated to look for indications of perforation (e.g., pneumomediastinum, pneumothorax) (Fig. 29.6). Proton pump inhibitors and prokinetic agents may be indicated post–foreign body removal. Gastrostomy tubes are very rarely used unless

there is extremely severe damage. Perforations from blunt foreign objects that caused esophageal wall necrosis usually require thoracotomy to clean out septic debris and close the esophageal defect. However, acute perforations from sharp objects (e.g., fish hooks) not associated with esophageal wall necrosis may often be treated by placing a gastrostomy tube, giving nothing per os, and allowing the perforation to spontaneously seal.

Prognosis

The prognosis for animals with esophageal foreign bodies without perforation is usually good. Perforation warrants a more guarded prognosis, depending on the size of the perforation and the presence/severity of thoracic contamination. Subsequent cicatrix and obstruction is possible if substantial mucosal damage occurs. Bone foreign bodies, small body size (i.e., < 10 kg), and chronicity appear to be risk factors for complications.

ESOPHAGEAL CICATRIX (BENIGN STRICTURE)

Etiology

Severe, deep inflammation of the esophagus from any cause (especially foreign bodies or severe gastroesophageal reflux) is usually required for cicatrix to occur.

Clinical Features

Esophageal cicatrix occurs in both dogs and cats. The main sign is regurgitation (especially of solids). Some animals are hyporexic due to pain experienced when food becomes lodged at the stricture by forceful esophageal peristalsis. Rare patients have severe respiratory stridor due to cicatrix in the nasopharynx or at the choanae (see Chapter 16).

Diagnosis

Partial obstructions due to cicatrix may be difficult to diagnose. Positive-contrast esophagrams in which barium is mixed with food are often necessary (Fig. 29.7). Esophagoscopy is definitive (Video 29.5), but a partial stricture may not be obvious in large dogs unless the endoscopist is experienced and the esophagus is carefully inspected. Likewise, it is easy to miss strictures at the lower esophageal sphincter. Strictures in the nasopharynx or at the choanae require retroflexed endoscopic examination of these areas.

Treatment

Surgical resection/anastomosis is not recommended. Treatment consists of correcting the suspected cause (e.g., esophagitis) and/or widening the stricture by ballooning or bougienage. It is important that the clinician have substantial training dilating strictures and the correct equipment. Ballooning has less chance of perforation than bougienage and may be accomplished with endoscopic or fluoroscopic guidance. Angioplasty catheters or esophageal dilation balloons are more useful than Foley catheters because the latter typically slide to one side of the obstruction during inflation.

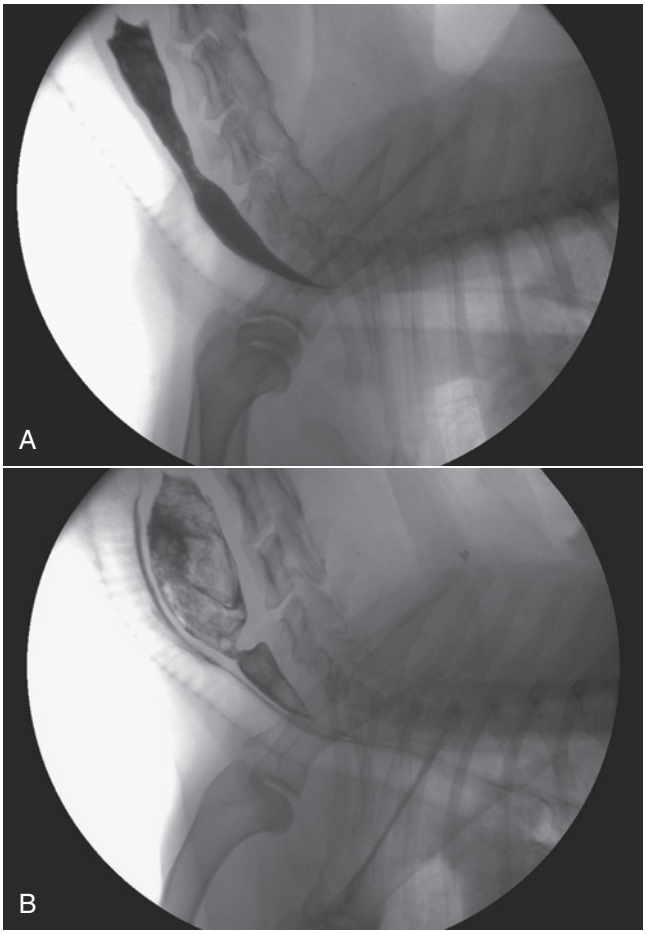


FIG 29.7
(A) Lateral contrast esophagram using liquid barium. There is some narrowing of the barium column but no obvious lesion. **(B)** Liquid barium has been mixed with canned food; a stricture in the midcervical esophagus is now very obvious. Note that the stricture is not at the thoracic inlet, which is where one might have suspected a stricture to be most likely on the first image.

Bougienage can likewise be done with endoscopic or fluoroscopic guidance. It can more easily cause a rupture but is relatively safe and equally effective if done by a trained individual. After the stricture has been dilated, significant traumatic esophagitis may be present. If it is present, it should be treated aggressively with proton pump inhibitors and gastric prokinetics. Some animals are cured after one dilatation, whereas others require multiple procedures.

In difficult patients in which the stricture recurs repeatedly after dilatation, more advanced techniques can be tried. Intralesional steroid injections, three-quadrant cuts into the stricture using endoscopic electrosurgery or laser, topical application of mitomycin C, placing a stent, and placing a balloon-esophagostomy tube have all been tried. Each has benefited some cases, but none is guaranteed to work; the author has seen each technique fail. Almost all strictures at the choanae require stenting. Nasopharyngeal strictures are very difficult to treat and should be immediately

referred to individuals with substantial experience in their treatment.

Prognosis

Early identification and appropriate treatment of high-risk animals (i.e., those with severe esophagitis or after foreign object removal) help decrease the likelihood of stricture formation. Resolving esophagitis decreases inflammation and lessens fibrous connective tissue formation. Long esophageal strictures (i.e., > 3-5 cm), continuing esophagitis at the stricture site, and very chronic strictures seem to have a more guarded prognosis. Most animals with benign esophageal strictures can be helped, but technical expertise is important. It is easy for a novice to perforate the esophagus or cause excessive trauma and make the stricture quickly recur or perhaps even come back worse than it was. Long-term gastrostomy tubes are rarely necessary.

ESOPHAGEAL NEOPLASMS

Etiology

Primary esophageal sarcomas in dogs are often due to *Spirocerca lupi*. Primary esophageal carcinomas are of unknown etiology. Leiomyomas and leiomyosarcomas are often found at the lower esophageal sphincter in older dogs. Thyroid carcinomas and pulmonary alveolar carcinomas may invade the esophagus in dogs. Squamous cell carcinomas are the most common esophageal neoplasm in cats.

Clinical Features

Dogs and cats with primary esophageal tumors may be asymptomatic until the tumor is advanced. These animals are sometimes diagnosed fortuitously when thoracic radiographs are obtained for other reasons. Regurgitation, anorexia, and/or fetid breath may occur if the tumor is large or causes esophageal dysfunction. If the esophagus is involved secondarily, clinical signs may result from esophageal dysfunction or tumor effects on other tissues.

Diagnosis

Plain thoracic radiographs may reveal a soft tissue density in the caudal lung fields. These tumors may be difficult to discern radiographically from pulmonary or mediastinal lesions and usually require contrast esophagrams (Fig. 29.8) or esophagoscopy (Fig. 29.9) to diagnose. Endoscopy typically allows differentiation of intraluminal from extraluminal masses causing esophageal stricture. Retroflexing the tip of an endoscope while it is within the stomach is the best method of identifying LES leiomyomas and leiomyosarcomas near the gastric cardia.

Treatment

Surgical resection is rarely curative (except for leiomyomas near the LES) because of the advanced nature of most esophageal neoplasms when they are diagnosed. However, resection may be palliative. Photodynamic therapy may be beneficial in dogs and cats with small superficial esophageal neoplasms. Surgery near the LES should be done only by an experienced surgeon; it is easy for an inexperienced surgeon to cause more disease than was present before.

Prognosis

The prognosis is usually poor (except for leiomyomas).

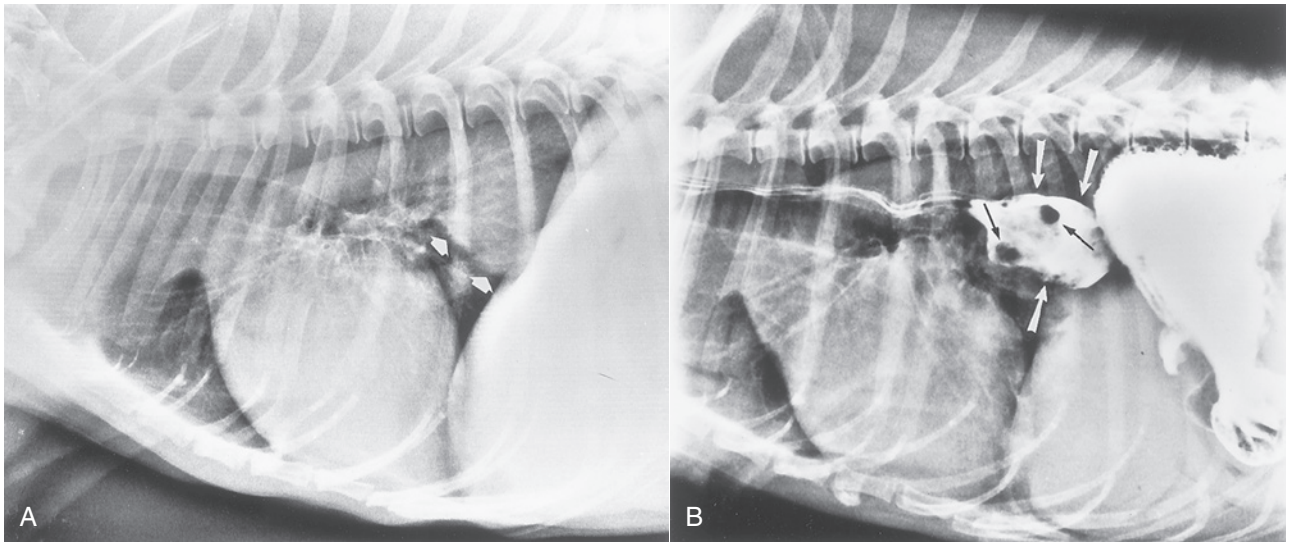


FIG 29.8
(A) Lateral thoracic radiograph of a dog with a previously unsuspected mass *(arrows)* not obviously associated with the esophagus. **(B)** Contrast esophagram in the same dog demonstrates that the esophagus is dilated *(large arrows)* and that there are intraesophageal filling defects *(small arrows)* in this dilated area. This dog had a primary esophageal carcinoma. (**A,** From Allen D, ed.: *Small animal medicine,* Philadelphia, 1991, JB Lippincott.)

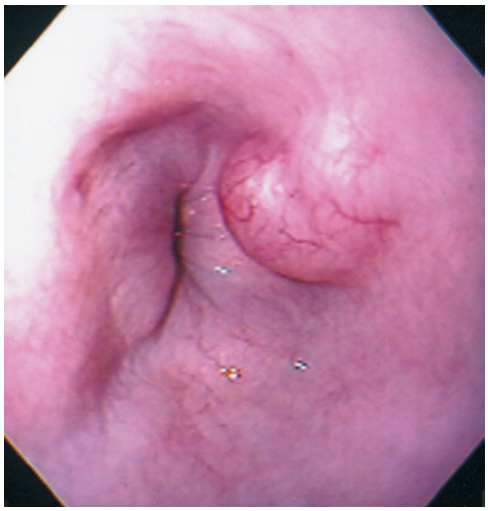


FIG 29.9
Endoscopic view of the lower esophageal sphincter of a dog. There is an intramural mass protruding into the lumen at 3 o'clock to the sphincter.

Suggested Readings

Adamama-Moraitou KK, et al. Benign esophageal stricture in the dog and cat: a retrospective study of 20 cases. *Can J Vet Res*. 2002;66:55.

Andrade N, et al. Evaluation of pharyngeal function in dogs with laryngeal paralysis before and after unilateral arytenoid lateralization. *Vet Surg*. 2015;44:1021.

Baloi PA, et al. Endoscopic ultrasonographic evaluation of the esophagus in healthy dogs. *Am J Vet Res*. 2013;74:1005.

Bexfield NH, et al. Esophageal dysmotility in young dogs. *J Vet Intern Med*. 2006;20:1314.

Bissett SA, et al. Risk factors and outcome of bougienage for treatment of benign esophageal strictures in dogs and cats: 28 cases (1995-2004). *J Am Vet Med Assoc*. 2009;235:844.

Cannon MS, et al. Clinical and diagnostic imaging findings in dogs with zygomatic sialoadenitis: 11 cases (1990-2009). *J Am Vet Med Assoc*. 2011;239:1211.

Davidson AP, et al. Inheritance of cricopharyngeal dysfunction in Golden Retrievers. *Am J Vet Res*. 2004;65:344.

Dewey CW, et al. Mycophenolate mofetil treatment in dogs with serologically diagnosed acquired myasthenia gravis: 27 cases (1999-2008). *J Am Vet Med Assoc*. 2010;236:664.

Doran I, et al. Acute oropharyngeal and esophageal stick injury in forty-one dogs. *Vet Surg*. 2008;37:781.

Fracassi F, et al. Reversible megaoesophagus associated with primary hypothyroidism in a dog. *Vet Rec*. 2011;168:329.

Fraune C, et al. Intralesional corticosteroid injection in addition to endoscopic balloon dilation in a dog with benign oesophageal strictures. *J Small Anim Pract*. 2009;50:550.

Gianella P, et al. Oesophageal and gastric endoscopic foreign body removal complications and follow-up of 102 dogs. *J Small Anim Pract*. 2009;50:649.

Gibbon KJ, et al. Phenobarbital-responsive ptyalism, dysphagia, and apparent esophageal spasm in a German Shepherd puppy. *J Am Anim Hosp Assoc*. 2004;40:230.

Gualtieri M, et al. Reflux esophagitis in three cats associated with metaplastic columnar esophageal epithelium. *J Am Anim Hosp Assoc*. 2006;42:65.

Harkin KR, et al. Dysautonomia in dogs: 65 cases (1993-2000). *J Am Vet Med Assoc*. 2002;220:633.

Jergans AE. Diseases of the esophagus. In: Ettinger SJ, et al., eds. *Textbook of veterinary internal medicine*. 7th ed. St Louis: Elsevier/Saunders; 2010.

Kook PH, et al. Wireless ambulatory esophageal pH monitoring in dogs with clinical signs interpreted as gastroesophageal reflux. *J Vet Intern Med*. 1716;28:2014.

Leib MS, et al. Esophageal foreign body obstruction caused by a dental chew treat in 31 dogs (2000-2006). *J Am Vet Med Assoc*. 2008;232:1021.

Levine JS, et al. Contrast videofluoroscopic assessment of dysphagic cats. *Vet Radiol Ultrasound*. 2014;55:465.

Mazzei MJ, et al. Eosinophilic esophagitis in a dog. *J Am Vet Med Assoc*. 2009;235:61.

McBrearty AR, et al. Clinical factors associated with death before discharge and overall survival time in dogs with generalized megaesophagus. *J Am Vet Med Assoc*. 2011;238:1622.

Mizutani T, et al. Novel strategy for prevention of esophageal stricture after endoscopic surgery. *Hepatogastroenterology*. 2010;57:1150.

Niemiec BA. Oral pathology. *Top Companion Anim Med*. 2008;23:59.

Nunn R, et al. Association between Key-Gaskell syndrome and infection by *Clostridium botulinum* type C/D. *Vet Rec*. 2004;155:111.

Poncet CM, et al. Prevalence of gastrointestinal tract lesions in 73 brachycephalic dogs with upper respiratory syndrome. *J Small Anim Pract*. 2005;46:273.

Ranen E, et al. Spirocercosis-associated esophageal sarcomas in dogs: a retrospective study of 17 cases (1997-2003). *Vet Parasitol*. 2004;119:209.

Rousseau A, et al. Incidence and characterization of esophagitis following esophageal foreign body removal in dogs: 60 cases (1999-2003). *J Vet Emerg Crit Care*. 2007;17:159.

Ryckman LR, et al. Dysphagia as the primary clinical abnormality in two dogs with inflammatory myopathy. *J Am Vet Med Assoc*. 1519;226:2005.

Sale C, et al. Results of transthoracic esophagotomy retrieval of esophageal foreign body obstructions in dogs: 14 cases (2000-2004). *J Am Anim Hosp Assoc*. 2006;42:450.

Sellon RK, et al. Esophagitis and esophageal strictures. *Vet Clin North Am Small Anim Pract*. 2003;33:945.

Shelton GD. Oropharyngeal dysphagia. In: Bonagura JD, et al., eds. *Current veterinary therapy XIV*. St Louis: Elsevier/Saunders; 2009.

Stanley BJ, et al. Esophageal dysfunction in dogs with idiopathic laryngeal paralysis: a controlled cohort study. *Vet Surg*. 2010;39:139.

Tarvin KM, et al. Prospective controlled study of gastroesophageal reflux in dogs with naturally occurring laryngeal paralysis. *Vet Surg*. 2016;45:916.

Willard MD, et al. Esophagitis. In: Bonagura JD, et al., eds. *Current veterinary therapy XIV*. St Louis: Elsevier/Saunders; 2009.

Wilson DV, et al. Postanesthetic esophageal dysfunction in 13 dogs. *J Am Anim Hosp Assoc*. 2004;40:455.

References

1. Manning K, et al. Intermittent at-home suctioning of esophageal content for prevention of recurrent aspiration pneumonia in 4 dogs with megaesophagus. *J Vet Intern Med*. 2016;30:1715.

CHAPTER 30

Disorders of the Stomach



GASTRITIS

ACUTE GASTRITIS

Etiology

Ingestion of spoiled or contaminated foods, foreign objects, toxic plants, chemicals, and/or irritating drugs (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) are common causes of acute gastritis. Infectious (i.e., viral and bacterial) causes occur but are poorly defined in dogs and cats.

Clinical Features

Dogs are more commonly affected than cats by acute gastritis, probably because of their less discriminating eating habits. Signs usually consist of acute onset of vomiting; food and bile are typically vomited, although small amounts of blood (usually specks or spots of blood as opposed to larger amounts) may be present. Affected animals are typically uninterested in food and may or may not feel sick. Fever and abdominal pain are uncommon.

Diagnosis

Unless the animal was seen eating some irritative substance, acute gastritis is usually a presumptive diagnosis of exclusion based on history and physical examination findings. Abdominal imaging and/or clinical pathologic data are indicated if the animal is severely ill or if other disease is suspected. In such a case, acute gastritis is a reasonable tentative diagnosis after alimentary foreign body, obstruction, parvoviral enteritis, uremia, diabetic ketoacidosis, hypoadrenocorticism, hepatic failure, hypercalcemia, and pancreatitis are ruled out. If the hyporexia/vomiting resolves after 1 to 2 days of symptomatic and supportive therapy, the tentative diagnosis is generally assumed to be correct (acute pancreatitis is still possible; see Chapter 37).

Because acute gastritis is a diagnosis of exclusion and its signs are suggestive of various other disorders (e.g., foreign bodies, intoxication), good anamnesis and physical examination are critical. The owner should monitor the pet, and if the animal's condition worsens or does not improve within 1 to 2 days, abdominal imaging (preferably ultrasound), a complete blood count (CBC), and a serum biochemistry profile are indicated.

Treatment

Withholding food and water for 24 hours often controls vomiting. If vomiting persists or is excessive, or if the animal becomes depressed because of the vomiting, central-acting antiemetics (e.g., maropitant, ondansetron) and/or fluids may be administered parenterally (see pp. 437-438). If there is minor hematemesis (i.e., a few specks of digested blood), then a proton pump inhibitor (e.g., omeprazole) might be administered but is rarely necessary. Begin oral intake by frequently offering small amounts of cool water. If the animal drinks without vomiting, then small amounts of an easily digested diet (e.g., one part cottage cheese and two parts potato; one part boiled chicken and two parts potato) are offered. Antibiotics and glucocorticoids are rarely indicated.

Prognosis

The prognosis is excellent as long as the fluid and electrolyte balance is maintained.

HEMORRHAGIC GASTROENTERITIS (ACUTE HEMORRHAGIC DIARRHEAL SYNDROME—SEE UNDER "DISORDERS OF THE INTESTINAL TRACT")

Etiology

The cause of acute hemorrhagic diarrheal syndrome (AHDS) is suspected to be *Clostridium* spp. The name has been changed to AHDS recently because histologically the damage is in the intestines, not the stomach.

Clinical Features

AHDS occurs in dogs and is a more severe disease than acute gastritis, typically causing profuse hematemesis and/or hematochezia. It classically occurs in smaller breeds that have not had access to garbage. This disorder has an acute course, which, if severe, can rapidly produce severe dehydration,

disseminated intravascular coagulation (DIC), and/or renal injury. In severe cases, the animal may be moribund by the time of presentation.

Diagnosis

These animals are typically hemoconcentrated (i.e., packed cell volume [PCV] ≥ 55%) with normal plasma total protein concentrations. Acute onset of typical clinical signs plus marked hemoconcentration allows a presumptive diagnosis. Thrombocytopenia and renal or prerenal azotemia may be seen in severely affected animals.

Treatment

Aggressive fluid therapy is initiated to treat or prevent shock, DIC secondary to hypoperfusion, and renal failure secondary to hypovolemia. Parenteral antibiotics (e.g., ampicillin) are often used because of the fear that intestinal bacteria are proliferating, but their value is doubtful and they are no longer recommended. If the patient becomes severely hypoalbuminemic, synthetic colloids or plasma may be required.

Prognosis

The prognosis is good for most animals that are presented in a timely fashion. Inadequately treated animals may die due to circulatory collapse, DIC, and/or renal failure.

CHRONIC GASTRITIS

Etiology

There are several types of chronic gastritis (e.g., lymphocytic/plasmacytic, eosinophilic, granulomatous, atrophic). Lymphocytic-plasmacytic gastritis might be an immune and/or inflammatory reaction to a variety of antigens. *Helicobacter* spp. and *Physaloptera rara* may produce such a reaction in some patients (especially cats and dogs, respectively). Eosinophilic gastritis may represent an allergic reaction, probably to food antigens. Atrophic gastritis may be the result of chronic gastric inflammatory disease and/or immune mechanisms. *Ollulanus tricuspis* may cause granulomatous gastritis in cats.

Clinical Features

Chronic gastritis appears to be more common in cats than in dogs. It is not clearly associated with chronic enteritis. Hyporexia and vomiting are the most common signs in affected dogs and cats. Frequency of vomiting varies from once weekly to many times a day. Some animals only demonstrate hyporexia, ostensibly because of low-grade nausea.

Diagnosis

Clinical pathologic findings are rarely helpful; eosinophilic gastritis inconsistently causes peripheral eosinophilia. Ultrasound sometimes documents mucosal thickening. Diagnosis requires gastric mucosal biopsy. Because gastritis may be generalized or localized, endoscopy is the best way of obtaining tissue samples. Endoscopy allows multiple biopsies over the entire mucosal surface, whereas surgical biopsy typically results in one sample that is randomly taken without knowledge of how the gastric mucosa appears. Gastric biopsy should always be performed regardless of the gross mucosal appearance. However, enteritis is far more common than gastritis, which is why duodenal biopsies are usually more important than gastric biopsies. Gastric lymphoma can be surrounded by lymphocytic inflammation, and obtaining inappropriately superficial tissue specimens can produce an incorrect diagnosis of inflammatory disease. Endoscopes with a 2.8-mm biopsy channel make it easier to avoid inappropriately superficial samples. Accurate histopathologic interpretation of alimentary tissue can be difficult; the clinician should not hesitate to request a second opinion if the histologic diagnosis does not fit the patient or the response (or lack thereof) to therapy. If *Ollulanus tricuspis* is suspected, vomitus or gastric washings should be examined for the parasites, but they might also be found in gastric biopsy specimens. *Physaloptera* can be seen endoscopically, but they can be very small if they are immature.

Treatment

Lymphocytic-plasmacytic gastritis sometimes responds to dietary therapy (e.g., low-fat, low-fiber, elimination diets) alone (see pp. 434-435). If such therapy is inadequate, glucocorticoids (e.g., prednisolone, 2.2 mg/kg/day) can be used concurrently. Even if glucocorticoids are required, appropriate dietary therapy may allow one to administer a substantially decreased dose, thus avoiding glucocorticoid adverse effects. If glucocorticoid therapy is necessary, the dose should be gradually decreased to find the lowest effective dose. However, the dose should not be tapered too quickly after obtaining a clinical response or the clinical signs may return and be more difficult to control than they were initially. In rare cases, azathioprine or similar drugs will be necessary (see Chapter 28). Proton pump inhibitors are sometimes beneficial. Ulceration should be treated as discussed on pages 470-471.

Canine eosinophilic gastritis usually responds well to a *strict* elimination diet. If dietary therapy alone fails, glucocorticoid therapy (e.g., prednisolone, 1.1-2.2 mg/kg/day) in conjunction with diet is usually effective. Feline hypereosinophilic syndrome responds poorly to most treatments.

Atrophic gastritis and granulomatous gastritis tend to be difficult to treat. Diets low in fat and fiber (e.g., one part cottage cheese and two parts potato) may help control signs. Atrophic gastritis might respond to antiinflammatory, antacid, and/or prokinetic therapy; the latter is designed to keep the stomach empty, especially at night. Idiopathic granulomatous gastritis is uncommon in dogs and cats and does not respond well to dietary or glucocorticoid therapy.

Prognosis

The prognosis for canine and feline lymphocytic-plasmacytic gastritis is often good with appropriate therapy. Lymphoma has been suggested to develop in cats with preexisting lymphocytic gastritis; however, it is impossible to know whether the original diagnosis of lymphocytic gastritis was incorrect,

if lymphoma developed independently of the gastritis, or if lymphoma developed from the gastritis.

The prognosis for canine eosinophilic gastritis is typically good. Feline eosinophilic gastritis can be a component of hypereosinophilic syndrome, which typically responds poorly to treatment. Hypereosinophilic syndrome has a guarded to poor prognosis.

HELICOBACTER-ASSOCIATED DISEASE

Etiology

Helicobacter pylori is the principal spirochete found in human gastric mucosa, whereas Non-*H. pylori* Helicobacter (NHPH) (e.g., *Helicobacter felis, Helicobacter heilmannii, Helicobacter bizzozeronii, Helicobacter salomonis*, etc.) are the principal gastric spirochetes in dogs and cats. *H. pylori* has rarely been found in cats.

Clinical Features

Most people infected with *H. pylori* are asymptomatic. Those with symptomatic *H. pylori* infections usually develop ulceration and gastritis with neutrophilic infiltrates. They can also develop low-grade mucosal-associated lymphoid tissue (MALT) lymphoma that can be cured with antibiotic therapy or gastric carcinoma. Similarly, most dogs and cats with gastric *Helicobacter* infections are asymptomatic. Some infected animals may have nausea, hyporexia, and/or vomiting associated with lymphocytic and occasionally neutrophilic infiltrates. Because so many infected animals are asymptomatic, cause and effect have not been clearly established between *Helicobacter* spp. and symptomatic gastric disease. Cats colonized with *H. pylori* seem to have more severe histologic lesions than those with *H. felis,* which in turn may be associated with more severe lesions than those with *H. heilmannii.* Currently, there is reasonable evidence that gastric *Helicobacter* infections cause clinical illness (i.e., vomiting, hyporexia) in some dogs and cats, but there is no good estimate of prevalence.

Diagnosis

Gastric biopsy is currently required to diagnose *Helicobacter* infection. The organisms are readily identified on H&E stain, but special stains (e.g., Giemsa, Warthin-Starry) as well as fluorescent *in situ* hybridization (FISH) make them stand out. The bacteria are not uniformly distributed throughout the stomach, and it is best to obtain biopsy specimens from the body, fundus, and antrum. The clinician may also diagnose this infection by cytologic evaluation of the gastric mucosa (Fig. 30.1) or by looking for gastric mucosal urease activity. Because of the uncertain pathogenicity of *Helicobacter* spp., the clinician is advised to look first for other more common explanations for the animal's clinical signs before deciding that *Helicobacter* is causing disease.

Treatment

A combination of metronidazole, amoxicillin, and bismuth (either subsalicylate or subcitrate) seems to be effective in alleviating clinical signs in veterinary patients. Contrary to people, there is no evidence that dogs or cats benefit from concurrent use of proton pump inhibitors. Azithromycin and clarithromycin have been substituted for bismuth in cats. Anecdotally, some animals seem to respond to just erythromycin or amoxicillin. Therapy should probably last for 14 days.

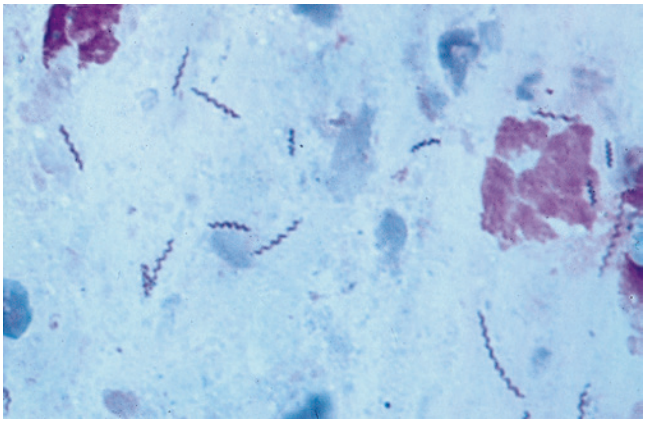


FIG 30.1
Air-dried smear of gastric mucosa obtained endoscopically and stained with Diff-Quik. Numerous spirochetes are seen. The affected dog was vomiting because of an ulcerated leiomyoma, and the spirochetes did not appear to be causing disease in this animal (×1000).

Prognosis

Animals with apparent *Helicobacter*-associated clinical illness seem to respond well to treatment and have a good prognosis. However, because cause and effect are uncertain, any animal not responding to therapy should be reexamined carefully, looking for other diseases. Recurrence of infection after treatment commonly occurs by 6 months, but it is not clear whether this represents a relapse of the original infection or reinfection from an outside source.

PHYSALOPTERA RARA

Etiology

Physaloptera rara is a nematode that has an indirect life cycle; beetles and crickets are the intermediate hosts. Frogs, snakes, mice, and birds may be paratenic hosts.

Clinical Features

In dogs, a single *P. rara* attached to the gastric mucosa can cause intractable vomiting. Cats are rarely affected, and their clinical illness associated with *P. rara* is less well characterized. The vomiting usually does not resolve with antiemetics. Vomitus may or may not contain bile, and affected animals usually appear otherwise healthy.

Diagnosis

Ova are seldom found in feces. If fecal examinations are performed, sodium dichromate or magnesium sulfate solutions are usually necessary to find the eggs. Most diagnoses are made when the parasites are found during

gastroduodenoscopy (see Fig. 27.21). There may be only one worm causing clinical signs, and it can be difficult to find if it is a juvenile worm or if it is attached within the pylorus. Alternatively, an empirical treatment trial (as described here) is reasonable.

Treatment

Pyrantel pamoate or ivermectin is usually effective. If the parasite is found during endoscopy, it can be removed with forceps.

Prognosis

Vomiting usually stops as soon as the worm(s) are removed or eliminated.

OLLULANUS TRICUSPIS

Etiology

Ollulanus tricuspis is a nematode with a direct life cycle transmitted via vomited material.

Clinical Features

Cats are the most commonly affected species, although dogs and foxes are occasionally infected. Vomiting is the principal clinical sign, but clinically normal cats may harbor the parasite. Gastric mucosal lesions may or may not be seen in infested cats.

Diagnosis

Cattery situations promote infection because the parasite is passed directly from one cat to another. However, occasionally cats with no known contact with other cats are infected. Looking for parasites in gastric washings or vomited material with a dissecting microscope is the best means of diagnosis. The parasite can be seen occasionally in gastric mucosal biopsy specimens.

Treatment and Prognosis

Therapy is uncertain, but fenbendazole might be effective. Occasionally animals have severe gastritis and become debilitated.

GASTRIC OUTFLOW OBSTRUCTION/ GASTRIC STASIS

BENIGN MUSCULAR PYLORIC HYPERTROPHY (PYLORIC STENOSIS)

Etiology

The cause of benign muscular pyloric hypertrophy is uncertain. Some research suggests that gastrin promotes development of pyloric stenosis.

Clinical Features

Benign muscular pyloric stenosis typically causes persistent vomiting in young animals (especially brachycephalic dogs and Siamese cats) but can be found in any animal. Affected animals usually vomit food shortly after eating. The vomiting is sometimes described as "projectile." Animals are otherwise clinically normal, although they may lose weight due to inadequate caloric retention. Some cats with pyloric stenosis vomit so much that secondary esophagitis, megaesophagus, and regurgitation occur, confusing the clinical picture. Hypochloremic-hypokalemic metabolic alkalosis sometimes occurs, but it is inconsistent and nonspecific for gastric outflow obstruction (excessive loss of gastric secretions for any reason and aggressive diuretic therapy are common causes).

Diagnosis

Gastric outflow obstruction is diagnosed based on plain/contrast radiographs, ultrasonography, gastroduodenoscopy (i.e., there are typically prominent folds of normal-appearing mucosa at the pylorus), and/or exploratory surgery (i.e., the surgeon can open the stomach and try to pass a finger through the pylorus to assess its patency) as well as eliminating extraalimentary tract diseases (see Box 26.6). Once diagnosed, the outflow area should be inspected endoscopically or surgically, and infiltrative pyloric disease ruled out through biopsy. At surgery the serosa appears normal, but the pylorus is usually thickened when palpated.

Treatment

Surgical correction is required. Pyloroplasty (e.g., a Y-U–plasty) is more consistently effective than pyloromyotomy. Improperly performed pyloroplasty or pyloromyotomy can cause perforation or worse obstruction. Some clinicians routinely performed one of these pyloric outflow procedures whenever an exploratory laparotomy fails to reveal the cause of vomiting; this is a very poor practice and should not be done.

Prognosis

Surgery should be curative, and the prognosis is good.

GASTRIC ANTRAL MUCOSAL HYPERTROPHY

Etiology

Antral mucosal hypertrophy is idiopathic. Gastric outflow obstruction is caused by proliferation of nonneoplastic mucosa that occludes the distal gastric antrum (Fig. 30.2). This disorder is different from benign muscular pyloric stenosis (i.e., where normal mucosa is thrown up into folds secondary to submucosal thickening).

Clinical Features

Principally found in older, small-breed dogs, antral hypertrophy clinically resembles pyloric stenosis (i.e., animals usually vomit food, especially after meals).

Diagnosis

Gastric outlet obstruction is diagnosed radiographically, ultrasonographically, or endoscopically; however, definitive diagnosis of antral mucosal hypertrophy requires mucosal

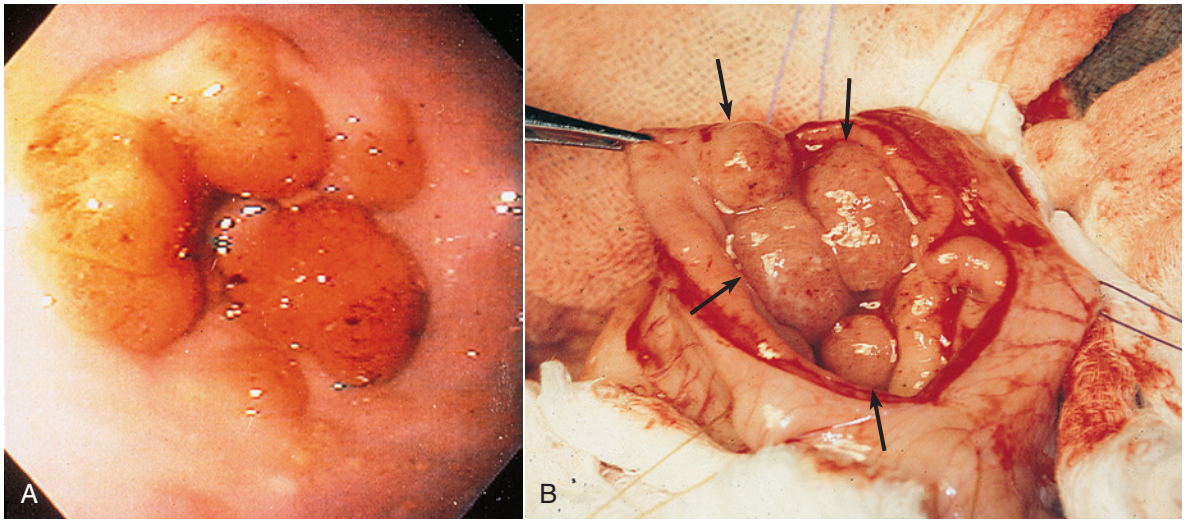


FIG 30.2
(A) Endoscopic view of the pyloric region of a dog that has gastric antral mucosal hypertrophy. If biopsy is not performed, these folds may easily be mistaken for neoplasia. **(B)** Intraoperative photograph of a dog's opened pylorus. Note the numerous folds of mucosa that are protruding *(arrows)* as a result of gastric antral mucosal hypertrophy.

biopsy. Endoscopically, the antral mucosa is redundant and may resemble a submucosal neoplasm causing convoluted mucosal folds (Video 30.1). In some cases the mucosa will be obviously reddened and inflamed. However, the mucosa in dogs with antral hypertrophy is usually not as firm or hard as expected with infiltrative carcinomas or leiomyomas. If antral mucosal hypertrophy is seen at surgery, there should be no evidence of submucosal infiltration or muscular thickening suggestive of neoplasia or benign pyloric stenosis, respectively. It is important to differentiate mucosal hypertrophy from these other diseases so that therapeutic recommendations are appropriate (e.g., gastric carcinomas typically have a terrible prognosis, and surgery is not always helpful).

Treatment

Antral mucosal hypertrophy is treated by mucosal resection, usually combined with pyloroplasty. Pyloromyotomy alone is typically insufficient to resolve clinical signs from mucosal hypertrophy.

Prognosis

The prognosis is excellent.

GASTRIC FOREIGN OBJECTS

Etiology

Objects that pass through the esophagus and then cannot leave the stomach are called gastric foreign objects. Vomiting may subsequently result from gastric outlet obstruction, gastric distention, or irritation. Linear foreign objects whose orad end lodges at the pylorus may cause intestinal perforation with subsequent peritonitis and must be dealt with expeditiously (see the section on intestinal obstruction on pp. 499-500).

Clinical Features

Dogs are affected more commonly than cats because of their less discriminating eating habits. Vomiting (*not* regurgitation) is a common sign, but some animals demonstrate only hyporexia while rare patients are asymptomatic.

Diagnosis

Acute onset of vomiting in an otherwise normal animal, especially a puppy, is potentially consistent with foreign body ingestion. Diagnosis results from palpating the object during physical examination or seeing it during imaging. Radiographs (plain and contrast), ultrasonography, and endoscopy are the most reliable means of diagnosis. However, diagnosis can be difficult if there is food in the stomach. Some diseases closely mimic gastric foreign body obstruction. Canine parvovirus in particular may initially cause an acute onset of intense vomiting, during which time viral particles might not be detected in the feces. Hypokalemic-hypochloremic metabolic alkalosis is consistent with loss of gastric fluid, but gastric outflow obstruction is only one cause of such loss. Anything causing vomiting can be responsible. Furthermore, not all animals with gastric outflow obstruction have these electrolyte changes. Excessive use of loop diuretics can produce identical electrolyte changes. Therefore these electrolyte changes are neither sensitive nor specific for gastric outflow obstruction.

Treatment

Many small foreign objects will spontaneously pass through the gastrointestinal tract; however, if there is doubt as to

whether a foreign body will or will not pass, it is best to remove it. Vomiting can be induced (e.g., apomorphine in the dog, 0.02 or 0.1 mg/kg administered intravenously or subcutaneously, respectively; xylazine in the cat, 0.4-0.5 mg/kg administered intravenously) to eliminate gastric foreign objects if the clinician believes that the object will not cause problems during forcible ejection (i.e., does not have sharp edges or points and is small enough to pass easily). If there is doubt as to the safety of this approach, the object should instead be removed endoscopically or surgically.

Before the animal is anesthetized for surgery or endoscopy, the electrolyte and acid-base status should be evaluated. Although electrolyte changes (e.g., hypokalemia) are common, they are impossible to accurately predict. Severe hypokalemia predisposes to cardiac arrhythmias and should usually be corrected before anesthesia.

Endoscopic removal of foreign objects requires a flexible endoscope and appropriate retrieval forceps. The animal should always be radiographed just before being anesthetized to confirm that the object is still in the stomach. Laceration of the esophagus and entrapment of the retrieval forceps in the object should be avoided. If endoscopic removal is unsuccessful, gastrostomy should be performed.

Prognosis

The prognosis is usually good unless the animal is debilitated or there is septic peritonitis secondary to gastric perforation.

IATROGENIC GASTRIC OUTFLOW OBSTRUCTION

Surgery of the gastric antrum and/or pylorus is technically difficult and characteristically unforgiving of mistakes. Any animal that has had surgery in this area and continues to vomit should be examined for iatrogenic outflow obstruction. Endoscopy is the best way to examine the outflow tract for iatrogenic mechanical obstruction (Video 30.2).

GASTRIC DILATION/VOLVULUS

Etiology

Gastric dilation/volvulus (GDV) is probably ultimately caused by poor gastric emptying of solids, which produces some degree of chronic gastric distention with subsequent stretching of hepatogastric and duodenogastric ligaments. Risk factors include large- and giant-breed conformation (especially those with deep, narrow chests), purebred status, age (i.e., middle aged to older animals), and having a first-degree relative with a history of GDV. Factors reported to predispose dogs to GDV include eating large volumes, eating once a day, eating rapidly, eating from an elevated platform, eating dry foods that have fats or oils listed as one of the first four ingredients, and being perceived as being a "nervous" dog. It is believed that, in many cases, the stomach is first partially twisted because of the stretched hepatogastric ligaments (i.e., typically the pylorus rotates ventrally from the right side of the abdomen below the body of the stomach to become positioned dorsal to the gastric cardia on the left side). At this point, affected dogs are clinically normal and can pass fluids and solids into the intestines. However, if subsequent aerophagia causes sufficient dilation, then gas and other gastric contents cannot be relieved through eructation or passed into the intestines. It is at this point that the patient has developed clinical GDV. The dog can continue to ingest air, but it cannot eliminate it. Splenic congestion and even torsion may occur concurrently with the spleen on the right side of the abdomen. Massive gastric distention obstructs the hepatic portal vein and posterior vena cava causing mesenteric congestion, decreased cardiac output, severe shock, DIC, and endotoxemia as well as putting pressure on the diaphragm, inhibiting respiration. The gastric blood supply (especially the short gastric vessels) may be impaired, causing gastric wall necrosis.

Clinical Features

GDV principally occurs in large- and giant-breed dogs with deep chests; it rarely occurs in small dogs or cats. Affected dogs typically retch nonproductively and may demonstrate abdominal pain (which may appear as "restlessness" to the client). Marked anterior abdominal distention may be seen later. However, abdominal distention is not always obvious in large, heavily muscled dogs. Eventually, depression and a moribund state occur.

Diagnosis

Physical examination findings (i.e., a dog of appropriate confirmation with large tympanic anterior abdomen and unproductive retching) allow presumptive diagnosis of GDV but do not permit differentiation between dilation and GDV. Plain abdominal radiographs, preferably right lateral and dorso-ventral projections, are required but should be done AFTER the patient is decompressed and shock is controlled. Volvulus is denoted by displacement of the pylorus and/or formation of a "shelf" of tissue in the gastric shadow (Fig. 30.3). It is impossible to distinguish between dilation and dilation/torsion on the basis of ability or inability to pass an orogastric tube.

Treatment

Treatment consists of initiating aggressive therapy for shock (hetastarch or hypertonic saline infusion [see pp. 432-434] may make treatment for shock quicker and easier) and decompressing the stomach. If the patient is asphyxiating, gastric decompression is initiated first. Decompression is usually performed with an orogastric tube, but it should not be excessively forced into the stomach lest too much pressure rupture the lower esophagus. After the gas is released, the stomach is lavaged with warm water to remove its contents (if blood is present in the retrieved lavage solution, gastric wall necrosis is probable). Most affected dogs can be successfully decompressed via intubation, but if the tube cannot be passed into the stomach, then the clinician may insert a large needle (e.g., 3-inch, 12- to 14-gauge) into the stomach just behind the rib cage in the left flank to decompress the stomach (which usually causes some abdominal

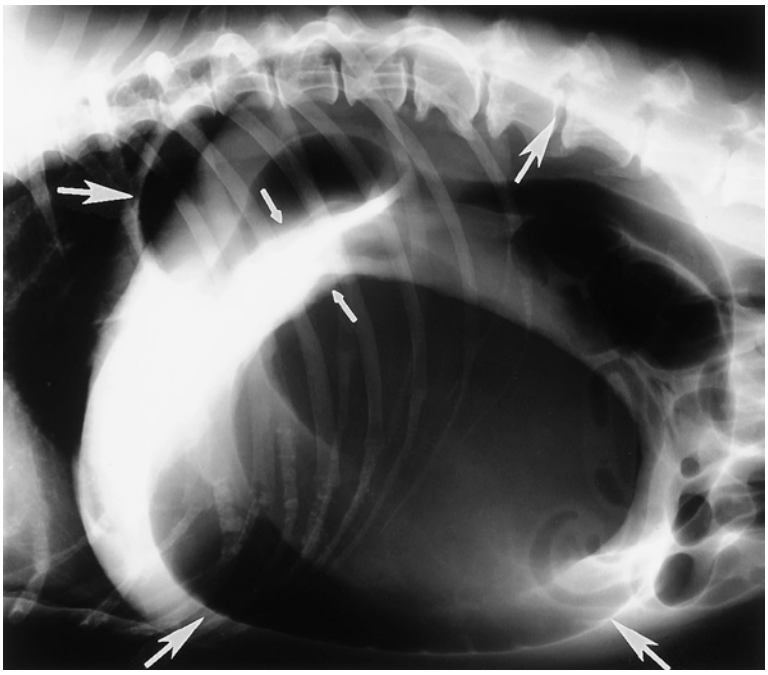


FIG 30.3
Lateral radiograph of a dog with gastric dilation/volvulus. The stomach is dilated *(large arrows),* and there is a "shelf" of tissue *(small arrows),* demonstrating that the stomach is malpositioned. Radiographs obtained from the right lateral position seem superior to those of other views in demonstrating this shelf. If the stomach were similarly distended but not malpositioned, the diagnosis would be gastric dilation.

contamination) or perform a temporary gastrostomy in the left paralumbar area (this is rarely done nowadays).

Mesenteric congestion caused by the enlarged stomach predisposes to infection and endotoxemia, making systemic antibiotic administration reasonable (e.g., cefazolin, 20 mg/kg administered intravenously). Serum electrolyte concentrations and acid-base status should be evaluated.

If the dog has GDV (see Fig. 30.3), surgery is necessary to reposition the stomach and should be performed as soon as the animal constitutes an acceptable anesthetic risk. Torsion (even when the stomach is deflated) impairs gastric wall perfusion and may cause necrosis. If there is no blood present in the gastric contents seen after gastric lavage, one can take more time to optimally resuscitate the patient; but if blood is present, then surgery needs to occur as quickly as possible. Areas of gastric wall necrosis should be resected or invaginated to prevent perforation and abdominal contamination. Gastropexy (e.g., incisional, circumcostal, belt loop, tube gastrostomy) is indicated to help prevent recurrence of GDV and seems correlated with prolongation of survival. Gastropexy is optional in dogs with gastric dilation without torsion, but it is strongly recommended to prevent future GDV. Gastropexy almost always prevents torsions but does not prevent dilation.

Postoperatively, the animal should be monitored by electrocardiogram (ECG) for 48 to 72 hours. Lidocaine or procainamide may be needed if severe cardiac arrhythmias diminish cardiac output (see Chapter 4). Hypokalemia is common in these patients and makes such arrhythmias refractory to medical control, so it should be prevented by intravenous supplementation. Serial plasma lactate measurements may indicate whether more aggressive fluid resuscitation is needed.

Although preventing exercise after meals and feeding small meals of softened food would intuitively seem useful, no data confirm this speculation. Prophylactic gastropexy (often performed at the time of neutering) can be considered in patients that appear at risk.

Prognosis

The prognosis depends on how quickly the condition is recognized and treated. Patients receiving appropriate therapy within 5 hours of onset of signs have mortality rates of approximately 15%. Factors associated with much worse prognosis include therapy being delayed more than 5 or 6 hours after onset, hypothermia, hypotension, depression, being comatose, having preoperative cardiac arrhythmias, gastric wall necrosis, peritonitis, sepsis, severe DIC, combination of partial gastrectomy and splenectomy, and postoperative acute renal failure. Increased preoperative blood lactate concentrations also seem suggestive of a poor outcome. Fewer than 10% of animals with gastropexy experience recurrence of GDV compared with over 50% of those without gastropexy. Prophylactic gastropexy may be elected for animals believed to be at increased risk for GDV. Laparoscopic-assisted gastropexy is a minimally invasive procedure.

PARTIAL OR INTERMITTENT CHRONIC GASTRIC VOLVULUS

Etiology

The causes for partial and intermittent chronic gastric volvulus are probably the same as for classic GDV.

Clinical Features

Dogs with chronic volvulus do not have the life-threatening progressive syndrome characterizing classic GDV. Although occurring in the same breeds as GDV, chronic gastric volvulus usually produces a chronic, intermittent, potentially difficult-to-diagnose problem. It may occur repeatedly and spontaneously resolve; dogs may appear normal between bouts. Some dogs have persistent nondistended volvulus and are asymptomatic.

Diagnosis

Plain radiographs are usually diagnostic (Fig. 30.4), but diagnosis may require repeated radiographs and/or contrast studies. Chronic volvulus will rarely be diagnosed endoscopically. In rare cases one may cause a temporary gastric volvulus by manipulating a gastroscope in an air-distended stomach, so the clinician must differentiate spontaneous from iatrogenic volvulus.

Treatment

If partial or intermittent chronic gastric volvulus is diagnosed, surgical repositioning and gastropexy are usually curative. Pexy will also help prevent classic GDV from occurring.

Prognosis

The prognosis is usually good once the problem is identified and surgically corrected.

IDIOPATHIC GASTRIC HYPOMOTILITY

Etiology

Idiopathic gastric hypomotility refers to an anecdotal syndrome characterized by poor gastric emptying and motility despite the lack of anatomic obstruction, inflammatory lesions, or other causes.

Clinical Features

Idiopathic gastric hypomotility has primarily been diagnosed in dogs. Affected dogs usually vomit food several hours after eating but otherwise appear well. Weight loss may or may not occur.

Diagnosis

Fluoroscopic studies document decreased gastric motility, but diagnosis requires ruling out gastric outlet obstruction, infiltrative bowel disease, inflammatory abdominal disease, and extraalimentary tract diseases (e.g., renal, adrenal, or hepatic failure; severe hypokalemia or hypercalcemia).

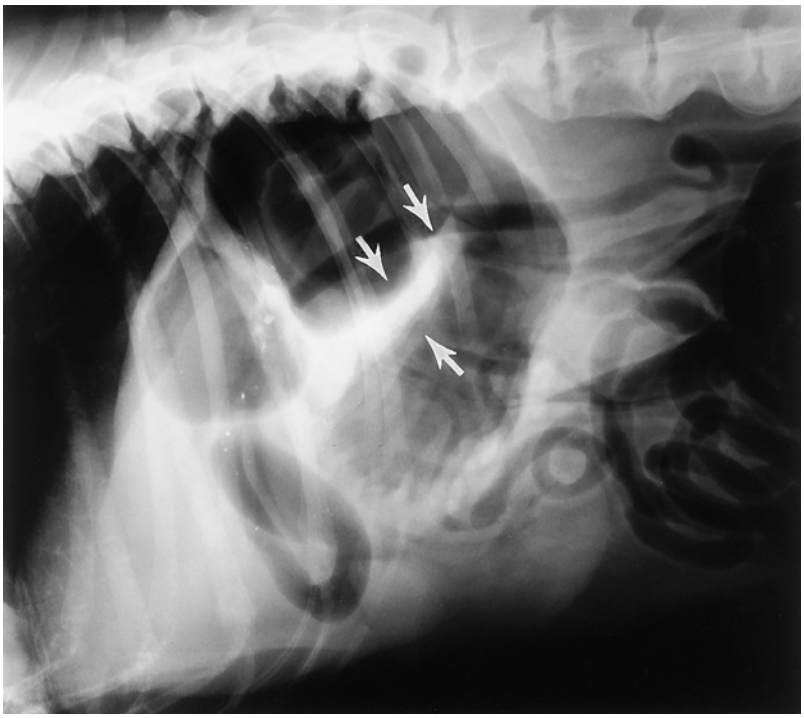


FIG 30.4
Lateral abdominal radiograph of an Irish Setter with chronic vomiting caused by gastric volvulus that did not cause dilation. A "shelf" of tissue *(arrows)* demonstrates that the stomach has twisted.

Treatment

Metoclopramide (see Table 28.3) increases gastric peristalsis in some but not all affected dogs. Cisapride, erythromycin, or ranitidine may be effective if metoclopramide fails. Diets low in fat and fiber may be helpful.

Prognosis

Dogs that respond to medical management have a good prognosis. Those that do not respond have a poor prognosis for cure, although they may still be acceptable pets.

BILIOUS VOMITING SYNDROME

Etiology

Bilious vomiting syndrome appears to be caused by gastroduodenal reflux that occurs when the dog's stomach is empty for long periods of time (e.g., during an overnight fast).

Clinical Features

Bilious vomiting syndrome usually affects otherwise normal dogs that are fed once daily in the morning. Classically, the pet vomits bile-stained fluid once a day, usually late at night or in the morning just before eating.

Diagnosis

The clinician must rule out gastrointestinal (GI) obstruction, GI inflammation, and extraalimentary tract diseases. Elimination of these disorders, in addition to the history as described, strongly suggests bilious vomiting syndrome.

Treatment

Feeding the dog an extra meal late at night to prevent the stomach from being empty for long periods of time is often curative. If vomiting continues, a gastric prokinetic may be administered late at night to prevent reflux. Rarely, a proton pump inhibitor is also required.

Prognosis

The prognosis is excellent. Most animals respond to therapy, and those that do not remain otherwise healthy.

GASTROINTESTINAL ULCERATION/EROSION

Etiology

Gastrointestinal ulceration/erosion (GUE) is more common in dogs than in cats. There are several potential causes. Drug-induced is one of the most common and most important causes. NSAIDs are a major cause of canine GUE because these drugs typically have longer half-lives in dogs than in people. Naproxen, ibuprofen, indomethacin, and flunixin are particularly dangerous to dogs. Concurrent use of more than one NSAID or use of an NSAID plus a glucocorticoid (especially dexamethasone) increases the risk of GUE. The newer COX-2–selective NSAIDs (e.g., carprofen, deracoxib, meloxicam, etodolac, firocoxib) are less likely to cause GUE; however, these drugs still have some activity against COX-1, and GUE can occur. Use of NSAIDs in animals with poor visceral perfusion (e.g., those in cardiac failure, shock) may also increase the risk of GUE.

Glucocorticoids are also common causes of GUE. Glucocorticoids such as prednisolone or prednisone, when used at doses typical for antiinflammatory effects, pose minimal risk for ulceration. However, patients receiving high doses of prednisolone, as well as those with additional risk factors for GUE (e.g., poorly perfused gastric mucosa, concurrent use of NSAIDs), are at high risk for ulceration. Some steroids such as dexamethasone are particularly ulcerogenic.

"Stress" ulceration is associated with severe hypovolemic, septic, or neurogenic shock, such as occurs after trauma, surgery, or endotoxemia. These ulcers are typically in the gastric antrum, body, and/or duodenum. Extreme exertion (e.g., in sled dogs, military working dogs) causes gastric erosions/ulcers, especially in the body and fundus, probably due to a combination of poor perfusion, high circulating levels of glucocorticoids, changes in core body temperature, and/or diet (i.e., high fat diets slowing emptying).

Gastric neoplasms and other infiltrative diseases (e.g., pythiosis) are important causes of GUE (see pp. 471-472), especially in older dogs and cats. Mast cell tumors and gastrinomas may cause ulceration as a paraneoplastic effect by increasing gastric acid secretion. Gastrinomas are principally found in the pancreas. They usually occur in older dogs and rarely in cats where they secrete gastrin, which in turn produces severe gastric hyperacidity, duodenal ulceration, esophagitis, and diarrhea.

Renal failure seldom causes GUE, but hepatic failure seems to be an important cause in dogs. Foreign objects rarely cause GUE, but they prevent healing and increase blood loss from preexisting ulcers.

Clinical Features

GUE is more common in dogs than in cats. Hyporexia may be the principal sign. If vomiting occurs, blood (i.e., fresh or digested) may or may not be present. Anemia and/or hypoproteinemia occasionally occur and may be severe enough to cause edema, pale mucous membranes, weakness, and/or dyspnea. Melena may occur if there is severe blood loss within a short period of time. Most affected dogs, even those with severe GUE, do not demonstrate pain during abdominal palpation. Perforation is associated with signs of septic peritonitis (see pp. 510-512). Some ulcers perforate and seal over before generalized peritonitis occurs. In such cases a small abscess may develop at the site, causing abdominal pain, hyporexia, and/or vomiting.

Diagnosis

A presumptive diagnosis of GUE is classically based on finding evidence of GI blood loss (e.g., hematemesis, melena, iron deficiency anemia, regenerative anemia with hypoalbuminemia) in an animal without a coagulopathy. However, lack of evidence of blood loss does not lessen the chance of GUE. History and physical examination may identify an

obvious cause (e.g., NSAID or dexamethasone administration). Perforation may cause peritonitis and signs of an acute abdomen and sepsis. Because mast cell tumors may resemble almost any cutaneous lesion (especially lipomas), *all* cutaneous masses or nodules should be evaluated cytologically. Hepatic failure is usually diagnosed based on the serum biochemistry profile. Contrast radiographs are diagnostic for foreign objects but rarely demonstrate GUE. Ultrasonography sometimes detects gastric thickening due to infiltrated lesions and/or mucosal defects (Fig. 30.5). Endoscopy (Video 30.3) is the most sensitive and specific tool for diagnosing GUE (see Figs. 27.14 to 27.17) and, in conjunction with biopsy, can be used to diagnose infiltrates (neoplastic or inflammatory) (see Fig. 27.16), foreign bodies (see Fig. 27.20), and inflammation causing GUE. Endoscopic findings may suggest gastrinoma if duodenal erosions are found. Serum gastrin concentrations should be measured if a gastrinoma is suspected or if there are no other likely causes.

Treatment

Therapy depends on the severity of GUE and whether an underlying cause is detected. Animals with suspected GUE that is not obviously life-threatening (i.e., no evidence of severe anemia, shock, sepsis, severe abdominal pain, or severe depression) may sometimes first be treated symptomatically if the clinician strongly suspects the cause is drug induced or "stress" induced.

Eliminating the underlying etiology (e.g., NSAIDs, shock) often results in resolution of the ulcer within 3 to 5 days. If the cause is unknown or cannot be removed or if it is important to resolve the ulcer quickly, then specific antiulcer medication is appropriate. Proton pump inhibitors or sucralfate are the major pharmacologic options. If appropriate medical therapy has not afforded clinical improvement after 5 or 6 days, or if the animal has life-threatening bleeding despite appropriate medical therapy, resection of the ulcer(s) must be considered. The stomach should be examined endoscopically before surgery to determine the number and location of the ulcers; it is surprisingly easy to miss ulcers during laparotomy/gastrotomy.

Prevention of GUE is desirable, and rational NSAID and glucocorticoid therapy are especially important. Sucralfate (Carafate; see Table 28.5) and histamine-2 (H_2) receptor antagonists (see Table 28.4) have been administered to prevent GUE in dogs receiving NSAIDs, but there is no good evidence that these drugs are effective prophylactic agents. Proton pump inhibitors are effective in preventing "stress"-induced ulceration as well as NSAID-induced GUE. Misoprostol (see Table 28.5) was designed to prevent NSAID-induced ulceration, and it can be used to treat ulcers. However, proton pump inhibitor therapy seems as effective and has fewer side effects. No drug has been shown to be effective in preventing steroid-induced GUE (especially dexamethasone).

Prognosis

The prognosis is favorable if the underlying cause can be controlled and if therapy prevents perforation of the ulcer.



FIG 30.5
Abdominal ultrasound of the stomach showing thickened gastric wall and an obvious defect representing an ulcer.

INFILTRATIVE GASTRIC DISEASES

NEOPLASMS

Etiology

Neoplastic infiltrations (e.g., adenocarcinoma, lymphoma, leiomyomas, leiomyosarcomas, and stromal tumors in dogs; lymphoma in cats) may produce GUE through direct mucosal disruption. Gastric lymphoma is typically a diffuse lesion but can produce masses. The cause and significance of benign gastric polyps are unknown. They seem to occur more commonly in the body and antrum.

Clinical Features

Dogs and cats with gastric tumors are usually asymptomatic until the disease is advanced. Hyporexia (not vomiting) is the most common initial sign. Vomiting caused by gastric neoplasia usually signifies advanced disease or gastric outflow obstruction. Adenocarcinomas are typically infiltrative and decrease emptying by impairing motility and/or obstructing the outflow tract. Weight loss is commonly caused by nutrient loss or cancer cachexia syndrome. Hematemesis occasionally occurs; leiomyomas seem to have the greatest potential to cause severe, acute, upper GI bleeding. Other bleeding gastric tumors are more likely to cause chronic iron deficiency anemia even if GI blood loss is not obvious. Polyps rarely cause signs unless they obstruct the pylorus.

Diagnosis

Iron deficiency anemia in a dog or cat without an obvious cause of blood loss suggests chronic GI bleeding. A regenerative anemia plus hypoalbuminemia suggests acute blood loss.

Plain and contrast imaging may reveal gastric wall thickening, decreased motility, and/or mucosal irregularities. The only sign of submucosal adenocarcinoma may be failure of one area to dilate during insufflation. Ultrasound-guided aspiration of thickened areas in the gastric wall will sometimes allow diagnosis of adenocarcinoma or lymphoma.

Most tumors will be obvious endoscopically, and it is usually easy to successfully biopsy mucosal lymphomas and nonscirrhous adenocarcinomas with flexible forceps. Leiomyomas, leiomyosarcomas, stromal tumors, and scirrhous adenocarcinomas can be very dense, to the point that sometimes diagnostic tissue samples cannot be obtained with flexible endoscopic forceps. Smooth muscle and stromal tumors also tend to be principally submucosal, making it difficult to obtain a deep enough biopsy with flexible forceps. Hence, a presumptive diagnosis of these tumors is often based upon gross appearance (i.e., thickened ulcerative lesion with hard, black center for scirrhous adenocarcinoma; submucosal mass pushing into the lumen, covered with relatively normal-appearing mucosa, often with one or more obvious ulcers for leiomyomas). Surgical biopsy may be required in such cases. Polyps are usually obvious endoscopically, but a biopsy specimen should always be obtained and evaluated to ensure that adenocarcinoma is not present.

Treatment

Most adenocarcinomas are well advanced before clinical signs are obvious, making complete surgical excision impossible. Leiomyomas, leiomyosarcomas, and stromal tumors are often resectable. Gastroduodenostomy may palliate gastric outflow obstruction caused by an unresectable tumor. Chemotherapy is rarely helpful except for dogs and cats with lymphoma.

Prognosis

The prognosis for adenocarcinomas is very poor unless they are detected early. With early diagnosis, leiomyomas and leiomyosarcomas are often cured surgically. Low-grade solitary gastric lymphoma in cats might be comparable to *Helicobacter*-induced, MALT-associated lymphoma in people; surgery and/or antibiotic therapy might be beneficial. However, most gastric lymphoma is part of a more generalized lesion of the GI tract, and chemotherapy is the only option (see Chapter 79). Resection of gastric polyps appears unnecessary unless they are causing outflow obstruction.

PYTHIOSIS

Etiology

Pythiosis is a fungal infection caused by *Pythium insidiosum*. Although principally found in the Gulf Coast area of the southeastern United States, it can be found anywhere from the east to the west coast. Any area of the alimentary tract or skin may be affected. The fungus typically causes intense submucosal infiltration of fibrous connective tissue and a purulent, eosinophilic, granulomatous inflammation causing GUE. Such infiltration prevents peristalsis, causing stasis.

Clinical Features

Pythiosis principally affects dogs, typically causing vomiting, anorexia, diarrhea, and/or weight loss. Because gastric outflow obstruction occurs frequently, vomiting is common. Colonic involvement may cause tenesmus and hematochezia. Esophageal involvement may cause severe regurgitation or hyporexia.

Diagnosis

Diagnosis requires serology or seeing the organism cytologically or histologically. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) tests are available to look for antibodies or antigen, respectively. Biopsy samples should include the submucosa because the organism is more likely to be there than in the mucosa. Diagnostic biopsy specimens can be procured with rigid endoscopy; however, the dense nature of the infiltrate makes it difficult to obtain diagnostic samples with flexible endoscopy. Cytologic analysis of a tissue sample obtained by scraping an excised piece of submucosa with a scalpel blade may be diagnostic; fungal hyphae that do not stain and appear as "ghosts" with typical Romanowsky-type stains are suggestive of pythiosis. The organisms may be sparse and difficult to find histologically, even in large tissue samples. Seeing an inflamed section of stomach that has a sharply demarcated border of infarcted tissue is strongly suggestive.

Treatment

Complete surgical excision provides the best chance for cure. Itraconazole, voraconazole, posaconazole, liposomal amphotericin B, and/or terbinafine may benefit some animals for varying periods of time, but cure is not expected. Immunotherapy has anecdotally been associated with remission of signs for varying periods of time.

Prognosis

Pythiosis often spreads to or involves structures that cannot be surgically removed (e.g., root of the mesentery, pancreas surrounding the bile duct), resulting in a grim prognosis.

Suggested Readings

Amorim I, et al. Canine gastric pathology: a review. *J Comp Path*. 2016;154:9.

von Babo V, et al. Canine non-hematopoietic gastric neoplasia. Epidemiologic and diagnostic characteristics in 38 dogs with post-surgical outcome of five cases. *Tierarztl Prax Ausg K Kleintiere Heimtiere*. 2012;40:243.

Beck JJ, et al. Risk factors associated with short-term outcome and development of perioperative complications in dogs undergoing surgery because of gastric dilatation-volvulus: 166 cases (1992-2003). *J Am Vet Med Assoc*. 1934;229:2006.

Belch A, et al. Modified tube gastropexy using a mushroom-tipped silicone catheter for management of gastric dilatation/volvulus in dogs. *J Small Anim Pract*. 2017;58:79.

Bell JS. Inherited and predisposing factors in the development of gastric dilatation volvulus in dogs. *Top Companion Anim Med*. 2014;29:60.

Bergh MS, et al. The coxib NSAIDs: potential clinical and pharmacologic importance in veterinary medicine. *J Vet Intern Med*. 2005;19:633.

Bilek A, et al. Breed-associated increased occurrence of gastric carcinoma in Chow-Chows. *Wien Tierarzti Mschr*. 2007;94:71.

Boag AK, et al. Acid-base and electrolyte abnormalities in dogs with gastrointestinal foreign bodies. *J Vet Intern Med*. 2005;19: 816.

Bridgeford EC, et al. Gastric *Helicobacter* species as a cause of feline gastric lymphoma: a viable hypothesis. *Vet Immunol Immunopathol*. 2008;123:106.

Buber T, et al. Evaluation of lidocaine treatment and risk factors for death associated with gastric dilatation and volvulus in dogs: 112 cases (1997-2005). *J Am Vet Med Assoc*. 2007;230:1334.

Case JB, et al. Proximal duodenal perforation in three dogs following deracoxib administration. *J Am Anim Hosp Assoc*. 2010;46:255.

Davignon DL, et al. Evaluation of capsule endoscopy to detect mucosal lesions associated with gastrointestinal bleeding in dogs. *J Small Anim Pract*. 2016;57:148.

Dowers K, et al. Effect of short-term sequential administration of nonsteroidal anti-inflammatory drugs on the stomach and proximal portion of the duodenum in healthy dogs. *Am J Vet Res*. 1794;67:2006.

Gould E, et al. A prospective, placebo-controlled pilot evaluation of the effects of omeprazole on serum calcium, magnesium, cobalamin, gastrin concentrations, and bone in cats. *J Vet Intern Med*. 2016;30:779.

Graham A, et al. Effects of prednisone alone or prednisone with ultralow-dose aspirin on the gastroduodenal mucosa of healthy dogs. *J Vet Intern Med*. 2009;23:482.

Grooters AM, et al. Development and evaluation of an enzyme-linked immunosorbent assay for the serodiagnosis of pythiosis in dogs. *J Vet Intern Med*. 2002;16:142.

Hensel P, et al. Immunotherapy for treatment of multicentric cutaneous pythiosis in a dog. *J Am Vet Med Assoc*. 2003;223:215.

Hobday MM, et al. Linear versus non-linear gastrointestinal foreign bodies in 499 dogs: clinical presentation, management and short-term outcome. *J Small Anim Pract*. 2014;55:560.

Jergens A, et al. Fluorescence *in situ* hybridization confirms clearance of visible *Helicobacter* spp associated with gastritis in dogs and cats. *J Vet Intern Med*. 2009;23:16.

Lascelles B, et al. Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003). *J Am Vet Med Assoc*. 2005;227:1112.

Leib MS, et al. Triple antimicrobial therapy and acid suppression in dogs with chronic vomiting and gastric *Helicobacter* spp. *J Vet Intern Med*. 2007;21:1185.

Levine JM, et al. Adverse effects and outcome associated with dexamethasone administration in dogs with acute thoracolumbar intervertebral disk herniation: 161 cases (2000-2006). *J Am Vet Med Assoc*. 2008;232:411.

Lyles S, et al. Idiopathic eosinophilic masses of the gastrointestinal tract in dogs. *J Vet Intern Med*. 2009;23:818.

MacKenzie G, et al. A retrospective study of factors influencing survival following surgery for gastric dilation-volvulus syndrome in 306 dogs. *J Am Anim Hosp Assoc*. 2010;46:97.

Monnig AA, et al. A review of stress-related mucosal disease. *J Vet Emerg Crit Care*. 2011;21:484.

Mooney E, et al. Plasma lactate concentration as a prognostic biomarker in dogs with gastric dilation and volvulus. *Top Comp Anim Med*. 2014;29:71.

Peters R, et al. Histopathologic features of canine uremic gastropathy: a retrospective study. *J Vet Intern Med*. 2005;19:315.

Raghavan M, et al. Diet-related risk factors for gastric dilatation-volvulus in dogs of high-risk breeds. *J Am Anim Hosp Assoc*. 2004;40:192.

Raghavan M, et al. The effect of ingredients in dry dog foods on the risk of gastric dilatation-volvulus in dogs. *J Am Anim Hosp Assoc*. 2006;42:28.

Sennello K, et al. Effects of deracoxib or buffered aspirin on the gastric mucosa of healthy dogs. *J Vet Intern Med*. 2006;20:1291.

Steelman-Szymeczek SJ, et al. Clinical evaluation of a right-sided prophylactic gastropexy via a grid approach. *J Am Anim Hosp Assoc*. 2003;39:397.

Swan HM, et al. Canine gastric adenocarcinoma and leiomyosarcoma: a retrospective study of 21 cases (1986-1999) and literature review. *J Am Anim Hosp Assoc*. 2002;38:157.

Tams TR, et al. Endoscopic removal of gastrointestinal foreign bodies. In: Tams TR, et al., eds. *Small animal endoscopy*. 3rd ed. St Louis: Elsevier/Mosby; 2011.

Taulescu MA, et al. Histopathological features of canine spontaneous non-neoplastic gastric polyps – a retrospective study of 15 cases. *Histol Histopathol*. 2014;29:65.

Tolbert K, et al. Efficacy of oral famotidine and 2 omeprazole formulations for the control of intragastric pH in dogs. *J Vet Intern Med*. 2011;25:47.

Tomlinson AW, et al. Pyloric localization in 57 dogs of breeds susceptible to gastric dilatation-volvulus using computed tomography. *Vet Rec*. 2016;24:626.

Ullmann B, et al. Gastric dilatation volvulus: a retrospective study of 203 dogs with ventral midline gastropexy. *J Small Anim Pract*. 2016;57:18.

Ward DM, et al. The effect of dosing interval on the efficacy of misoprostol in the prevention of aspirin-induced gastric injury. *J Vet Intern Med*. 2003;17:282.

Webb C, et al. Canine gastritis. *Vet Clin N Am*. 2003;33:969.

Wiinberg B, et al. Quantitative analysis of inflammatory and immune responses in dogs with gastritis and their relationship to *Helicobacter* spp infection. *J Vet Intern Med*. 2005;19:4.

Williamson KK, et al. Efficacy of omeprazole versus high dose famotidine for prevention of exercise-induced gastritis in racing Alaskan sled dogs. *J Vet Intern Med*. 2010;24:285.

Zacher L, et al. Association between outcome and changes in plasma lactate concentration during presurgical treatment in dogs with gastric dilatation-volvulus: 64 cases (2002-2008). *J Am Vet Med Assoc*. 2010;236:892.

CHAPTER 31

Disorders of the Intestinal Tract



ACUTE DIARRHEA

ACUTE ENTERITIS

Etiology

Acute enteritis is most commonly caused by infectious agents, poor diet, abrupt dietary changes, inappropriate foods, additives (e.g., chemicals), and/or parasites. Recent boarding at a kennel, being a scavenger, or having a recent diet change are risk factors for developing acute diarrhea. Except for parvovirus, parasites, and obvious dietary indiscretions, the cause is rarely diagnosed, because most affected animals spontaneously improve with or without supportive therapy.

Clinical Features

Diarrhea of unknown cause is common, especially in puppies and kittens. Signs consist of diarrhea with or without vomiting, dehydration, fever, anorexia, depression, crying, and/or abdominal pain. Very young animals may become hypothermic, hypoglycemic, and stuporous.

Diagnosis

History and physical and fecal examinations are used to identify possible causes. Fecal flotation (preferably a centrifugal flotation using zinc sulfate flotation solution) and direct fecal examinations are always indicated because parasites may worsen the problem even if they are not the main cause. The need for other diagnostic procedures depends on severity of the illness and the risk of contagion. Clinically mild enteritis is usually treated symptomatically, with few diagnostic tests being performed. If the animal is febrile, has hemorrhagic stools, is part of an outbreak of enteritis, or is particularly ill, then additional tests (e.g., complete blood count [CBC] to identify neutropenia, fecal enzyme-linked immunosorbent assay [ELISA] for canine parvovirus, serologic analysis for feline leukemia virus [FeLV] and feline immunodeficiency virus [FIV], blood glucose to identify hypoglycemia, and serum electrolytes to detect hypokalemia) are reasonable. Abdominal imaging should be evaluated if obvious abdominal pain or masses are detected or if obstruction or foreign body are suspected.

Treatment

Symptomatic therapy usually suffices. The cause is usually unknown or is a virus for which there is no specific therapy. The goal of symptomatic therapy is reestablishment of fluid, electrolyte, and acid-base homeostasis. Animals with severe dehydration (i.e., ≥8%-10% as determined by sunken eyes, fast weak pulse, and marked depression, or a history of significant fluid loss coupled with inadequate fluid intake) should receive intravenous (IV) fluids, whereas fluids administered orally or subcutaneously usually suffice for patients less severely dehydrated. Potassium supplementation is usually indicated, but bicarbonate is rarely needed. Oral rehydration sometimes allows home management of animals, especially when litters of young animals are affected. (See the discussion on fluid, electrolyte, and acid-base therapy in Chapter 28 for details.)

Antidiarrheals are seldom necessary except when excessive fecal losses make maintenance of fluid and electrolyte balance difficult. Opiates are usually the most effective antidiarrheals. Bismuth subsalicylate (see Table 28.6) is useful in stopping diarrhea in dogs with mild to moderate enteritis. However, absorption of the salicylate may cause nephrotoxicity in some animals (especially when combined with other potentially nephrotoxic drugs), and many dogs dislike the taste. Cats rarely need these medications. (See the discussion on drugs that prolong intestinal transit time in Chapter 28.) If antidiarrheals are needed for more than 2 to 5 days, the animal should be carefully reassessed. Probiotics typically shorten the duration of acute diarrhea.

Severe intestinal inflammation often causes vomiting that is difficult to control. Central-acting antiemetics (e.g., maropitant or ondansetron; see Table 28.3) are more likely to be effective than peripheral-acting drugs.

Although food is typically withheld from animals with severe enteritis to "rest" the intestinal tract, such starvation may be counterproductive. Administering even small amounts of food to the intestines helps them recover sooner

and prevents bacteria from translocating across the mucosa. Denying oral intake is occasionally necessary when eating causes severe vomiting or explosive diarrhea with substantial fluid loss. However, if feeding does not make the pet's vomiting and diarrhea *much* worse, feeding small amounts of food is probably more beneficial than withholding food. Frequent small feedings of easily digested, nonirritative foods (e.g., cottage cheese, boiled chicken, potato) is the most common approach. If food must be withheld, it should be reoffered as soon as possible. Parenteral nutrition is rarely needed in animals with severe enteritis.

If the animal is febrile or neutropenic or has systemic inflammatory response syndrome (SIRS; formerly called *septic shock*), broad-spectrum systemic antibiotic therapy (e.g., clindamycin or a β-lactam antibiotic plus either an aminoglycoside or a fluoroquinolone) are indicated (see the discussion of drugs used in gastrointestinal [GI] disorders, pp. 442-443). The clinician should observe for hypoglycemia, especially in young animals. Adding dextrose (2.5%-5%) to IV fluids or administering an IV bolus of 50% dextrose (2-5 mL/kg) may be necessary to prevent/counter hypoglycemia.

If the cause of the diarrhea is unknown, the clinician should assume it to be infectious and disinfect the premises accordingly. Bleach diluted in water (i.e., 1:32, respectively) destroys parvovirus and many other infectious agents causing diarrhea. Animals must not be injured by inappropriate contact with such disinfectants. Personnel coming in contact with the animals, cages, and litter should wear protective clothing (e.g., boots, gloves, gowns) that can be discarded or disinfected when leaving the area.

After the enteropathy appears to be clinically resolved, the animal is gradually returned to its normal diet over a 5- to 10-day period. If this change is associated with more diarrhea, then the switch is postponed for another 3 to 5 days.

Prognosis

The prognosis depends on the animal's condition and can be influenced by its age and other GI problems. Very young or emaciated animals and those with SIRS or substantial intestinal parasite burdens have a more guarded prognosis. If intussusception occurs secondary to acute enteritis, the prognosis is guarded.

ENTEROTOXEMIA

Etiology

The cause is assumed to be bacterial, although causative organisms are almost never identified.

Clinical Features

Acute onset of severe, often mucoid-bloody diarrhea with/without vomiting is typical. In severe cases, mucus casts of the intestines are expelled, making it appear that the intestinal mucosa is being lost. In contrast to animals with acute enteritis, these patients usually feel ill and may exhibit symptoms of shock early in the course of the disease. CBCs typically reveal a neutrophilic leukocytosis, often with a left shift and sometimes with white blood cell (WBC) toxicity.

Diagnosis

Exclusion of other causes by history and physical examination coupled with severe WBC changes (e.g., toxicity, left shift) on the CBC permit presumptive diagnosis. The pet should be checked for intestinal parasites that may be contributing to the problem. Fecal cultures are rarely useful.

Treatment

These patients typically need aggressive IV fluid therapy. Broad-spectrum antibiotic therapy (e.g., ampicillin plus sulbactam) is typically administered although its value is unknown. The serum albumin concentration must be monitored and colloids given if needed. Disseminated intravascular coagulation (DIC) may require plasma and/or heparin therapy.

Prognosis

The prognosis depends on how ill the patient is at presentation.

DIETARY-INDUCED ACUTE DIARRHEA

Etiology

Dietary causes of diarrhea are common, especially in young animals. Poor-quality ingredients (e.g., rancid fat), bacterial enterotoxins or mycotoxins, allergy or intolerance to ingredients (usually in older patients), or inability to digest certain foods (due to enzyme deficiencies) are common causes. Some intestinal brush border enzymes are produced in response to the presence of substrates (e.g., disaccharidases). If the diet is suddenly changed, some animals (especially puppies and kittens) are unable to digest or absorb certain nutrients until the intestinal brush border adapts to the new diet. Other animals may never be able to produce the necessary enzymes (e.g., lactase) to digest certain nutrients (e.g., lactose).

Clinical Features

Diet-induced diarrhea occurs in both dogs and cats. The diarrhea tends to reflect small intestinal dysfunction (i.e., there is usually no fecal blood or mucus) unless there is colonic involvement. The diarrhea usually starts shortly after the new diet is initiated (e.g., 1-3 days) and is mild to moderate in severity. Affected animals infrequently have other signs unless parasites or complicating factors are present.

Diagnosis

History and physical and fecal examinations are used to eliminate other common causes. If diarrhea occurs shortly after a suspected or known dietary change (e.g., after the pet is brought home), a tentative diagnosis of diet-induced disease is reasonable. However, the pet may also be showing the first clinical signs of a recently acquired infection. The animal should always be checked for intestinal parasites,

because they may contribute to the problem even when they are not the principal cause.

Treatment

An easily digested (so-called "bland") diet (e.g., boiled potato plus boiled skinless chicken) fed in multiple small feedings (see pp. 434-435) usually causes resolution of diarrhea in 1 to 3 days. Once the diarrhea resolves, the diet can be gradually changed back to the pet's regular diet.

Prognosis

The prognosis is usually excellent unless a young animal with minimal nutritional reserves becomes emaciated, dehydrated, or hypoglycemic.

INFECTIOUS DIARRHEA

CANINE PARVOVIRAL ENTERITIS

Etiology

Two types of parvoviruses infect dogs. Canine parvovirus-1 (CPV-1), also known as "minute virus of canines," is a relatively nonpathogenic virus that sometimes is associated with gastroenteritis, pneumonitis, and/or myocarditis in puppies 1 to 3 weeks old. Canine parvovirus-2 (CPV-2) is responsible for classic parvoviral enteritis, and there now are at least three strains (CPV-2 a, b, and c). CPV-2 usually causes signs 5 to 12 days after the dog is infected via the fecal-oral route by destroying rapidly dividing cells (i.e., bone marrow progenitors and intestinal crypt epithelium).

Clinical Features

The virus has mutated since it was first recognized, and the most recently recognized mutations may be more pathogenic in some dogs. CPV-2b and CPV-2c can also infect cats. Clinical signs depend on the virulence of the virus, size of the inoculum, host's defenses, age of the pup, and presence of other enteric pathogens and/or parasites. Doberman Pinschers, Rottweilers, Pit Bulls, Labrador Retrievers, and German Shepherds may be more susceptible than other breeds. Viral destruction of intestinal crypts may produce villus collapse, diarrhea, vomiting, intestinal bleeding, and subsequent bacterial invasion, but some animals have mild or even subclinical disease. Many dogs are initially presented because of depression, hyporexia, and/or vomiting (which can closely mimic foreign object ingestion) without diarrhea. Diarrhea is often absent for the first 24 to 48 hours of illness and may not be bloody if and when it does occur. Intestinal protein loss may occur secondary to inflammation, causing hypoalbuminemia. Vomiting is usually prominent and may be severe enough to mimic foreign body obstruction and/or cause esophagitis. Damage to bone marrow progenitors may produce transient or prolonged neutropenia, making the animal susceptible to serious bacterial infection, especially if a damaged intestinal tract allows bacterial translocation across the mucosa. Fever and/or SIRS are common in severely ill dogs but are often absent in less severely affected animals. Puppies infected *in utero* or before 8 weeks of age may develop myocarditis. Rarely, parvoviral infection may be associated with erythematous cutaneous lesions (erythema multiforme).

Diagnosis

Diagnosis is often tentatively made based on history and physical examination findings. Neutropenia is suggestive but neither sensitive nor specific for canine parvovirus enteritis; salmonellosis or any overwhelming infection can cause similar leukogram changes. Furthermore, the neutropenia may be very shortlived (i.e., < 12 hours). Regardless of whether diarrhea occurs, infected dogs shed large numbers of viral particles in the feces (i.e., $>10^9$ particles/g). Electron microscopic evaluation of feces detects parvovirus, but CPV-1 (usually nonpathogenic except in neonates) is morphologically indistinguishable from CPV-2. Detecting antibodies to CPV appears useful for determining if vaccination has been successful but not for diagnosis of acutely ill patients. Fecal polymerase chain reaction (PCR) testing is very sensitive and specific but must be performed at diagnostic laboratories. Fecal "point-of-care" testing is considered the standard testing for most practices. There are different point-of-care methodologies (i.e., ELISA, immunochromatography, immunomigration). All are highly specific, but the sensitivity for both CPV-2b and CPV-2c is less than desired. Vaccination with a modified live parvoviral vaccine may cause a weak positive result for 5 to 15 days after vaccination. ELISA results may be negative if the assay is performed too early in the clinical course of the disease (i.e., virus is not yet being shed in feces). Therefore, if faced with a dog that seems likely to have parvoviral enteritis but is negative on the point-of-care test, the clinician should either repeat the test in 3 to 4 days or send feces to a diagnostic laboratory for PCR testing. Shedding decreases rapidly and may be undetectable by 10 to 14 days after infection, especially if the virus is being bound by fecal antibodies and/or diluted by diarrhea. Rarely, clinically normal dogs and dogs with chronic enteropathies will test positive; this may be due to asymptomatic infection or intestinal passage of the virus.

A positive test result confirms the presumptive diagnosis of parvoviral enteritis. A negative result warrants consideration of diseases that can mimic parvovirus (e.g., salmonellosis, intussusception). If the dog dies, there are typical histologic lesions (i.e., crypt necrosis), and fluorescent antibody and fluorescent *in situ* hybridization techniques can establish a definitive diagnosis.

Treatment

Treatment of canine parvoviral enteritis is fundamentally the same as for any severe, acute, infectious enteritis and depends upon the clinical severity. Severely ill dogs need in-clinic treatment, whereas mildly affected animals can often be treated at home. Fluid and electrolyte therapy is crucial and is typically combined with antibiotics (Box 31.1). Most dogs survive if they can be supported long enough. However, very

BOX 31.1

General Guidelines for Treatment of Canine Parvoviral Enteritis*

Fluids†‡

Administer balanced electrolyte solution with 30-40 mEq potassium chloride/L.
Calculate maintenance requirements (i.e., 66 mL/kg/day, with dogs < 5 kg needing up to 80 mL/kg/day).
Estimate deficit (better to slightly overestimate rather than underestimate deficit).
Dogs with very mild cases may receive subcutaneous fluids (intravenous [IV] fluids still preferred), but watch for sudden worsening of the disease.
Dogs with moderate to severe cases should receive fluids via the IV route (can use intramedullary route if IV access cannot be established).
Add 2.5%-5% dextrose to the IV fluids if hypoglycemia or systemic inflammatory response syndrome is present or is a risk.
Administer plasma or hetastarch if dog has serum albumin ≤ 2 g/dL.
- Plasma: 6-10 mL/kg over 4 hours; repeat until the desired serum albumin concentration is attained (this approach tends to be much more expensive than using hetastarch).
- Hetastarch: 10-20 mL/kg (give in increments, not all at once) (generally do not use both plasma and hetastarch).

Antibiotics†

Administer to febrile or severely neutropenic dogs.
Prophylactic antibiotics for afebrile neutropenic patients (e.g., cefazolin).
Broad-spectrum antibiotics for febrile, neutropenic patients (e.g., β-lactam for gram-positive and anaerobic bacteria [e.g., ampicillin and sulbactam] plus broad spectrum for gram-negative bacteria [e.g., amikacin or enrofloxacin]).

Antiemetics

Given if needed for vomiting or nausea:
- Maropitant (some risk of bone marrow suppression in puppies < 11-16 weeks of age)
- Ondansetron
- Metoclopramide (best used as an add-on to maropitant or ondansetron if those drugs are inadequate—a constant rate infusion is more effective than intermittent bolusing).

Anthelmintics

Pyrantel (should be given after feeding).
Ivermectin (this drug is absorbed in the oral mucous membranes; do not give to breeds likely to have adverse effects, such as Collies, Old English Sheepdogs, etc.).

Probiotics

Controversial
Fecal transplantation
Currently being tried – of uncertain value

Dogs With Secondary Esophagitis

If regurgitation occurs in addition to vomiting, administer:
- Proton pump inhibitor (Pantoprazole injectable)

Special Nutritional Therapy

Try to feed dog small amounts as soon as feeding does not cause major exacerbation in vomiting.
"Microenteral" nutrition (slow drip of enteral diet administered via nasoesophageal tube) if dog refuses to eat and administration does not make vomiting worse.
Administer parenteral nutrition if prolonged anorexia occurs.
- Peripheral parenteral nutrition is more convenient than total parenteral nutrition.

Monitor Physical Status

Physical examination (1-3 times per day depending on severity of signs)
Body weight (1-2 times per day to assess changes in hydration status)
Potassium (every 1-2 days depending on severity of vomiting/diarrhea)
Serum protein (every 1-2 days depending on severity of signs)
Glucose (every 4-12 hours in dogs that have systemic inflammatory response syndrome or were initially hypoglycemic)
Packed cell volume (every 1-2 days)
White blood cell count: either actual count or estimated from a slide (every 1-2 days in febrile animals)

*The same guidelines generally apply to dogs with other causes of acute enteritis/gastritis.
†Usually the first considerations when an animal is presented.
‡A history of decreased intake plus increased loss such as vomiting and/or diarrhea confirms dehydration, regardless of whether dog appears to be dehydrated.

young puppies, dogs in severe SIRS, and certain breeds seem to have higher morbidity and mortality. Common therapeutic mistakes include inadequate fluid therapy, overzealous fluid administration (especially in dogs with severe hypoproteinemia), failure to administer glucose to hypoglycemic patients, failure to supplement adequate potassium, not recognizing sepsis, and not finding concurrent GI disease (e.g., parasites, intussusception).

If the serum albumin concentration is less than 2 g/dL, it is probably advantageous to administer plasma or colloids

(e.g., hetastarch). Plasma has antibodies that are presumed to be beneficial, but there is no evidence that they affect outcome. Colloids are typically preferred because they are less expensive and more effective in raising plasma oncotic pressure. Antibiotic therapy is necessary if there is evidence of infection (i.e., fever, SIRS) or increased risk of infection (i.e., severe neutropenia). If the animal is neutropenic but afebrile, administration of a first-generation cephalosporin is reasonable for prophylaxis. If the animal is in SIRS, an antibiotic combination with a broad aerobic and anaerobic spectrum is recommended (e.g., ampicillin plus either amikacin or enrofloxacin). Aminoglycosides should not be administered until the patient is rehydrated and renal perfusion is reestablished. Administering enrofloxacin to young, large-breed dogs may damage cartilage, but this is preferable to death. Severe vomiting complicates therapy and may require administration of maropitant or ondansetron (see Table 28.3). Maropitant seems to help alleviate visceral pain in addition to being an effective antiemetic. If these drugs are ineffective, then combining them with constant rate infusion of metoclopramide often enhances efficacy. If esophagitis occurs, a proton pump inhibitor may be useful (see Table 28.4). Human granulocyte colony-stimulating factor (G-CSF, 5 µg/kg SQq24h) to increase neutrophil numbers, Tamiflu (oseltamivir phosphate, 2 mg/kg orally [PO] q12-24h) to combat the virus, and equine antiendotoxin serum have been advocated, but there is no evidence that they substantively affect outcome. Flunixin meglumine has been anecdotally suggested for patients in SIRS, but there is substantial risk of iatrogenic ulceration and/or perforation. There is some evidence that recombinant feline interferon omega (rFeIFN-ω, 2.5×10^6 units/kg IV) improves outcome, but it is not readily available.

If possible, feeding small amounts of liquid diet via a nasoesophageal (NE) tube seems to help the intestines heal more rapidly. An easily digested diet may be fed once vomiting has ceased. Parenteral nutrition can benefit patients that are persistently unable to hold down oral food. Partial parenteral nutrition (also called *peripheral parenteral nutrition*) is easier and less expensive than total parenteral nutrition. The dog should be kept away from other susceptible animals for 2 to 4 weeks after discharge, and the owner should be conscientious about feces disposal. Vaccination of other dogs in the household should be considered.

When trying to prevent the spread of parvoviral enteritis, the clinician must remember that (1) parvovirus persists in the environment for long periods of time (i.e., months), making it difficult to prevent exposure; (2) asymptomatic dogs may shed virulent CPV-2; (3) maternal immunity sufficient to inactivate vaccine virus may be present in some puppies; and (4) dilute bleach (1:32) is one of the few readily available disinfectants that kills the virus, but it can take 10 minutes to be effective.

Vaccination of pups should generally commence at 6 to 8 weeks of age. The antigen density and immunogenicity of the vaccine as well as the amount of antibody transferred from the bitch determine when the pup can be successfully immunized. Inactivated vaccines generally are not as successful as attenuated vaccines, and giving a series of vaccinations is recommended. Attenuated vaccines are more successful in producing a long-lasting immunity. Typically, administering an attenuated vaccine at 6, 9, and 12 weeks of age is usually successful. If the initial vaccination is after 16 weeks of age, then two doses 2 to 4 weeks apart suffice. If vaccination is before 5 to 6 weeks of age, an inactivated vaccine is safer. After the initial series, one booster between 6 to 12 months of age is recommended. Revaccination every 3 years should be sufficient after the initial series and first booster. There is no strong evidence that parvoviral vaccination should be given separately from modified live canine distemper vaccinations. However, modified live vaccinations should not be administered to patients younger than 5 weeks of age or those suspected of incubating or being affected with distemper. Vaccination with CPV-2b virus protects against infection with CPV-2c. If necessary, serum antibody titers (which are assumed to be protective) may be measured to determine if the vaccination appeared to be effective. Regardless of the vaccine or protocol used, there is no guarantee of success. Parvoviral enteritis has occurred in supposedly well-vaccinated dogs.

If parvoviral enteritis develops in one dog in a multiple-dog household, it is reasonable to administer booster vaccinations to the other dogs, preferably using an inactivated vaccine in case they are incubating the infection at the time of immunization. If the client is bringing a puppy into a house with a dog that has recently had parvoviral enteritis, the puppy should be kept elsewhere until it has received its immunizations.

Prognosis

Dogs treated in a timely fashion with proper therapy typically live, especially if they survive the first 4 days of clinical signs. Intussusception secondary to parvoviral enteritis may cause persistent diarrhea in pups otherwise recovering. Dogs that have recovered from CPV-2 enteritis develop long-lived immunity that may be lifelong.

FELINE PARVOVIRAL ENTERITIS

Etiology

Feline parvoviral enteritis (feline distemper, feline panleukopenia) is caused by feline panleukopenia virus (FPV), which is distinct from CVP-2b. However, CPV-2a, CPV-2b, and CPV-2c can infect cats and cause disease. Kittens need to be vaccinated after 12 weeks of age to ensure protection.

Clinical Features

Many infected cats never show clinical signs of disease. Signs in affected cats are usually similar to those described for dogs with parvoviral enteritis. If a pregnant queen is infected, the result may be abortion or congenital abnormalities. If the fetus is infected later in pregnancy or immediately after birth, cerebellar hypoplasia may result.

Diagnosis

Diagnosis is similar to that described for canine parvovirus. The sensitivity and specificity of the point-of-care canine ELISA tests for fecal CPV in cats are comparable to that in dogs. However, it is important to note that the test may be positive for only 1 to 2 days after infection; by the time the cat is clinically ill, this test may not be able to detect viral shedding in the feces.

Treatment/Prevention

Cats with parvoviral infection are treated much the same way as described for dogs. Administering recombinant feline interferon omega has not been beneficial. A major difference between dogs and cats centers on immunization: parvoviral vaccine (both inactivated and attenuated live) typically is more effective in cats than in dogs. Attenuated live vaccines are preferred, but kittens younger than 4 weeks of age should receive inactivated vaccines (two doses 3-4 weeks apart). Also, the vaccine cannot be administered orally, but intranasal administration is effective. Immunity generally lasts for more than 5 to 7 years after the initial series and booster.

Prognosis

As with dogs, many affected cats live if overwhelming sepsis is prevented and they can be supported long enough. Thrombocytopenia, hypoalbuminemia, and hypokalemia are negative prognostic signs.

CANINE CORONAVIRAL ENTERITIS

Etiology

Canine coronavirus invades and destroys mature cells on the intestinal villi. Because intestinal crypts remain intact, villi regenerate more quickly in dogs with coronaviral enteritis than in dogs with parvoviral enteritis; bone marrow cells are not affected.

Clinical Features

Coronaviral enteritis is typically less severe than classic parvoviral enteritis and rarely causes hemorrhagic diarrhea, septicemia, or death. Dogs of any age may be infected. Signs usually last less than 1 to 1½ weeks, and small or very young dogs may die as a result of dehydration or electrolyte abnormalities if they are not properly treated. Dual infection with parvovirus may produce a high incidence of morbidity and mortality.

Diagnosis

Because canine coronaviral enteritis is usually much less severe than many other enteritides, it is seldom definitively diagnosed. Most dogs are treated symptomatically for acute enteritis until they improve. There is a commercial PCR available for testing feces. Electron microscopic examination of feces obtained early in the course of the disease can be diagnostic, but the virus is fragile and easily disrupted by inappropriate specimen handling. Coronavirus can be found in the feces of many clinically normal dogs; therefore, simply stating that coronavirus is present is not helpful. A history of contagion and elimination of other causes are reasons to suspect canine coronaviral enteritis.

Treatment

Fluid therapy, motility modifiers (see Chapter 28), and time should resolve most cases of coronaviral enteritis. Symptomatic therapy is usually successful except, perhaps, for very young animals. A vaccination is available but of uncertain value.

Prognosis

The prognosis for recovery is usually good.

OTHER CANINE ENTERIC VIRUSES

Canine circovirus is believed to be a cause of vomiting, diarrhea, and hemorrhagic diarrhea in dogs. It is believed that dual infection with this and CPV-2 produces more severe disease. Rotavirus has also been suggested as a cause of canine diarrhea. Diagnosis is probably important only in kennel situations where contagion is an issue.

FELINE CORONAVIRAL ENTERITIS

Cats may be infected with feline or canine enteric coronavirus. Infections in adults are often asymptomatic, whereas kittens may have mild transient diarrhea and fever. Deaths are rare, and the prognosis for recovery is excellent. This disease is important because (1) affected animals seroconvert and may become positive on feline infectious peritonitis serologic analysis and (2) mutation by the feline coronavirus may be the cause of feline infectious peritonitis. There is a commercially available PCR test on feces.

FELINE LEUKEMIA VIRUS–PANLEUKOPENIA-LIKE SYNDROME

Etiology

FeLV-associated panleukopenia is uncommon. The intestinal lesion histologically resembles that produced by feline parvovirus. The bone marrow and lymph nodes are not consistently affected as they are in cats with parvoviral enteritis. Rarely, there can be co-infection with FeLV and FPV.

Clinical Features

Chronic weight loss, vomiting, and diarrhea are common. The diarrhea often has characteristics of large bowel disease. Anemia is common.

Diagnosis

Finding FeLV infection in a cat with chronic diarrhea is suggestive. Cats are typically neutropenic. Histologic lesions resembling FPV in a cat with FeLV should be definitive.

Treatment

Symptomatic therapy (fluid/electrolyte therapy, antibiotics, antiemetics, and/or highly digestible bland diets as needed)

and elimination of other problems that compromise the intestines (e.g., parasites, poor diet) may be beneficial.

Prognosis

This disease has a poor prognosis because of other FeLV-related complications.

FELINE IMMUNODEFICIENCY VIRUS–ASSOCIATED DIARRHEA

Etiology

FIV may be associated with diarrhea. Acute infection with FIV is often associated with transient diarrhea, and terminal FIV may be associated with an "AIDS-like enteropathy," which can produce chronic diarrhea, severe weight loss, and/or purulent colitis. The pathogenesis is unclear and may involve multiple mechanisms.

Clinical Features

Severe large bowel disease is common and can occasionally cause colonic rupture. These animals generally appear ill.

Diagnosis

Detection of antibodies to FIV plus diarrhea allow presumptive diagnosis.

Treatment

Therapy is supportive (e.g., fluids/electrolytes, antiemetics, antibiotics, and/or highly digestible bland diets as needed).

Prognosis

The long-term prognosis is guarded to very poor, although some cats can be maintained for months.

SALMON POISONING/ELOKOMIN FLUKE FEVER

Etiology

Salmon poisoning is caused by *Neorickettsia helminthoeca.* Dogs are infected when they eat fish (especially salmon) infected with a fluke *(Nanophyetus salmincola)* that carries the rickettsia. The rickettsia spreads to the intestines and most lymph nodes, causing inflammation. This disease is principally found in the U.S. Pacific Northwest, because the snail intermediate host *(Oxytrema silicula)* for *N. salmincola* lives there. The Elokomin fluke fever agent may be a strain of *N. helminthoeca*.

Clinical Features

Dogs, not cats, are affected. The severity of signs varies and typically consists of an initial fever that eventually falls and becomes subnormal. Fever is followed by hyporexia and weight loss, which may also involve vomiting and/or diarrhea. The diarrhea is typically small bowel but may become bloody. Lymphadenomegaly is the most common physical examination finding.

Diagnosis

Presumptive diagnosis is usually based on the animal's habitat plus a history of recent consumption of raw fish or exposure to streams or lakes. Finding *Nanophyetus* spp. ova (operculated trematode ova) in feces is suggestive. Finding rickettsia in fine-needle aspirates or biopsies of enlarged lymph nodes is confirmatory, but aspirate cytology is not as sensitive as desired. Prior antimicrobial therapy can make it difficult to demonstrate the organisms.

Treatment

Treatment consists of symptomatic control of dehydration, vomiting, and diarrhea plus elimination of the rickettsia and fluke. Tetracycline, oxytetracycline, doxycycline, and maybe enrofloxacin (see Chapter 92) eliminate the rickettsia. The fluke is killed with praziquantel (see Table 28.7).

Prognosis

The prognosis depends on the clinical severity at the time of diagnosis. Most dogs respond favorably to tetracyclines and supportive therapy within 24 hours. The key to success is awareness of the disease. Untreated salmon poisoning has a poor prognosis.

BACTERIAL DISEASES: COMMON THEMES

The following bacterial diseases all have certain aspects in common. First, all of these bacteria may be found in feces from clinically normal dogs and cats. Simply growing the bacteria or finding bacterial toxin in the patient's feces does not confirm they are responsible for clinical disease. Diagnosis can be made only by finding clinical disease consistent with a particular organism, evidence of the organism or its toxin, eliminating other causes of the clinical signs, and seeing the expected response to appropriate therapy. If the clinician cultures feces, it is crucial to call the laboratory first, explain what is being sought, and follow instructions regarding sample collection and submission.

The problems with making a diagnosis using the previously mentioned criteria are obvious, and caution is warranted before making definitive statements regarding cause and effect. In many cases, the best chance of making a definitive diagnosis involves following the guidelines described and using molecular techniques on isolates to demonstrate toxin production.

CAMPYLOBACTERIOSIS

Etiology

There are several species of *Campylobacter*. *Campylobacter jejuni* is the species most commonly associated with GI disease, although *C. upsaliensis* is rarely implicated. *Campylobacter* spp. prefer high temperatures (i.e., 39° C-41° C); hence poultry is an important reservoir. *C. jejuni* and *C. upsaliensis* can be found in the intestinal tract of healthy dogs

and cats as or more frequently than in the feces of diarrheic animals.

Clinical Features

Symptomatic campylobacteriosis is principally diagnosed in animals younger than 6 months old living in crowded conditions (e.g., kennels, humane shelters) or as a nosocomial infection. Mucoid diarrhea (with or without blood), anorexia, and/or fever are the primary signs. Campylobacteriosis tends to be self-limiting in dogs, cats, and people but occasionally causes chronic diarrhea.

Diagnosis

Occasionally, *Campylobacter* forms may be found during cytologic examination of a fecal smear (i.e., "commas," "seagull wings"), but such cytologic findings are nonspecific and poorly sensitive. PCR analysis of feces appears sensitive and specific and can speciate *Campylobacter*.

Treatment

If campylobacteriosis is suspected, erythromycin (11-15 mg/kg PO q8h), enrofloxacin (5 mg/kg PO q24h), or neomycin (15 mg/kg PO q12h) is usually effective. β-Lactam antibiotics are often ineffective. The patient should be treated for at least 1 to 3 days beyond resolution of clinical signs, assuming that they respond within 5 days. Antibiotic therapy may not eradicate the bacteria, and reinfection is likely in kennel conditions. Chronic infections may require prolonged therapy (e.g., weeks). Therapeutic failure suggests either antibiotic resistance or a different disease is present.

Public Health Concerns

Campylobacteriosis is a potential zoonosis, and there are cases with convincing evidence of transmission from pets to people (especially *C. jejuni*). Infected dogs and cats should be isolated, and individuals working with the animal or its environment or wastes should wear protective clothing and wash with disinfectants. However, food products are the primary source of this infection in people. Currently, there is no indication to culture asymptomatic dogs and cats if the owners are diagnosed with campylobacteriosis.

Prognosis

With appropriate antibiotic therapy, the prognosis for recovery is good.

SALMONELLOSIS

Etiology

Numerous *Salmonella enterica* serovars cause disease in dogs and cats, but *Salmonella* Typhi (the cause of typhoid fever in people) is not one of them. *Salmonella* Typhimurium is the serovar of *S. enterica* most commonly associated with disease in dogs and cats. The bacteria may originate from animals shedding the organism (e.g., infected dogs and cats) or from contaminated foods (especially poultry and eggs). Dogs fed raw meat diets appear to be at increased risk of infection (not necessarily disease).

Clinical Features

Salmonellosis is an uncommon diagnosis in dogs and cats. *Salmonella* spp. may produce acute or chronic diarrhea, septicemia, and/or sudden death, especially in very young or geriatric animals. Salmonellosis in young animals can produce a syndrome that closely mimics parvoviral enteritis (including severe neutropenia), which is one reason ELISA testing for parvovirus is useful. Salmonellosis occasionally develops during or after canine parvoviral enteritis, making the situation more confusing.

Diagnosis

Culture of *Salmonella* spp. from normally sterile areas (e.g., blood) confirms that it is causing disease, but simply identifying it in feces does not allow confident diagnosis. *Salmonella* can be identified in feces by culture or PCR (faster and more sensitive than fecal culture). Tentative diagnosis of clinical salmonellosis requires finding the organism, having clinical signs consistent with salmonellosis, and eliminating other causes. The prevalence of *Salmonella* in healthy dogs is often similar to that in diarrheic dogs, and some areas (e.g., sled dogs in Alaska) have very high prevalences (i.e., 60%-70%). Consultation with an infectious disease expert may be helpful.

Treatment

Treatment depends on clinical signs. Animals that are not particularly clinically ill and have diarrhea as the sole sign may need only supportive fluid therapy. Nonsteroidal drugs (to lessen intestinal secretion) have been used in such patients. Antibiotics are of dubious value and have been suggested to promote a carrier state (which is unproven). Septicemic (i.e., febrile) animals should receive supportive therapy and parenteral antibiotics as determined by susceptibility testing, but quinolones, potentiated sulfa drugs, amoxicillin, and chloramphenicol are often good initial choices (see the discussion of drugs used in GI disorders, pp. 442-443).

Prognosis

The prognosis is usually good in diarrheic animals but guarded in septicemic patients.

Public Health Concerns

Infected animals are potentially public health risks (especially for infants, older adults, and immunosuppressed people), although most human infections come from contaminated food and exposure to reptiles. Dogs eating raw meat diets appear to be at increased risk of shedding *Salmonella* spp. Diarrheic or septicemic dogs and cats shedding *Salmonella* should be isolated from other animals until they are asymptomatic. In these patients, reculturing feces (four to six negative cultures) or performing PCR testing (three negative tests) is needed to ensure that shedding has stopped

after resolution of clinical signs. Individuals in contact with clinically ill animals, their environment, and their waste should wear protective clothing and wash with disinfectants such as phenolic compounds or diluted bleach (1:32 dilution). Although the risk of zoonotic transmission from dogs and cats to people seems small, it appears possible (but is not true typhoid fever).

CLOSTRIDIAL DISEASES, INCLUDING ACUTE HEMORRHAGIC DIARRHEAL SYNDROME

Etiology

Clostridium perfringens and *Clostridium difficile* can be found in clinically normal dogs. For *C. perfringens* to produce disease, environmental conditions must be appropriate for the bacteria to produce toxin.

Clinical Features

Infection with *C. perfringens* seemingly may produce various syndromes: an acute, bloody, self-limiting nosocomial diarrhea; acute hemorrhagic diarrheal syndrome (used to be called *hemorrhagic gastroenteritis*); or chronic large bowel diarrhea. These clostridial diseases are primarily recognized in dogs. Acute hemorrhagic diarrheal syndrome is discussed in detail separately. Disease associated with *C. difficile* is poorly characterized in small animals but might include large bowel diarrhea, especially after antibiotic therapy.

Diagnosis

Finding spore-forming bacteria on fecal smears (Fig. 31.1), culturing the bacteria from the feces, and detecting *C. perfringens* enterotoxin are neither sensitive nor specific for disease due to *C. perfringens.* Finding *C. difficile* toxin in the feces, although useful in people, is of uncertain value in dogs and cats. If toxin will be sought, then using ELISA to first check for bacterial antigen and, if positive, then ELISA to check for toxin A and B is the best approach. However, commercially available toxin assays for *C. difficile* toxin have not been validated for the dog or cat. Elimination of other causes of diarrhea plus resolution of signs when treated appropriately (see next paragraph) in addition to finding the organism and/or toxin is typically the basis for presumptive diagnosis of *C. difficile*–induced disease.

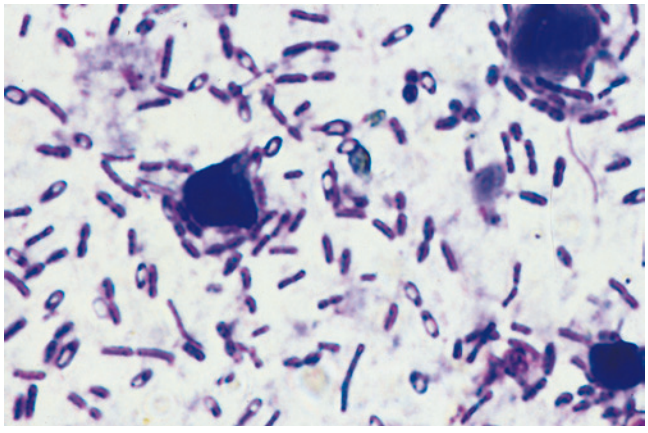


FIG 31.1
Photomicrograph of air-dried canine feces stained with Diff-Quik. Numerous spores are seen as clear vacuoles in darkly stained rods (×1000).

Treatment

If *C. perfringens* disease besides acute hemorrhagic diarrheal syndrome (AHDS) is suspected, tylosin (10-20 mg/kg PO q24h or divided q12h) or amoxicillin (22 mg/kg PO q12h) are typically effective in patients that are systemically ill or that have chronic disease. If the diagnosis is correct, response is expected within 2 to 5 days. Metronidazole is not as consistently effective as tylosin or amoxicillin. Antibiotic treatment by itself often fails to permanently cure patients with chronic diarrhea attributed to *C. perfringens*, but if a high-fiber diet is fed concurrently with administration of tylosin, the patient can often be maintained on diet alone once it is in remission. Animals that reliably respond to tylosin or amoxicillin but which relapse every time the antibacterial is withdrawn (despite remaining on a high-fiber diet) can be treated indefinitely with the drug (undesirable due to concerns with promotion of antibacterial resistance) or one can consider fecal transplantation or probiotic therapy. In contrast, if AHDS is suspected, then fluids are the most important therapy.

If disease caused by *C. difficile* is suspected, supportive fluid and electrolyte therapy may be necessary depending on the severity of signs. Metronidazole should be effective in killing this bacterium, but one must be sure to use a sufficiently high dose to achieve adequate metronidazole concentrations in the feces. Oral vancomycin is often used to treat people with this disease, but it has generally been unnecessary in dogs or cats, and this drug should be avoided in veterinary medicine as it is a "drug of last resort" in human medicine.

Prognosis

The prognosis is excellent in dogs with diarrhea caused by *C. perfringens* but uncertain for those cases caused by *C. difficile*.

Public Health Concerns

There is no obvious public health risk from dogs or cats shedding *C. perfringens* despite anecdotal evidence of transmission between people and dogs. Dogs occasionally shed strains of *C. difficile* that are found in people but do not appear to be a risk factor for human infection or disease.

ACUTE HEMORRHAGIC DIARRHEAL SYNDROME

Etiology

This disease used to be called "Hemorrhagic Gastroenteritis." Cause is uncertain but believed to involve *C. perfringens.*

Clinical Features

Patients are classically smaller breed dogs (e.g., Yorkshire Terriers, Schnauzers, Miniature Pinschers, Maltese). Many (not all) initially vomit (may be bloody or not). Hemorrhagic diarrhea quickly ensues.

Diagnosis

Diagnosis is by exclusion of other causes. Most patients have an increased PCV.

Treatment/Prognosis

Timely fluid therapy is associated with an excellent prognosis. Antimicrobial therapy has not been found beneficial.

MISCELLANEOUS BACTERIA

Etiology

Escherichia coli is of major importance as a cause of diarrhea in most mammalian species, and the subject is beyond the scope of this text. There are several different strains that produce different syndromes (e.g., enterotoxigenic *E. coli* associated with acute canine and feline diarrhea; adherent-invasive *E. coli* [AIEC] associated with histiocytic ulcerative colitis, especially in Boxers and French Bulldogs, etc.). *Yersinia enterocolitica, Aeromonas hydrophila,* and *Plesiomonas shigelloides* may cause acute or chronic enterocolitis in dogs and/or cats as well as in people. However, these bacteria (especially the latter two) are uncommonly diagnosed in the United States. *Y. enterocolitica* is primarily found in cold environments and in pigs, which may serve as a reservoir. It is also a cause of food poisoning because of its ability to grow in cold temperatures.

Clinical Features

All of these bacteria may cause small bowel diarrhea. Select *E. coli* and *Y. enterocolitica* produce chronic large bowel diarrhea.

Diagnosis

E. coli can be cultured from the feces of almost all mammals. With the exception of histiocytic ulcerative colitis, it is extremely difficult to associate an *E. coli* isolate with intestinal disease in a particular patient. If it is necessary to try to determine whether or not a particular *E. coli* is responsible for disease, then virulence factor testing is needed (but not necessarily sufficient by itself). Animals with persistent colitis, especially those that are in contact with pigs, may reasonably be cultured for *Y. enterocolitica*.

Treatment

With the exception of *E. coli*–associated histiocytic ulcerative colitis, therapy is supportive. The affected animal should be isolated from other animals. People in contact with the animal and/or its environment and wastes should wear protective clothing and clean themselves with disinfectants. Antibiotic therapy generally has not shortened duration of acute diarrhea caused by these bacteria. If chronic diarrhea is believed due to these bacteria, then appropriate antibiotics as determined by culture and sensitivity are used. The preferred length of antibiotic therapy is uncertain but should probably be continued for 1 to 3 days beyond clinical remission (except for histiocytic ulcerative colitis— see page 495).

Prognosis

The prognosis is usually good.

Public Health Concerns

Public health concerns are currently undetermined.

HISTOPLASMOSIS

Etiology

Caused by *Histoplasma capsulatum,* histoplasmosis is a mycotic infection that may affect the GI, respiratory, and/or reticuloendothelial systems, as well as the bones and eyes. Classically considered in animals from the Mississippi and Ohio River valleys, it has been diagnosed in patients that have always lived in nonendemic areas.

Clinical Features

Alimentary tract involvement is primarily found in dogs; diarrhea (with or without blood or mucus) and weight loss are common. Lungs, liver, spleen, lymph nodes, bone marrow, bones, and/or eyes may also be affected. Cats more commonly have respiratory dysfunction (e.g., dyspnea, cough), fever, and/or weight loss, but they occasionally have alimentary involvement.

In GI histoplasmosis, the colon is often the most severely affected segment. Diffuse, severe, granulomatous, ulcerative mucosal disease can produce bloody stool, intestinal protein loss, intermittent fever, and/or weight loss. Small intestinal involvement occasionally occurs. The disease may smolder for long periods of time, causing mild to moderate nonprogressive signs. Occasionally, histoplasmosis causes focal colonic granulomas or is present in grossly normal-appearing colonic mucosa.

Diagnosis

Definitive diagnosis requires finding the yeast (Fig. 31.2). There is an ELISA for antigen shed in urine that appears to have good sensitivity/specificity. Serologic tests for antibody to *H. capsulatum* are poorly sensitive/specific. Dogs from endemic areas with chronic large bowel diarrhea are especially suspect. Protein-losing enteropathy (PLE) is common in dogs with severe alimentary histoplasmosis, and PLE in a dog with large bowel disease is a strong indication to check for histoplasmosis.

Rectal examination sometimes reveals thickened rectal mucosa. Cytologic preparations from rectal mucosal scrapings sometimes reveal the yeast. Colonic biopsy is usually diagnostic, but special stains may be necessary. Mesenteric lymph node samples or repeated colonic biopsy is rarely required. Fundic examination occasionally reveals active chorioretinitis. Abdominal imaging often shows

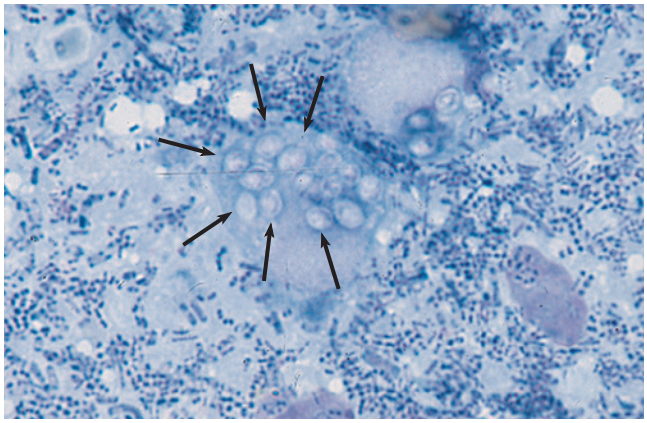


FIG 31.2
Cytologic preparation of a colonic mucosal scraping demonstrating *Histoplasma capsulatum*. Note the macrophage with numerous yeasts in the cytoplasm *(arrows)* (Wright-Giemsa stain; ×400). (From Allen D, ed.: *Small animal medicine,* Philadelphia, 1991, JB Lippincott.)

hepatosplenomegaly, and thoracic radiographs sometimes demonstrate miliary interstitial disease, sometimes with hilar lymphadenopathy. Cytologic evaluation of hepatic or splenic aspirates may be diagnostic. The CBC or a buffy coat smear rarely reveals yeasts in circulating WBCs. Thrombocytopenia may occur. Cytologic examination of bone marrow may be diagnostic. Fecal culture for the yeast is unreliable.

Treatment

It is crucial to eliminate histoplasmosis before beginning empirical glucocorticoid therapy for suspected canine inflammatory bowel disease (IBD). Glucocorticoid therapy typically allows a previously treatable case to rapidly progress and kill the animal. Itraconazole by itself or preceded by lipid emulsion amphotericin B is often effective (see Chapter 97). Treatment should usually be continued for at least 4 to 6 months to lessen chances for relapse.

Prognosis

Many dogs can be cured if treated relatively early. Multiple organ system involvement worsens the prognosis, as does central nervous system (CNS) involvement.

PYTHIOSIS

Etiology

Pythiosis is caused by *Pythium insidiosum*. Most common in the southeastern United States, it has been found in dogs as far west as California.

Clinical Features

Pythiosis may occur anywhere in the alimentary tract, but gastric, small intestinal, and large intestinal involvement are most common. Rectal lesions often cause partial obstruction. Fistulae may develop, resembling perianal fistulae, and the dog may be presented for constipation and/or hematochezia. Animals with advanced disease often lose weight. In rare cases there will be infarction of mucosa or vessels with subsequent ischemia. Cats are rarely affected.

Diagnosis

A serologic test is available (Chapter 27) and appears to have good sensitivity and specificity. If biopsy is performed, surgical biopsy or biopsy with rigid biopsy forceps are typically necessary to obtain submucosa, which is where the organisms are usually found. Eosinophils are typically prominent in affected tissues. Special stains (e.g., Warthin-Starry) are often required to find the organism.

Treatment

Complete surgical excision is preferred. No medication has consistently been effective, although itraconazole or lipid emulsion amphotericin B plus/minus terbinafine might be temporarily beneficial. Anecdotally, immunotherapy is beneficial in a few patients.

Prognosis

The prognosis is poor unless the lesion can be completely excised.

PROTOTHECOSIS

Etiology

Prototheca zopfii is an alga that invades tissue. It appears to be acquired from the environment, and some type of deficiency in the host's immune system might be necessary for the organism to produce disease.

Clinical Features

Affecting dogs and occasionally cats, protothecosis principally involves the skin, colon, and eyes but may disseminate throughout the body. Collies may be overrepresented. Colonic involvement causes bloody stools and other signs of colitis, much like histoplasmosis. Protothecosis is much less common than histoplasmosis, and the GI form primarily affects dogs.

Diagnosis

Diagnosis requires demonstrating the organism (Fig. 31.3), typically from biopsy or mucosal cytology. Some animals with disseminated disease shed the organism into the urine. The organism typically grows well if cultured.

Treatment

No drug works consistently. High doses of lipid emulsion amphotericin B seem useful in some patients. Coadministration of tetracycline might be helpful.

Prognosis

The prognosis for disseminated disease is poor because no treatment consistently works and relapse after treatment is common.

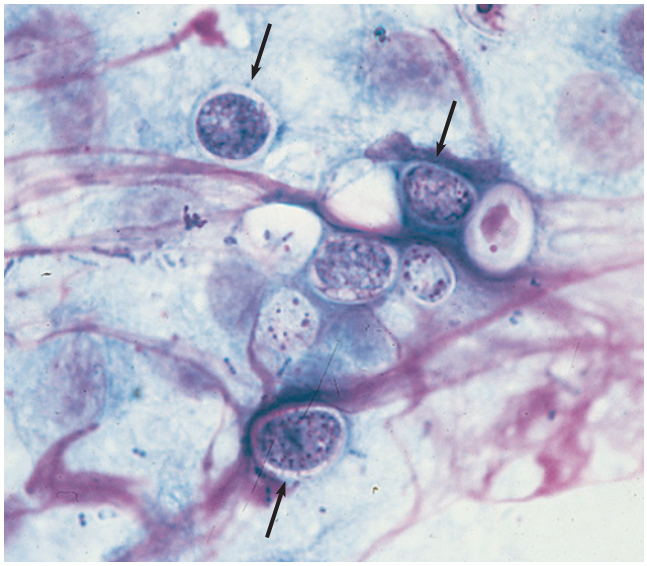


FIG 31.3
Cytologic preparation of a colonic mucosal scraping demonstrating *Prototheca* spp. Note the bean-shaped structures that have a granular internal structure and appear to have a halo *(arrows)* (Wright-Giemsa stain; ×1000). (Courtesy Dr. Alice Wolf, Texas A&M University.)

ALIMENTARY TRACT PARASITES

WHIPWORMS

Etiology

Trichuris vulpis is principally found in the eastern United States. Animals acquire the infection by ingesting ova; the adults burrow into the colonic and cecal mucosa and cause inflammation, bleeding, and/or intestinal protein loss.

Clinical Features

Dogs and rarely cats acquire whipworms, which produce a wide spectrum of mild to severe colonic disease that can include hematochezia and protein-losing enteropathy. Severe trichuriasis may cause severe hyponatremia and hyperkalemia, mimicking hypoadrenocorticism. Marked hyponatremia might be responsible for CNS signs (e.g., seizures). Whipworms generally do not affect cats as severely as dogs.

Diagnosis

T. vulpis should always be sought in dogs with large bowel diarrhea. Diagnosis is primarily made through finding ova (Fig. 31.4) in the feces. Ova are relatively dense and float only in properly prepared flotation solutions. However, they are shed intermittently and sometimes are found only if multiple fecal examinations are performed. Adults can be seen at colonoscopy (mild infestations may only affect the cecum).

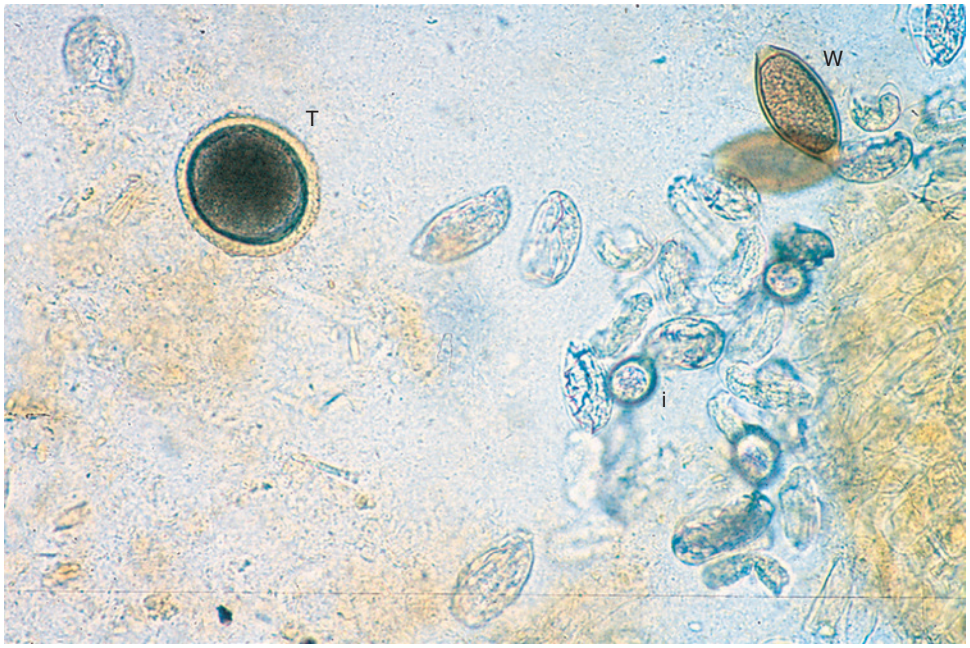


FIG 31.4
Photomicrograph of a fecal flotation analysis from a dog, demonstrating characteristic ova from whipworms *(W)*, *Toxocara canis (T)*, and *Isospora* spp. *(i)*. The remaining ova are those of an unusual tapeworm, *Spirometra* spp. (×250). (Courtesy Dr. Tom Craig, Texas A&M University.)

Treatment

Because of the potential difficulty in diagnosing *T. vulpis,* it is reasonable to empirically treat dogs with chronic large bowel disease with fenbendazole or other appropriate drugs (see Table 28.7) before proceeding to endoscopy. Ideally, patients should be treated monthly for 3 months to kill whipworms that were not in the intestinal lumen at the first treatment. Ova persist in the environment for long periods.

Prognosis

The prognosis for recovery is good.

ROUNDWORMS

Etiology

Roundworms are common in dogs *(Toxocara canis* and *Toxascaris leonina)* and cats *(Toxocara cati* and *Toxascaris leonina).* Dogs and cats can obtain roundworms from ingesting ova (either directly or via paratenic hosts). *T. canis* is often obtained transplacentally from the mother; *T. cati* may use transmammary passage, and *T. leonina* can use intermediate hosts. Tissue migration of immature forms can cause hepatic fibrosis and significant pulmonary lesions. Adult roundworms live in the small intestinal lumen and migrate against the flow of ingesta. They can cause inflammatory infiltrates (e.g., eosinophils) in the intestinal wall.

Clinical Features

Roundworms may cause or contribute to diarrhea, stunted growth, a poor haircoat, and poor weight gain, especially in young animals. Runts with "potbellies" suggest severe roundworm infection. Sometimes, roundworms gain access to the stomach, in which case they may be vomited. If parasites are numerous, they may obstruct the intestines or bile duct.

Diagnosis

Diagnosis is easy because ova are produced in large numbers and are readily found by fecal flotation (Fig. 31.5; see also Fig. 31.4). Occasionally, neonates develop clinical signs of roundworm infestation, but ova cannot be found in the feces. Transplacental migration results in large worm burdens, causing signs in these animals before the parasites mature and produce ova.

Treatment

Various anthelmintics are effective (see Table 28.7), but pyrantel is especially safe for young dogs and cats, particularly those with diarrhea. Affected animals should be retreated at 2- to 3-week intervals to kill roundworms that were initially in tissues but migrated into the intestinal lumen since the last treatment. Puppies can be treated as young as 2 weeks of age, and treatment can be repeated every 2 weeks until 3 months of age.

High-dose fenbendazole therapy (i.e., 50 mg/kg/day PO from day 40 of gestation until 2 weeks postpartum) has been suggested to reduce the somatic roundworm burden in bitches and lessen transplacental transmission to puppies. Newborn puppies can be treated with fenbendazole (100 mg/kg for 3 days), which kills more than 90% of prenatal larvae.

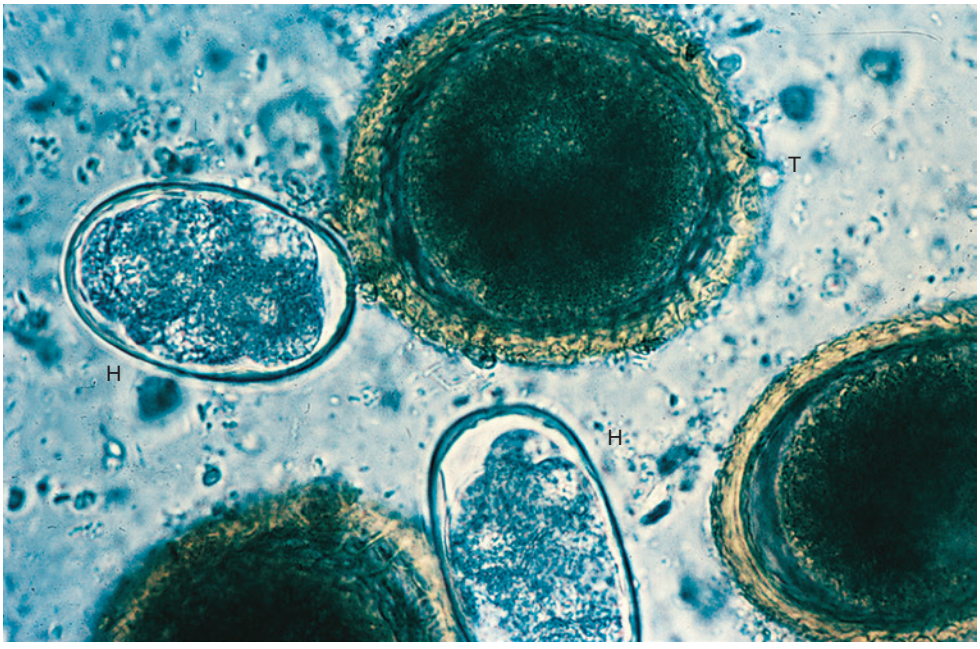


FIG 31.5
Photomicrograph of a fecal flotation analysis from a dog demonstrating characteristic ova from hookworms *(H)* and *Toxocara canis (T)* (×400). (Courtesy Dr. Tom Craig, Texas A&M University.)

This treatment can be repeated 2 to 3 weeks later. Preweaning puppies should be treated at 2, 4, 6, and 8 weeks of age to lessen contamination of the environment, because *T. canis* and *T. cati* pose a human health risk (i.e., visceral and ocular larval migrans). Preweaning kittens should be treated at 6, 8, and 10 weeks of age.

Prognosis

The prognosis for recovery is good unless the animal is already severely stunted when treated, in which case it may never attain its anticipated body size.

Public Health Concerns

Visceral larval migrans is an important zoonosis and the primary reason why veterinarians should be aggressive about treating puppies multiple times before they are 3 to 4 months old and then treating them annually.

HOOKWORMS

Etiology

Ancylostoma and *Uncinaria* spp. are more common in dogs than in cats. Infestation is usually via ingestion of ova or through transcolostral transmission; freshly hatched larvae may also penetrate the skin. Adults live in the small intestinal lumen, where they attach to the mucosa. Plugs of intestinal mucosa and/or blood are ingested, depending on the worm species. In severe infestations, hookworms may be found in the colon.

Clinical Features

Dogs are typically more severely affected than cats. Young animals may have life-threatening blood loss or iron deficiency anemia, melena, frank fecal blood, diarrhea, and/or failure to thrive. Peracute disease occurs in puppies receiving a large parasitic burden via transmammary transmission; they may die of GI blood loss before ova are found in the feces. Acute disease occurs when older puppies receive a large exposure; the primary sign is bloody diarrhea, and ova are readily found. Chronic disease occurs in dogs with enough parasites to cause chronic iron deficiency anemia but not diarrhea. Secondary disease occurs in older dogs with other GI disease in which the hookworms add on to the illness of the primary disease. Older dogs rarely have disease solely caused by hookworms unless they harbor a massive infestation.

Diagnosis

Finding ova in the feces is diagnostic (see Fig. 31.5) and easy because hookworms are prolific egg producers. However, 5- to 10-day-old puppies with peracute disease may be exsanguinated before ova appear in the feces. Such prepatent infections rarely occur in older animals that have received a sudden, massive exposure. Diagnosis is suggested by signalment and clinical signs in these animals. Iron deficiency anemia in a puppy or kitten free of fleas is highly suggestive of hookworm infestation.

Treatment

Various anthelmintics are effective (see Table 28.7). Treatment should be repeated in approximately 3 weeks to kill parasites entering the intestinal lumen from the tissues. In anemic puppies and kittens with peracute disease, blood transfusion may be life saving.

Hookworms are a potential human health hazard (i.e., cutaneous larval migrans). Use of heartworm preventives containing pyrantel or milbemycin helps minimize hookworm infestations.

Prognosis

The prognosis is good in mature dogs and cats but guarded in severely anemic puppies and kittens. If the puppies or kittens are severely stunted in their growth, they may never attain their anticipated body size.

Public Health Concerns

Cutaneous larval migrans is an important reason to control hookworms.

TAPEWORMS

Etiology

Several tapeworms infect dogs and cats, the most common being *Dipylidium caninum*. Tapeworms usually have an indirect life cycle; the dog or cat is infected when it eats an infected intermediate host. Fleas and lice are intermediate hosts for *D. caninum,* whereas wild animals (e.g., rabbits) are intermediate hosts for some *Taenia* spp. People and sheep are intermediate hosts for *Echinococcus granulosus,* and rodents are intermediate hosts for *E. multilocularis*.

Clinical Features

Aesthetically offensive, tapeworms are rarely pathogenic in small animals. *Mesocestoides* spp. can reproduce in the host and cause disease (e.g., abdominal effusion), and *Echinococcus* spp. rarely causes hydatid cysts in dogs. The most common sign in dogs and cats infested with tapeworms is anal irritation associated with shed segments "crawling" on the area. Typically the owner sees motile tapeworm segments on the feces and requests treatment. Occasionally a segment enters an anal sac and causes inflammation. Very rarely, large numbers of tapeworms cause intestinal obstruction.

Diagnosis

Taenia spp. and especially *D. caninum* eggs are typically confined in segments not detected by routine fecal flotations. *Echinococcus* spp. and some *Taenia* spp. ova may be found in the feces. Tapeworms are usually diagnosed when the owner reports tapeworm segments (e.g., "rice grains") on feces or the perineal area.

Treatment

Praziquantel and episprantel are effective against all species of tapeworms (see Table 28.7). Prevention of tapeworms

involves controlling the intermediate hosts (i.e., fleas and lice for *D. caninum*).

Public Health Concerns

Echinococcus spp. are a major human health hazard and an important reason to use anticestode drugs in dogs. *Diphyllobothrium* spp. and *Spirometra* spp. can also cause significant human disease.

STRONGYLOIDIASIS

Etiology

Strongyloides stercoralis principally affects puppies, especially those in crowded conditions. These parasites produce motile larvae that penetrate unbroken skin or mucosa; thus the animal may be infested from its own feces even before the larvae are evacuated from the colon. In this manner, animals can quickly acquire large parasitic burdens. Most animals are infested after being exposed to fresh feces containing motile larvae. Humane shelters and pet stores are likely sources for infestation.

Clinical Features

Infested animals may be asymptomatic, or they can have mucoid or hemorrhagic diarrhea and be systemically ill (e.g., lethargy). Respiratory signs (i.e., verminous pneumonia) occur if parasites penetrate the lungs.

Diagnosis

S. stercoralis is diagnosed by finding larvae in fresh feces, either by direct fecal examination or by Baermann sedimentation. *Strongyloides* larvae must be differentiated from *Oslerus* spp. larvae. The feces must be fresh because old feces may contain hatched hookworm larvae, which resemble those of *Strongyloides* spp.

Treatment

Fenbendazole (used for 5 days instead of 3; see Table 28.7), thiabendazole, and ivermectin are effective anthelmintics. This disease is a potential human health hazard because larvae penetrate unbroken skin. Immunosuppressed people are at risk for severe disease after being infected.

Prognosis

The prognosis is guarded in young animals with severe diarrhea and/or pneumonia.

Public Health Concerns

Strongyloides stercoralis is zoonotic, but dogs are rarely documented to be the cause of human infection.

COCCIDIOSIS

Etiology

Cystoisospora spp. are the coccidia infecting cats and dogs. The pet is usually infested by ingesting infective oocysts from the environment. The coccidia invade and destroy villous epithelial cells.

Clinical Features

Infections with *Cystoisospora* are very common in puppies and kittens and may be asymptomatic or may cause copious, watery diarrhea with or without blood. Rarely, a kitten or puppy may lose enough blood to require a blood transfusion.

Diagnosis

Coccidiosis is diagnosed by finding oocysts on fecal flotation examination (see Fig. 31.4). Repeated fecal examinations may be necessary, and small numbers of oocysts do not ensure that the infestation is insignificant. Diagnosis can be confusing because *Cystoisospora* oocysts must be distinguished from *Eimeria* oocysts (these are "passing through" after the dog was copraphagic) and giardial cysts. If a necropsy is performed, multiple areas of the intestine should be sampled because the infection may be localized to one area.

Treatment

If coccidia are believed to be causing a problem, sulfadimethoxine or trimethoprim-sulfa should be administered for 10 to 20 days (see Table 28.7). The sulfa drug does not eradicate the coccidia but inhibits it so that body defense mechanisms can reestablish control. Amprolium, toltrazuril, and ponazuril have been reported to be effective, but these are off label uses in the United States.

Prognosis

The prognosis for recovery is usually good unless there are underlying problems that allowed the coccidia to become pathogenic in the first place.

CRYPTOSPORIDIA

Etiology

Cryptosporidium spp. may infect animals that ingest sporulated oocysts. These oocysts originate from infested animals but may be carried in water. Thin-walled oocysts are produced, which can rupture in the intestine and produce autoinfection. The organism infests the brush border of small intestinal epithelial cells and causes diarrhea.

Clinical Features

Cryptosporidiosis is a potential cause of diarrhea in dogs and cats, but determining cause and effect is often difficult because it can be found in clinically normal patients. Dogs with diarrhea due to cryptosporidiosis are usually younger than 6 months of age, but a similar age predilection has not been recognized for cats.

Diagnosis

Diagnosis requires finding the oocysts by fecal flotation examination, immunofluorescence assay (IFA), ELISA, or PCR. *C. parvum* is the smallest of the coccidians and is easy to miss on fecal examination. It is best to submit the feces to

a laboratory experienced in diagnosing cryptosporidiosis. The laboratory must be warned that the feces may contain *C. parvum,* a potential zoonosis.

Treatment and Prognosis

Nitazoxanide and paromomycin (both potentially toxic in the cat) are used to treat cryptosporidiosis in people. Tylosin has been suggested to be effective, but this is dubious. Azithromycin (7-10 mg/kg PO q12h) might be safe and effective. Immunocompetent persons and cattle often spontaneously eliminate the infestation, but whether small animals do so is unknown. Any time cryptosporidiosis is diagnosed one should look for causes of immunosuppression in the host. Most young dogs with diarrhea associated with cryptosporidiosis die or are euthanized. Many cats have asymptomatic infestations, and those with diarrhea have an uncertain prognosis.

GIARDIASIS

Etiology

Animals are infected with the protozoan *Giardia* when they ingest cysts shed from infected animals, often via water. Organisms are principally found in the small intestine, where they interfere with digestion through uncertain mechanisms. In people *Giardia* organisms may occasionally ascend into the bile duct and cause hepatic problems.

Clinical Features

Patients may be asymptomatic or have mild to severe diarrhea, which may be persistent, intermittent, or self-limiting. Diarrhea can begin 5 days after exposure, before cysts appear in the feces. Typically the diarrhea is "cow patty"–like without blood or mucus, but there is substantial variation. Some animals experience weight loss; others do not. Diarrhea caused by *Giardia* can mimic large bowel diarrhea in some patients. In cats there may be an association between shedding giardial oocysts and shedding either cryptosporidial or coccidian oocysts.

Diagnosis

Giardiasis is diagnosed by finding motile trophozoites (Fig. 31.6) in fresh feces or duodenal washes, finding cysts with fecal flotation techniques or IFA, or finding giardial antigens in feces using ELISA or PCR methodology. Zinc sulfate solutions are the best for demonstrating cysts (especially when centrifugal flotation is performed); other flotation solutions may distort them. At least three fecal examinations should be performed over the course of 7 to 10 days before discounting giardiasis. However, there can be false-positive results due to particles in the feces (e.g., pollen) that resemble giardial cysts. Fecal ELISA techniques (e.g., SNAP Giardia Test, Idexx Laboratories) have high sensitivity and are easier than centrifugal fecal flotation examinations, but none offers 100% sensitivity. The ELISA is better at ruling out giardiasis than ruling it in. Some asymptomatic patients are repeatedly ELISA positive even though oocysts cannot be demonstrated on fecal examination. ELISA is not useful in determining efficacy of therapy because the antigen often persists for 4+ weeks after successful therapy. PCR of feces is very specific but is too insensitive to be reliable. Therefore IFA testing of feces is believed to be more specific than ELISA, but it requires sending feces to a diagnostic laboratory. Testing asymptomatic patients that are not in close contact with a known infected patient is of dubious value.

Treatment

Treatment of giardiasis consists of (1) decontaminating the environment, (2) bathing the patient to remove cysts from the hair, and (3) administering drugs to eliminate the intestinal infection. Because of the difficulty in finding *Giardia* organisms, therapeutic trials are often used (see Table 28.7).

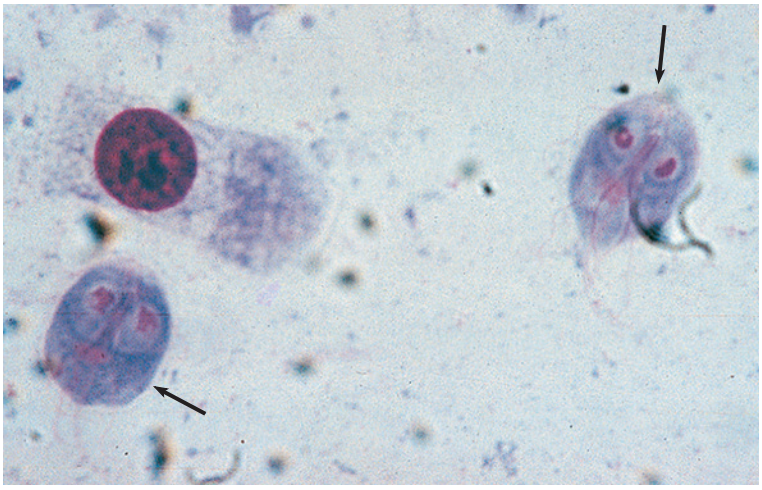


FIG 31.6
Giardia trophozoites *(arrows)* in a canine fecal smear that has been stained to enhance internal structures (×1000). (Courtesy Dr. Tom Craig, Texas A&M University.)

This approach has limitations because no drug is 100% effective (i.e., therapeutic failure does not rule out giardiasis). Seven days of metronidazole, 5 days of fenbendazole, or 5 days of febantel plus pyrantel plus praziquantel appear to be the preferred treatments. Metronidazole has few adverse effects if properly dosed and seems reasonably effective. Tinidazole and ronidazole appear to be effective. Quinacrine, furazolidone, and albendazole are either not available or not recommended.

It can be difficult to eliminate *Giardia* spp. because reinfection is easy; giardial cysts are resistant to environmental influences and relatively few are required to reinfect a patient. This is why bathing the patient and cleansing the environment are important. Quaternary ammonium compounds and pine tars are effective disinfectants. Concurrent host intestinal disease (or immunodeficiency) makes it particularly difficult to eliminate the organism. Rarely, *Giardia* becomes resistant to some drugs. Other protozoal agents (e.g., *Tritrichomonas*) are often mistaken for *Giardia*, which can cause confusion when the patient does not respond to therapy. Vaccination is generally unsuccessful as a treatment for patients not responding to the aforementioned drugs. It is reasonable to treat asymptomatic housemates of an affected pet. One-time treatment of asymptomatic patients not associated with clinically ill patients that are fortuitously diagnosed is reasonable, but repeated treatment of such patients is not recommended.

Prognosis

The prognosis for recovery is usually good, although in some cases the organisms are difficult to eradicate.

Public Health Concerns

There are seven genetic assemblages (A-G); two of them (A and B) may occur in people *and* animals, whereas the other five only occur in animals. The risk of zoonotic transmission from dogs and cats to people in the face of routine sanitary practices appears minor. The risk to young children (who do not routinely practice good sanitation) is unknown.

TRICHOMONIASIS

Etiology

Trichomoniasis in cats is caused by *Tritrichomonas blagburnii*. Animals are probably infected by the fecal-oral route. Dogs are rarely affected, and it is not clear whether they contract *T. blagburnii* or *T. foetus*.

Clinical Features

Trichomoniasis typically is associated with large bowel diarrhea, which rarely contains blood or mucus. Exotic cat breeds (e.g., Somalis, Ocicats, Bengals) are seemingly at increased risk for clinical disease. Affected cats are typically otherwise normal, although there may be anal irritation and defecation in inappropriate places. Diarrhea typically resolves spontaneously, although it can be months to years before it does so. *T. blagburni* has been detected in the feces of asymptomatic cats, too.

Diagnosis

Diagnosis requires identifying the motile trophozoite, but live *Tritrichomonas* trophozoites can be mistaken for *Giardia* trophozoites (Fig. 31.7, *A*) as well as nonpathogenic *Pentatrichomonas hominis*. Prompt examination of fresh feces diluted with warm saline solution is the easiest technique, but it is insensitive (approximately 14%). Fecal culture using a pouch technique is available but seldom used. PCR of feces is the most sensitive test available. The organism can sometimes be found in colonic mucosal biopsies.

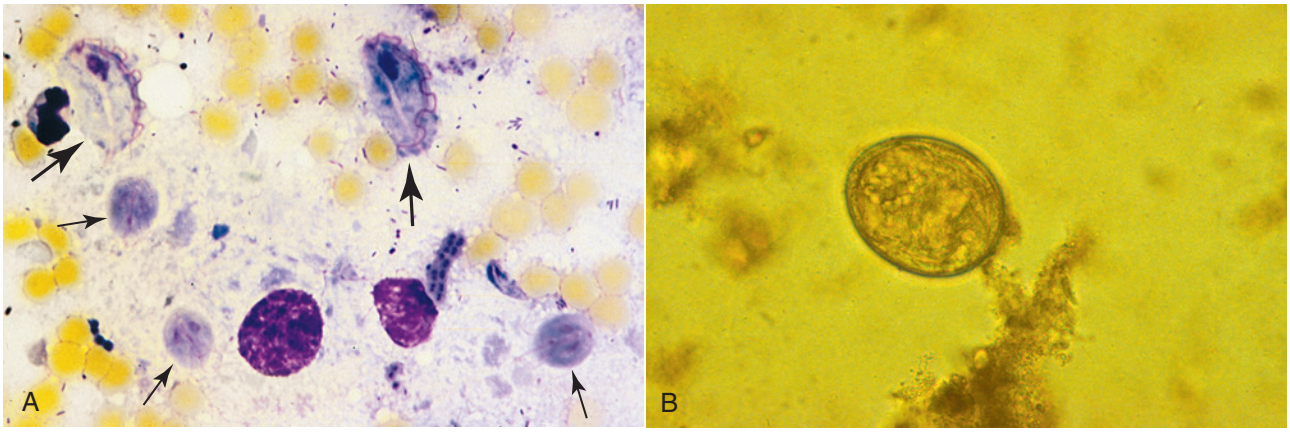


FIG 31.7
(A) Comparison of *Giardia* trophozoites *(small arrows)* and *Tritrichomonas* trophozoites *(large arrows)* in a smear that has been stained to enhance internal structures. Note that the *Tritrichomonas* trophozoites are larger and have one large undulating membrane (×1000). **(B)** Ova of *Heterobilharzia americana* in a fecal sedimentation. (Both images courtesy Dr. Tom Craig, Texas A&M University.)

Treatment and Prognosis

Because *T. blagburnii* does not have a cyst stage, it is much more fragile in the environment than is *Giardia*. Therefore, unlike *Giardia*-infected patients, *Tritrichomonas*-infected patients only need routine sanitation. Ronidazole (30 mg/kg PO q24h for 10-14 days) is the only drug currently known to safely and reliably eliminate *Tritrichomonas,* but neurologic signs have been reported. If trichomoniasis is diagnosed, it is important to look for other causes of diarrhea (e.g., *C. perfringens,* diet, *Cryptosporidium* spp.); treatment for one of these other causes may resolve the diarrhea. Clinical signs of trichomoniasis in most affected cats will eventually subside, although diarrhea may recur if the patient undergoes stressful events (e.g., elective surgery). There appears to be minimal risk of zoonotic transmission.

HETEROBILHARZIA

Etiology

Heterobilharzia americana infects dogs and establishes itself in the liver. Ova laid in the veins end up in the intestinal wall and in the liver, where they elicit a granulomatous inflammation. The organism is primarily found in Gulf Coast states and southern Atlantic coast states.

Clinical Features

Large bowel and/or hepatic disease are the primary presentations. Diarrhea, hematochezia, and weight loss are typical findings. PLE may occur, and the granulomatous reaction is associated with hypercalcemia in some dogs. Hepatic disease ranges from mild to severe.

Diagnosis

Finding the ova in feces or in mucosal biopsy specimens is diagnostic. There is a commercially available PCR test for feces.

Treatment and Prognosis

Fenbendazole plus praziquantel is successful in killing the parasite and the ova. However, the prognosis is seemingly dependent on the severity of the granulomatous reaction in the bowel and liver.

MALDIGESTIVE DISEASE

EXOCRINE PANCREATIC INSUFFICIENCY

Etiology

Canine exocrine pancreatic insufficiency (EPI) is caused by pancreatic acinar cell atrophy or destruction due to pancreatitis.

Clinical Features

EPI occurs in dogs and cats. Chronic small intestinal diarrhea, a ravenous appetite, and weight loss are classic findings in dogs. Cats may also have hyporexia and lethargy. Steatorrhea (i.e., slate-gray stools) is sometimes seen, and animals occasionally have weight loss without diarrhea. The diarrhea is classified as a small bowel problem (because of weight loss). Physical examination and routine clinical pathologic findings are not diagnostic. The most sensitive and specific test for EPI is measurement of serum trypsin-like immunoreactivity (TLI), which must be species specific. Finding undetectable levels of canine pancreatic lipase immunoreactivity (cPLI) might be suggestive of EPI but is not specific. Treatment involves administering good quality pancreatic enzymes with food and manipulation of dietary fat content. Cats often clinically benefit from cobalamin supplementation. The reader is referred to Chapter 37 for more information on EPI.

NON–PROTEIN-LOSING MALABSORPTIVE DISEASES

DIETARY-RESPONSIVE SMALL INTESTINAL DIARRHEA

Etiology

Dietary-responsive diarrhea is an all-inclusive term that includes dietary allergy (a hyperimmune response to a dietary antigen) and dietary intolerance (a non–immune-mediated response to a dietary substance). From a clinical standpoint, there is minimal value in distinguishing between the two. This is a very common cause of chronic GI signs in both dogs and cats.

Clinical Features

Affected patients may have vomiting and/or diarrhea (large and/or small bowel) plus/minus allergic skin disease.

Diagnosis

Diagnosis consists of showing response to feeding an elimination diet that is appropriate for the patient (see discussion of dietary management in Chapter 28). There is typically minimal value in distinguishing between allergy and intolerance. Tests for IgE antibodies in the patient's blood to specific antigens are not as sensitive or specific as seeing response to an elimination diet. The diet must be carefully chosen. It should consist of either relatively nonallergenic substances (e.g., hydrolyzed diets) or foods that have proteins to which the patient has not previously been exposed (e.g., novel protein diets). Hydrolyzed diets (especially ultra-hydrolyzed) are generally excellent choices for food trials when looking for dietary-responsive diarrhea, but they are not the gold standard for response to elimination diets. Some dogs respond better to novel protein diets. It would be best to try one and, if unsuccessful, then try the other. High-fat diets are generally avoided in such patients (because fat is difficult to digest), but there is no evidence that elimination diets have to be low in fat to be effective in cats. Most dogs and cats that respond to an appropriate diet do so within 3 weeks, although rare individuals require longer.

Treatment

Most patients that respond can simply be fed the diet they responded to in the dietary trial (assuming it is balanced) for the rest of their lives. Rare patients develop allergies to the elimination diet and require different elimination diets to be fed on rotating 2- to 3-week cycles.

Prognosis

The prognosis is usually good.

ANTIBIOTIC-RESPONSIVE SMALL INTESTINAL ENTEROPATHY

Etiology

Antibiotic-responsive enteropathy (ARE; also called *antibiotic-responsive diarrhea* or *dysbiosis*) is a syndrome in which there are many *E. coli* or similar enterics coupled with an intestinal host defense that is not capable of maintaining tolerance and subsequently has an abnormal response to these bacteria. Presumably, enterocytes are damaged by deconjugation of bile acids, fatty acid hydroxylation, generation of alcohols, increased permeability, generation of inflammatory cytokines, and/or other mechanisms.

Clinical Features

ARE can be found in any dog. Clinical signs are principally diarrhea or weight loss (or both), although vomiting and/or hyporexia may also occur.

Diagnosis

Currently available diagnostic tests for ARE have poor sensitivity and specificity. Quantitative duodenal fluid cultures are difficult to obtain and interpret. Serum cobalamin and folate concentrations have poor sensitivity and specificity for this disorder. Duodenal mucosal cytology and histopathology are routinely nondiagnostic for ARE. Most affected dogs have nonspecific mild to moderate lymphoplasmacytic infiltrates in the intestinal mucosa.

Treatment

Because of the difficulty in diagnosing ARE with laboratory tests, a therapeutic trial is reasonable when this disorder is suspected. Therapy consists of removal of potential causes (e.g., blind or stagnant loops of intestine [very rare]) and administering antibacterial drugs. Because mixed bacterial populations are expected, broad-spectrum oral antibiotics effective against aerobic and anaerobic bacteria are recommended. Tylosin (10-20 mg/kg q24h or divided q12h) is often effective. Metronidazole by itself (15 mg/kg q24h) sometimes is sufficient. A combination of metronidazole (15 mg/kg q24h) and enrofloxacin (7 mg/kg q24h) is effective in some patients not responding to the previous treatments, but this combination should only be used when ARE is strongly suspected and prior therapy has failed (it is important to avoid long-term quinolone therapy to lessen problems with bacterial resistance to antibiotics).

The clinician should treat 3 weeks before deciding that the therapy was ineffective. If therapy appears successful, it is often wise to continue to treat for an additional 1 to 2 weeks to establish cause and effect. Some animals can then have the antibiotic therapy stopped while the dietary therapy is maintained, but others will need repeated or indefinite antibiotic therapy. The clinician should warn the owner that the goal is typically control, not cure. Patients that have nearly constant diarrhea when not being treated with antibiotics may need constant antimicrobial therapy (undesirable) or alternative therapies (e.g., fecal transplantation, probiotics). Patients who have episodes every 3 to 4 months might best be treated when they relapse as opposed to having them on antibiotics constantly.

As of this writing, fecal transplantation is being tried in many dogs with chronic diarrheas, and it might eventually replace antibiotic therapy as the first line therapy for ARE or chronic enteropathy (CE). It is too early to know whether this will take place.

Prognosis

The prognosis is usually good for control of ARE, but the clinician must be concerned with possible underlying causes.

RELATION OF SMALL INTESTINAL DIETARY-RESPONSIVE DIARRHEA AND ANTIBIOTIC-RESPONSIVE ENTEROPATHY

Currently, approximately 70% of dogs with chronic diarrhea are suggested to have dietary-responsive diarrhea, whereas approximately 15% are suggested to have antibiotic-responsive enteropathy. However, it may be more complex than that. Although there are some dogs that only respond to dietary therapy and some that only respond to antibiotic therapy, there appears to be a substantial number that respond to either therapy (i.e., it just depends upon which is done first). Even patients that respond to antibiotic therapy by itself seem to often respond better when concurrently treated with an elimination diet. Further complicating the issue is a smaller subset that appears to require simultaneous dietary and antibiotic therapy. Therefore recommendations for therapeutic trials for CE patients should involve a definite sequence. Parasites should be eliminated first. After that, dietary trials are appropriate (often starting with a hydrolyzed diet for 3 weeks and then going to a novel protein diet for 3 weeks if that fails). Cobalamin may be supplemented during this time, even if blood levels have not been measured. By itself, cobalamin benefits relatively few CE dogs, but it is safe and easy and does help some. If this trial is not successful, then antibiotics (e.g., tylosin) may be added to the elimination diet (preferably another hydrolyzed diet if both diets had previously failed) for another 3 weeks. The hope is that even if antibiotics were necessary for resolution of clinical signs, one will be able to stop the antibacterial drugs and maintain clinical remission by feeding the elimination diet (i.e., it is often easier to maintain remission than

attain remission). If these therapeutic trials fail, the next step may be further therapeutic trials (e.g., fecal transplantation, probiotics), or perhaps biopsy (which should be done before administering antiinflammatory or immunosuppressive drugs).

SMALL INTESTINAL "INFLAMMATORY BOWEL DISEASE" (CHRONIC ENTEROPATHY)

Clinical Features

Contrary to human medicine, there is not a uniformly accepted definition of the term *inflammatory bowel disease* (IBD) in veterinary medicine. Some have suggested the term *chronic enteropathy* (CE) as an alternative. In this text, IBD is defined as an *idiopathic* inflammation affecting any portion of the canine or feline small or large intestine. The cause is believed to involve an inappropriate response by the intestinal immune system to bacterial and/or dietary antigens that evolves into a self-perpetuating state of inflammation. Lymphocytic-plasmacytic enteritis (LPE) is the most commonly diagnosed form of canine and feline IBD. Chronic small intestinal diarrhea is common, but patients can have weight loss despite normal stools. If the duodenum is severely affected, vomiting may be the major sign. PLE can occur with the more severe forms. The clinical and histologic features of IBD can closely resemble those of alimentary lymphoma (see pp. 502-503), especially well-differentiated, small cell alimentary lymphoma in cats.

Eosinophilic gastroenterocolitis (EGE) is usually an allergic reaction to dietary substances (e.g., beef, milk). Clinical signs usually but not always respond to dietary change, and glucocorticoids may be necessary. It is less common than LPE. Some cats have eosinophilic enteritis as part of a hypereosinophilic syndrome (HES). The cause of feline HES is unknown, but immune-mediated and neoplastic mechanisms may be responsible. Less severely affected cats without HES seem to have a condition similar to canine EGE.

Diagnosis

If IBD is defined as idiopathic inflammation, it is a diagnosis of exclusion and not just a histologic diagnosis. No physical examination, history, clinical pathology, imaging, or histologic findings are diagnostic of IBD. Diagnosis requires elimination of known causes of diarrhea (e.g., dietary-responsive, antibiotic-responsive, parasitic, neoplastic, fungal, etc.) plus histology showing mucosal inflammatory infiltrates, architectural changes (e.g., villus atrophy, crypt changes), and/or epithelial changes. Mucosal cytologic evaluation is unreliable for diagnosing lymphocytic inflammation because lymphocytes and plasma cells are normally present in intestinal mucosa. Unfortunately, histologic diagnosis of mucosal inflammation is subjective, and biopsy samples are frequently overinterpreted with substantial inconsistency among pathologists. It can be extremely difficult to histologically distinguish well-differentiated small cell lymphocytic lymphoma from severe LPE, even with full-thickness tissue samples. Animals with intense dietary reactions rarely have biopsy findings that resemble lymphoma. If the tissue specimens are of poor quality (i.e., small size, excessive artifact), it is easy to mistakenly diagnose lymphoma as LPE. Biopsy of more than one intestinal site (e.g., duodenum and ileum, as opposed to just duodenum) is sometimes critical in finding inflammatory and neoplastic changes. Diagnosis of feline LPE is similar to that of canine LPE. Many cats with IBD have mild to moderate mesenteric lymphadenopathy, which ultrasonographically mimics lymphoma. Cats symptomatic with severe IBD should be evaluated for the presence of "triaditis" (i.e., simultaneous inflammation of the intestines, pancreas, and liver).

Diagnosis of EGE is similar to diagnosis of LPE. Dogs with EGE may have eosinophilia and/or concurrent eosinophilic respiratory or cutaneous dietary allergies with pruritus. German Shepherds seem overrepresented. Diagnosis of feline EGE centers on finding intestinal eosinophilic infiltrates, but splenic, hepatic, lymph node, and bone marrow infiltrates and peripheral eosinophilia are common.

Treatment

"Mild" LPE is typically dietary-responsive or ARE that was not diagnosed before biopsy. Severe LPE is usually dietary- and/or antibiotic-responsive enteropathy that has become self-perpetuating such that antiinflammatory therapy is necessary. It is often important to co-administer dietary and antimicrobial therapy along with antiinflammatory/immunosuppressive therapy. Prednisolone (2.2 mg/kg/day PO) is typically first-line therapy in these patients. If a patient responds to prednisolone but cannot tolerate the steroid side effects, then budesonide may be considered. Disease not responding to prednisolone, especially if associated with hypoalbuminemia, sometimes requires immunosuppressives (e.g., cyclosporine, chlorambucil, azathioprine). Cyclosporine seems to be reasonably effective and works faster than azathioprine. However, relatively few dogs with non–protein-losing chronic enteropathies require these immunosuppressive drugs. Failure of a dog to respond to the various therapeutic trials followed by aggressive antiinflammatory or immunosuppressive therapy usually means that the diagnosis is incorrect. Typically such patients are ultimately found to be dietary-responsive or antibiotic-responsive animals.

Feline LPE is approached a bit differently. First, some cats with chronic diarrhea will have complete resolution of clinical signs after parenteral cobalamin supplementation. Dietary-responsive diarrhea is common, but finding an elimination diet that the cat will eat can be challenging; hence, the clinician may have to settle for a mediocre elimination diet that the patient will eat as opposed to a more strict elimination diet that the patient refuses. Antimicrobials (e.g., tylosin or metronidazole) are often helpful, but administering the drug can be difficult or impossible for some clients. Because some cats make it extremely difficult to perform good dietary and/or antimicrobial trials,

glucocorticoid therapy is common in cats with chronic enteropathies. Fortunately, cats are more resistant to iatrogenic hyperadrenocorticism and have alimentary histoplasmosis less often than dogs. Prednisolone is preferred to prednisone, and methylprednisolone is typically more effective than prednisolone. If oral administration is not possible, reposital injections of methylprednisolone (Depo-Medrol) may become necessary. Budesonide is primarily indicated when the cat responds to prednisolone but cannot tolerate the systemic side effects of glucocorticoids (e.g., those with diabetes mellitus). Chlorambucil is used instead of azathioprine in cats with biopsy-proven severe LPE that does not respond to other therapy (see Chapter 28) or for cats with well-differentiated small cell lymphoma. If the cat responds to pharmacologic therapy, hopefully the clinician will be able to eventually stop the drugs and maintain the patient in clinical remission with dietary therapy alone.

Canine EGE treatment should focus on dietary management such as an ultrahydrolyzed diet. If signs do not resolve with dietary therapy, then addition of glucocorticoid therapy to the dietary therapy is usually effective. Many affected dogs only respond to glucocorticoids if they are also eating an elimination diet. Sometimes an animal initially responds to dietary management but relapses while still eating this diet because the animal becomes allergic to one of the ingredients; therefore, it is sometimes necessary to find a second acceptable elimination diet. Some animals are very prone to developing dietary intolerances, necessitating switching back and forth from one elimination diet to another at 2-week intervals to prevent relapse. (See Chapter 28 for more information on these therapies.)

Feline EGE associated with HES usually requires high-dose prednisolone (4.4-6.6 mg/kg/day PO), and response is often poor. Cats with eosinophilic enteritis not caused by HES often respond favorably to elimination diets plus glucocorticoid therapy.

If the dog or cat responds to any of these therapies, it is usually a good idea to continue this therapy without change for another 2 to 3 weeks to ensure that clinical improvement is the result of the therapy and not an unrelated transient improvement. Once the clinician is convinced that the prescribed therapy and improvement are cause-and-effect, the patient should be slowly weaned from the drugs, starting with those that have the greatest potential for adverse effects. If it is not possible to completely withdraw drug therapy, then the lowest effective dose should be determined. Dietary therapy is typically the last to be altered.

Prognosis

The prognosis for dogs and cats with non–protein-losing chronic enteropathies is often good if therapy is begun before the patient becomes emaciated. These diseases are typically controlled but not cured; hence, many patients will require a special diet for the rest of their lives. LPE has been suggested to be a prelymphomatous lesion. This is uncertain in the dog (see p. 497 for immunoproliferative enteropathy in Basenjis), and the relationship between small cell lymphoma (SCL) and LPE is confusing in the cat (see pp. 502-503). If a dog or cat with a prior diagnosis of LPE is later diagnosed as having lymphoma, it may be just as likely that either the initial diagnosis of IBD was wrong (i.e., the patient had lymphoma) or that the lymphoma developed independently of the IBD.

DIETARY-RESPONSIVE LARGE INTESTINAL DIARRHEA

The use of elimination diets for large bowel disease in dogs and cats is essentially the same as for small bowel disease.

FIBER-RESPONSIVE LARGE BOWEL DIARRHEA

Clinical Features

A common problem in both dogs and cats, diarrhea is typically a mild large bowel problem, blood and mucus being infrequent. This is probably the same disease that was once called *irritable bowel syndrome* in the dog. Irritable bowel syndrome in people is a very different disease, and this terminology is no longer commonly used in veterinary medicine.

Diagnosis/Treatment

A therapeutic trial with a fiber-supplemented diet often produces marked clinical improvement within 3 to 5 days.

Prognosis

Most patients respond well.

CLOSTRIDIAL COLITIS

Clinical Features

This is a common problem in dogs and cats. It is not certain that the disease is caused by *Clostridium perfringens*, and "tylosin-responsive" or "amoxicillin-responsive" disease may be more accurate terminology.

Diagnosis/Treatment/Prognosis

This is discussed in detail under Clostridial Diseases (page 482).

LARGE INTESTINAL INFLAMMATORY BOWEL DISEASE

Clinical Features

In dogs, *Clostridium* colitis, parasites, dietary intolerance, and fiber-responsive diarrhea are responsible for most patients referred for "intractable" large bowel "IBD." Canine lymphocytic-plasmacytic colitis (LPC) is rarely diagnosed. Cats are more commonly diagnosed with LPC, but whether that is because it is harder to perform therapeutic trials in cats than dogs or because LPC is more common in cats is uncertain. In both species, LPC causes large bowel diarrhea (i.e., soft stools with or without blood or mucus; no

appreciable weight loss). In cats hematochezia is the most common clinical sign, and diarrhea is the second most common sign. Feline LPC may occur by itself or concurrently with small bowel IBD, whereas canine large bowel IBD seems to be infrequently associated with small bowel IBD.

Diagnosis

Diagnosis requires excluding other causes (e.g., parasites, dietary-responsive diarrhea, fiber-responsive diarrhea, Clostridial colitis, and fungal/algal colitis) plus demonstrating colonic mucosal inflammation. In particular, *Tritrichomonas* must be eliminated in cats.

Treatment

Antiinflammatory glucocorticoid (i.e., prednisolone) therapy is usually effective. Dogs sometimes benefit from sulfasalazine, mesalamine, or olsalazine therapy. Feeding a fiber-supplemented diet may enhance therapeutic effectiveness.

Prognosis

The prognosis for patients with colonic IBD tends to be better than for small bowel IBD.

GRANULOMATOUS/HISTIOCYTIC ULCERATIVE COLITIS

Etiology

This disease principally affects Boxers and French Bulldogs, but other breeds can be affected. It is caused by adherent-invasive *E. coli* and may reflect immune system idiosyncrasies in the commonly affected breeds.

Clinical Features

Affected animals initially often appear just like any other dog with chronic colitis (i.e., healthy except for the diarrhea ± hematochezia). However, this disease tends to be progressive; chronic cases can develop weight loss and hypoalbuminemia and eventually die.

Diagnosis

Although colonoscopy is often delayed to see how patients with chronic colitis will respond to anthelmintic, dietary, and antimicrobial therapeutic trials, early endoscopy should be considered for Boxers and French Bulldogs with chronic large bowel signs. Histopathology is required for diagnosis. Finding PAS-positive macrophages in the mucosa (usually the deeper mucosa) is diagnostic.

Treatment

This is an antibiotic-responsive disease, but increased bacterial resistance to commonly used antibiotics is making it difficult to treat. Therefore colonic mucosal biopsy for culture is strongly recommended. It is critical to treat for at least 8 weeks (even if the patient seems normal by week 2). Stopping antibiotics before 8 weeks has been associated with recurrence of infection and resistance to previously used antibiotics.

Prognosis

Prognosis is good if the patient is diagnosed before it is cachexic and antibiotics are administered long enough. Presumptive treatment for "IBD" with glucocorticoids is associated with mortality.

PROTEIN-LOSING ENTEROPATHY

CAUSES OF PROTEIN-LOSING ENTEROPATHY

Any intestinal disease producing sufficient inflammation, infiltration, congestion, or bleeding can produce a PLE (or gastropathy if it affects the stomach) (see Box 26.10). In dogs, lymphangiectasia and alimentary tract lymphoma seem to be the most common causes in adult dogs, whereas hookworms and chronic intussusception appear to be more common in very young dogs. If IBD is responsible, it is usually a very severe form. ARE has also been noted to cause PLE, which is reasonable since IBD may originate from ARE. Immunoproliferative enteritis of Basenjis, GI ulceration/erosion, and bleeding tumors may also produce PLE. Cats have PLE less frequently than dogs, and the major cause is lymphoma although severe IBD can occasionally cause it.

INTESTINAL LYMPHANGIECTASIA

Etiology

Intestinal lymphangiectasia (IL) primarily affects dogs. Lymphatic obstruction causes dilation and rupture of intestinal lacteals with subsequent leakage of protein, lymphocytes, and chylomicrons into the intestinal submucosa, lamina propria, and lumen. Because these proteins may be digested and resorbed, there must be sufficient loss so that the intestine's ability to resorb the protein is exceeded. Rupture of lymphatics in the intestinal wall or at the mesenteric border can produce lipogranulomas, which exacerbate lymphatic obstruction. A common misconception is that most of the intestine must be affected, but many severely symptomatic patients only have segmental disease (e.g., just jejunum or just ileum affected). Most cases of canine IL are idiopathic.

Clinical Features

Yorkshire Terriers, Soft-Coated Wheaten Terriers, and Lundehunds appear to be at higher risk than other breeds. Soft-Coated Wheaten Terriers may have concomitant protein-losing nephropathy. Diarrhea is inconsistent and may not occur; low protein transudative ascites is the only sign in a substantial number of dogs. These dogs can be hypercoagulable; pulmonary thromboembolism occasionally occurs.

Diagnosis

Clinical pathologic evaluation is not diagnostic. Severe hypoalbuminemia (serum albumin < 2.0 g/dL) and hypocholesterolemia are expected, but panhypoproteinemia is inconsistent. Lymphopenia is inconsistent. Finding

hyperechoic intestinal mucosal striations at ultrasound is very suggestive of lymphangiectasia (Fig. 31.8), but the sensitivity of this finding for lymphangiectasia is uncertain. Diagnosis generally requires intestinal histopathology, but gross endoscopic appearance can sometimes be diagnostic. It is important to perform ileoscopy as well as duodenoscopy. Feeding fat the night before endoscopy or ultrasonography seems to make diagnosis easier. If numerous dilated lacteals (Fig. 31.9) are seen endoscopically in a patient that is hypoalbuminemic due to PLE, one may diagnose lymphangiectasia.

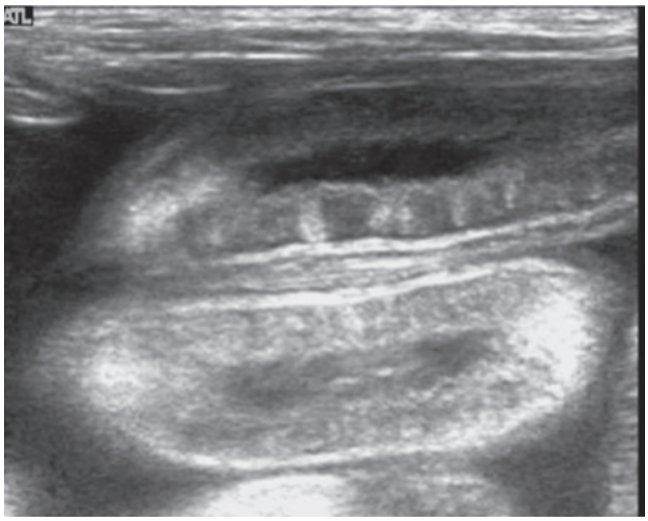


FIG 31.8
An ultrasonographic image of the small intestines of a dog with lymphangiectasia. Note the hyperechoic streaks resembling the spokes on a wagon wheel. These are fat-filled lymphatics. (Courtesy of Dr. Marie-Aude Genain, University of Cambridge, Department of Veterinary Medicine, Queen's Veterinary School Hospital.)



FIG 31.9
Endoscopic image of the duodenum of a dog with lymphangiectasia. The large white "dots" are dilated lacteals in the tips of the villi.

However, a few dilated lacteals may be found in any normal dog. Not seeing mucosal striations at ultrasonography or dilated lacteals at endoscopy does not lessen the chance of lymphangiectasia because the disease may be confined to a section of bowel not examined by ultrasound or endoscopy. When biopsying, high-quality tissue samples are critical. Submitting distorted, poorly oriented mucosal fragments or shredded villi makes it difficult to diagnose lymphangiectasia. Surgical biopsies are sometimes required. Finding lipogranulomas (Fig. 31.10) or obviously dilated, tortuous lymphatics on the intestines during surgery is extremely suggestive of IL.

Treatment

The underlying cause of IL is rarely determined, necessitating reliance on symptomatic therapy. An ultra–low-fat diet essentially devoid of long-chain fatty acids helps prevent further intestinal lacteal engorgement and subsequent protein loss. In many cases diagnosed early, this dietary therapy alone will cause the serum albumin to undergo a major increase within 7 to 12 days. More advanced cases will require concurrent prednisolone (1.1-2.2 mg/kg/day PO) or cyclosporine (3-5 mg/kg PO q12h) therapy. Cases that respond to diet alone may ultimately benefit from a 2- to 3-month course of prednisolone or cyclosporine to help prevent enlargement of lipogranulomas with subsequent relapse. If cyclosporine is used and the patient is not responding, therapeutic drug monitoring is indicated. Cases diagnosed late in the clinical course may not respond to therapy.

Monitoring serum albumin concentration (be sure to use the same laboratory each time) is critical to assessing response to therapy. If the animal improves, it should be fed the ultra–low-fat diet indefinitely.



FIG 31.10
Small intestines from a dog with intestinal lymphangiectasia. The white spots are lipogranulomas caused by rupture of lymphatics within the submucosa and/or muscularis of the intestine.

Prognosis

Some dogs respond well to ultra–low-fat diets, although some require antiinflammatory/immunosuppressive therapy in addition to the diet. A few dogs die despite all therapy. Early diagnosis and therapy may be associated with a better prognosis.

PROTEIN-LOSING ENTEROPATHY IN SOFT-COATED WHEATEN TERRIERS

Etiology

Soft-Coated Wheaten Terriers have a predisposition to PLE and protein-losing nephropathy. The cause is uncertain, although food hypersensitivity has been reported to be present in some affected dogs.

Clinical Features

Individual dogs may have PLE or protein-losing nephropathy (or both). Typical clinical signs may include vomiting, diarrhea, weight loss, and ascites. Affected dogs are often middle aged when diagnosed.

Diagnosis

Hypoalbuminemia and hypocholesterolemia are common, as with any PLE. Histopathology of intestinal mucosa may reveal lymphangiectasia, lymphangitis, and/or lymphocytic inflammation.

Treatment and Prognosis

Treatment is typically as for lymphangiectasia and/or IBD. The prognosis appears guarded to poor for clinically ill animals, with most dying within a year of diagnosis.

IMMUNOPROLIFERATIVE ENTEROPATHY OF BASENJIS

Etiology

Immunoproliferative enteropathy in Basenjis is an intense lymphocytic-plasmacytic small intestinal infiltrate often associated with villous clubbing, mild lacteal dilation, gastric rugal hypertrophy, lymphocytic gastritis, and/or gastric mucosal atrophy. It probably has a genetic basis or predisposition, and intestinal bacteria may play an important role.

Clinical Features

The disease tends to be a severe form of LPE that waxes and wanes, particularly when the animal is stressed (e.g., traveling). Weight loss, small intestinal diarrhea, vomiting, and/or hyporexia are commonly seen. Most affected Basenjis start showing clinical signs by 3 to 4 years of age.

Diagnosis

Marked hypoalbuminemia and hyperglobulinemia are common, especially in advanced cases. The early stages of the disease resemble many other intestinal disorders. In advanced cases the clinical signs are so suggestive that a presumptive diagnosis is often made without biopsy. However, because other diseases (e.g., lymphoma, histoplasmosis) may mimic immunoproliferative enteropathy, alimentary tract biopsy is necessary before aggressive immunosuppressive therapy is begun.

Treatment

Therapy includes diet modification (i.e., highly digestible elimination diet) and antimicrobials (see pp. 442-443), usually plus immunosuppressive therapy (i.e., glucocorticoids and/or cyclosporine). Response to therapy is variable, and affected dogs that respond are at risk for relapse, especially if stressed.

Although a genetic basis is suspected, not enough is known to be able to confidently recommend a breeding program. Intestinal biopsy of asymptomatic dogs is questionable.

Prognosis

Many affected animals die 2 to 3 years after diagnosis. The prognosis is poor for recovery, but some dogs can be maintained for prolonged periods of time with careful monitoring and care. In a few dogs, GI lymphoma eventually develops.

ENTEROPATHY IN CHINESE SHAR-PEIS

Etiology

Chinese Shar-Peis are prone to a severe enteropathy as well as other immune system abnormalities (i.e., Shar-Pei fever syndrome, renal amyloidosis) that probably reflect the immunologic abnormality that predisposes them to exaggerated inflammatory reactions in the GI tract. Shar-Peis are also recognized as often having extremely low serum cobalamin levels.

Clinical Features

Diarrhea and/or weight loss (i.e., small intestinal dysfunction) are the main clinical signs.

Diagnosis

Small intestinal biopsy is necessary for diagnosis. Eosinophilic and lymphocytic-plasmacytic intestinal infiltrates are typically found.

Treatment

Elimination diets, antimicrobial drugs, and antiinflammatory/immunosuppressive drugs are typically used. Shar-Peis are recognized as being prone to exceptionally low blood cobalamin levels, so supplementation is reasonable.

Prognosis

Affected Chinese Shar-Peis have a guarded prognosis.

ENTEROPATHY IN SHIBA DOGS

Etiology

Enteropathy in Shiba dogs has only recently been reported; the cause is unknown.

Clinical Features

Diarrhea and weight loss (i.e., small intestinal dysfunction) are the most common signs. Hyporexia is also a frequent problem.

Diagnosis

Leukocytosis, hypoalbuminemia, and hypocholesterolemia may occur. Typical histopathologic findings are moderate to severe lymphocytic/plasmacytic infiltrates in the duodenum and ileum. Architectural changes are also expected (i.e., crypt distention, blunt villi, lymphangiectasia).

Treatment

Optimal therapy is uncertain. Therapy for IBD (i.e., elimination diets, antimicrobial drugs, and antiinflammatory/immunosuppressive drugs) is currently recommended.

Prognosis

Most affected dogs die within 3 months of diagnosis.

IDIOPATHIC GRANULOMATOUS ENTERITIS AND/OR COLITIS

Canine granulomatous enteritis or colitis is diagnosed histologically and is usually caused by fungi or algae, and sometimes by bacteria. Idiopathic granulomatous infiltrates are uncommon. The clinician should request special stains, culture, and perhaps PCR testing before diagnosing idiopathic granulomatous disease. Regardless of cause, clinical signs are typically more severe than most cases of large bowel disease and may often cause a protein-losing enteropathy. If it is idiopathic and the disease is localized, surgical resection should be considered. If it is diffuse, glucocorticoids and cyclosporine may be considered. Too few cases of idiopathic granulomatous enteritis or colitis have been described and treated to allow generalizations. The prognosis is poor.

INTESTINAL OBSTRUCTION

SIMPLE INTESTINAL OBSTRUCTION

Etiology

Simple intestinal obstruction (i.e., lumenal obstruction without peritoneal leakage, severe venous occlusion, or bowel devitalization) is usually caused by foreign objects. Infiltrative disease and intussusception may also be responsible.

Clinical Features

Simple intestinal obstructions usually cause vomiting with or without hyporexia, depression, or diarrhea. Abdominal pain is uncommon. The more orad the obstruction, the more frequent and severe vomiting tends to be. If the intestine becomes devitalized and septic peritonitis results, the animal may be presented in a moribund state or in SIRS.

Diagnosis

Vomiting of gastric contents (which can occur with gastric outflow obstruction or intestinal obstruction) classically produces a hypokalemic-hypochloremic metabolic alkalosis and paradoxical aciduria, whereas vomiting of intestinal contents classically causes varying degrees of hypokalemia often with some degree of lactic acidosis from poor perfusion. However, these changes are not reliable for diagnosis. Hence, serum electrolyte and acid-base determinations are important when planning therapy.

Abdominal palpation, plain abdominal radiographs, or ultrasonographic imaging can be diagnostic if they reveal a foreign object, mass, or obvious obstructive ileus (see Fig. 27.5, *A*). Abdominal ultrasonography performed by a competent clinician tends to be the most sensitive technique (unless intestines are filled with gas) because it can reveal dilated or thickened intestinal loops not obvious on radiographs. Furthermore, ultrasound may allow aspirate cytology of masses and diagnosis of some diseases (e.g., lymphoma) without surgery. If it is difficult to distinguish obstruction from physiologic ileus, abdominal contrast radiographs may be considered, but they are rarely needed if good ultrasound support is available. Finding a foreign object is usually sufficient to establish a diagnosis, but not all foreign objects cause obstruction.

Treatment

If an abdominal mass, foreign object, or obstructive ileus is found, a presumptive diagnosis of obstruction is typically made, and endoscopy or exploratory surgery is planned. Routine preanesthetic laboratory tests with subsequent stabilization of the patient are indicated before proceeding to endoscopy or surgery.

Prognosis

If septic peritonitis is absent and massive intestinal resection is not necessary, the prognosis is usually good.

INCARCERATED INTESTINAL OBSTRUCTION

Etiology

Incarcerated intestinal obstruction involves a loop of intestine trapped or "strangulated" as it passes through a hernia (e.g., abdominal wall, mesenteric) or similar rent. The entrapped intestinal loop quickly dilates, accumulating fluid in which bacteria flourish and release endotoxins. SIRS occurs rapidly. This is a true surgical emergency, and animals deteriorate quickly if the entrapped loop is not removed.

Clinical Features

Dogs and cats with incarcerated intestinal obstruction typically have acute vomiting, abdominal pain, and progressive depression. Palpation of the entrapped loop often causes severe pain and occasionally vomiting. On physical examination, "muddy" mucous membranes and tachycardia may be noted, suggesting SIRS.

Diagnosis

A presumptive diagnosis is made by finding a distended, painful intestinal loop, especially if the loop is contained within a hernia. Radiographically, a markedly dilated segment of intestine is detected (Fig. 31.11) that is sometimes obviously outside the peritoneal cavity. Otherwise, an obviously strangulated loop of intestine will be found at exploratory surgery.

Treatment

Immediate surgery and aggressive therapy for SIRS are indicated. Devitalized bowel should be resected, with care taken to avoid spillage of septic contents into the abdomen.

Prognosis

The prognosis is guarded. Rapid recognition and prompt surgery are necessary to prevent mortality.

MESENTERIC TORSION/VOLVULUS

Etiology

The intestines twist about the root of the mesentery, causing severe vascular compromise. Much of the intestine is typically devitalized by the time surgery is performed.

Clinical Features

This uncommon cause of intestinal obstruction principally occurs in large dogs (especially German Shepherds). Mesenteric torsion typically causes an acute onset of severe nausea, retching, vomiting, abdominal pain, and depression. Bloody diarrhea may or may not occur. Abdominal distention is not as severe as expected in animals with gastric dilation/volvulus (GDV).

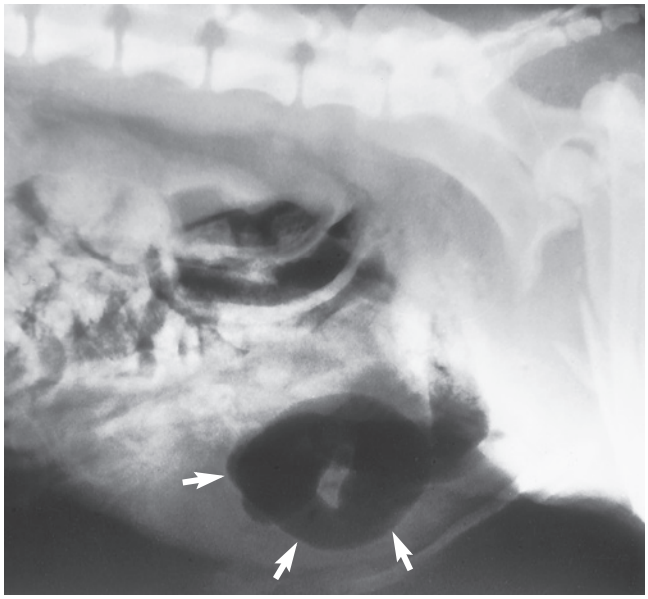


FIG 31.11
Lateral abdominal radiograph of a dog with a ruptured prepubic tendon and incarcerated intestinal obstruction. Note the dilated section of intestine in the area of the hernia *(arrows)*. (From Allen D, editor: *Small animal medicine,* Philadelphia, 1991, JB Lippincott.)

Diagnosis

Abdominal radiographs are often diagnostic and typically show widespread uniform ileus (see Fig. 27.6).

Treatment

Immediate surgery is necessary. The intestines must be properly repositioned and devitalized bowel resected.

Prognosis

The prognosis is extremely poor; most animals die despite heroic efforts. Animals that live may develop short bowel syndrome if massive intestinal resection is necessary.

LINEAR FOREIGN OBJECTS

Etiology

Numerous objects can assume a linear configuration in the alimentary tract (e.g., string, thread, nylon stockings, cloth). The foreign object lodges or fixes at one point (e.g., base of the tongue, pylorus) while the rest trails off into the intestines. The small intestine seeks to propel the object aborally via peristaltic waves and in this manner gathers around it and becomes pleated. As the intestines continue trying to propel it aborally, the linear object cuts or "saws" into the intestines, often perforating them at multiple sites on the antimesenteric border. Fatal peritonitis can result.

Clinical Features

Linear foreign objects appear to be more frequent in cats than in dogs. Vomiting food, bile, and/or phlegm is common, but some animals show only hyporexia or depression. Rare patients (especially dogs with chronic linear foreign bodies) can be relatively asymptomatic for days to weeks while the foreign body continues to embed itself in the intestines.

Diagnosis

The history may be suggestive of a linear foreign body (e.g., the cat was playing with cloth or string). Bunched, painful intestines are occasionally detected by abdominal palpation. The object is sometimes seen lodged at the base of the tongue, but failure to find a foreign object at the base of the tongue does not eliminate linear foreign body. Even when such objects lodge under the tongue, they can be very difficult to find despite a careful oral examination; some become embedded in the frenulum. If necessary, chemical restraint (e.g., IV ketamine, 2 mg/kg) should be used to allow adequate oral examination. Rarely, the end of the linear foreign object protrudes from the anus.

Foreign objects lodged at the pylorus and trailing off into the duodenum must be diagnosed by abdominal palpation, imaging, or gastroduodenoscopy. The objects themselves are infrequently seen radiographically and only rarely produce dilated intestinal loops suggesting anatomic ileus; proximity to the stomach and pleating of the intestines around the

object usually prevent the intestines from dilating. Plain radiographs may reveal small gas bubbles in the intestines, especially in the region of the duodenum, and obvious intestinal pleating may occasionally be seen (Fig. 31.12). If contrast radiographs are performed (use an isotonic iodine contrast agent), they typically reveal a pleated or bunched intestinal pattern, which is diagnostic of linear foreign body. These objects are sometimes seen endoscopically, lodged at the pylorus.

Treatment

Abdominal surgery is typically required to remove linear foreign objects. If the animal is otherwise healthy, if the linear foreign object has been present for only 1 or 2 days, and if it is fixed under the tongue, the object may be cut loose from its attachment at the base of the tongue to see if it will now pass through the intestines without further problem. Surgery is indicated if the animal does not appear better 12 to 24 hours after the object is cut free from its point of fixation.

If there is doubt as to the length of time the object has been present or if it is fixed at the pylorus, surgery is usually a safer therapeutic approach. Endoscopic removal occasionally succeeds, but the clinician must be careful because it is easy to rupture devitalized intestine and cause peritonitis. If the clinician can pass the tip of the endoscope to near the aborad end of the object and pull it out by grabbing the aborad end, surgery is sometimes unnecessary.

Prognosis

The prognosis is usually good if severe septic peritonitis is absent and massive intestinal resection is unnecessary. If a

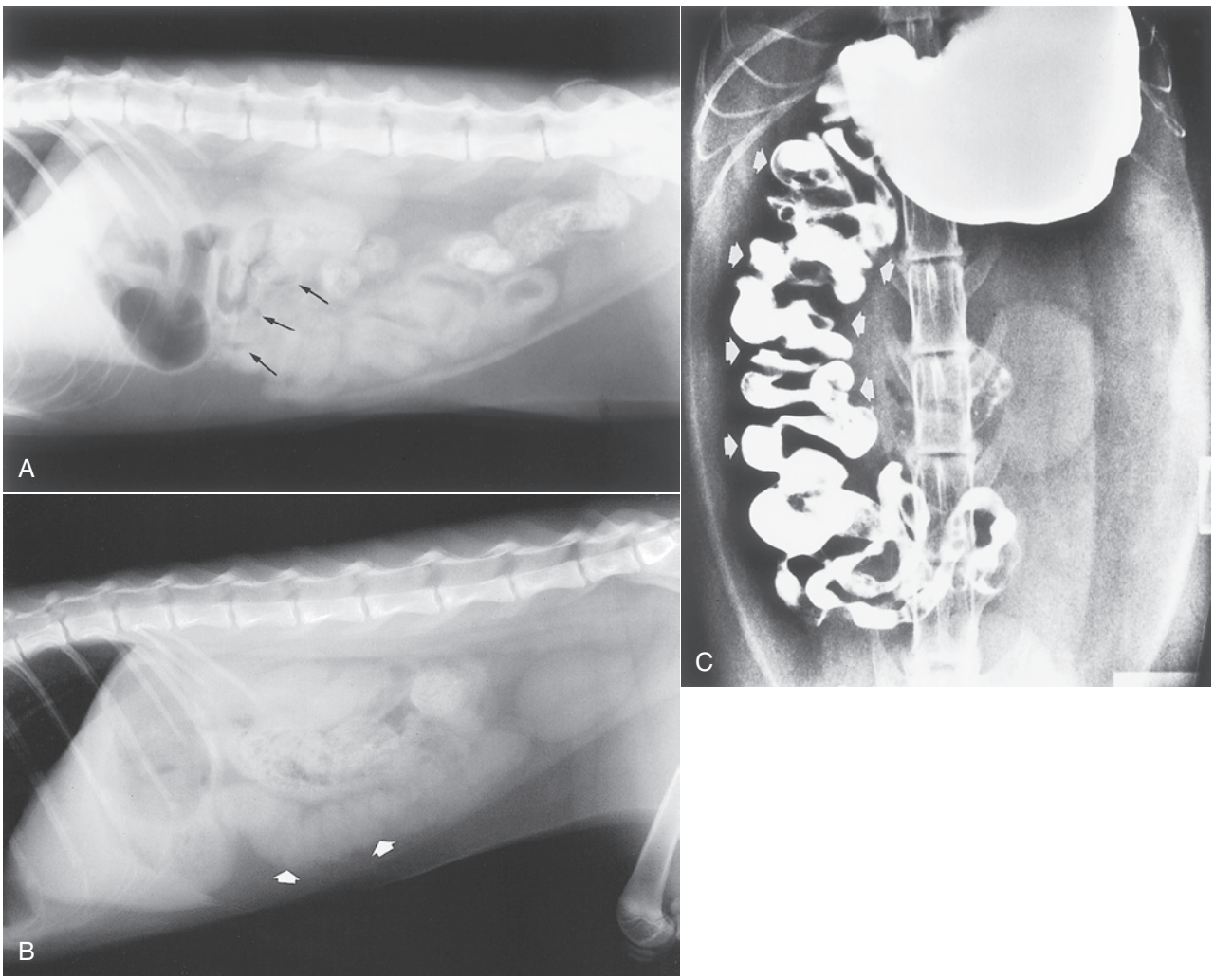


FIG 31.12
(A) Plain abdominal radiograph of a cat with a linear foreign body lodged at the pylorus. Note the small gas bubbles in the mass of intestines *(arrows)*. **(B)** Plain abdominal radiograph of a cat with a linear foreign body. Note the obviously pleated small bowel *(arrows)*. **(C)** Contrast radiograph of a cat with a linear foreign body. Note the pleated, bunched pattern of intestines *(arrows)*. (**A** from Allen D, editor: *Small animal medicine,* Philadelphia, 1991, JB Lippincott.)

linear foreign object has been present a long time, it may embed itself in the intestinal mucosa, making intestinal resection necessary. When massive intestinal resection is necessary, short bowel syndrome might result.

INTUSSUSCEPTION

Etiology

Intussusception is a telescoping of one intestinal segment (the intussusceptum) into an adjacent segment (the intussuscipiens). It may occur anywhere in the alimentary tract, but ileocolic intussusceptions (i.e., ileum entering colon) seem most common. Ileocolic intussusceptions seem to be associated with active enteritis (especially in young animals), which ostensibly disrupts normal motility and promotes the smaller ileum to intussuscept into the larger-diameter colon. However, ileocolic intussusception may occur in animals with acute renal failure, leptospirosis, prior intestinal surgery, and other problems. Main Coon Cats may have a much higher incidence of intussusception than the general population.

Clinical Features

Acute ileocolic intussusception causes obstruction of the intestinal lumen and congestion of the intussusceptum's mucosa. Scant bloody diarrhea, vomiting, abdominal pain, and a palpable abdominal mass are classic. Chronic ileocolic intussusceptions typically produce less vomiting, abdominal pain, and hematochezia. These animals often have intractable diarrhea and hypoalbuminemia because of protein loss from the congested mucosa. PLE in a young dog without hookworms or a puppy that seems to be having an unexpectedly long recovery from parvoviral enteritis should prompt suspicion of chronic intussusception. Acute jejunojejunal intussusceptions usually do not cause hematochezia. Mucosal congestion can be more severe than that in ileocolic intussusception; intestinal devitalization eventually occurs, and bacteria and their toxins may gain access to the peritoneal cavity.

Diagnosis

Palpation of an elongated, obviously thickened intestinal loop establishes a presumptive diagnosis; however, some infiltrative diseases produce similar findings. Ileocolic intussusceptions that are short and do not extend far into the descending colon may be especially difficult to palpate because they are just under the vertebral column and within the rib cage. Occasional intussusceptions "slide" in and out of the colon and can be missed during abdominal palpation. If the intussusception protrudes as far as the rectum, it may resemble a rectal prolapse. Therefore if tissue is protruding from the rectum, the clinician should perform a careful rectal palpation to determine whether a fornix exists (i.e., it is a rectal prolapse) as opposed to an intussusception (in which a fornix is absent).

Plain abdominal radiographs infrequently allow diagnosis of ileocolic intussusceptions because they usually cause minimal intestinal gas accumulation. Abdominal ultrasonography is quick and reasonably sensitive and specific for detecting intussusceptions (see Fig. 27.8, *B*). Colonoscopy can be definitive if the intussuscepted intestine is seen extending into the colon (Fig. 31.13). Jejunojejunal intussusceptions may be easier to palpate because of their location.

A reason for the intussusception (e.g., parasites, mass, enteritis) should always be sought. Fecal examination for parasites and evaluation of full-thickness intestinal biopsy specimens obtained at the time of surgical correction of the intussusception should be performed. In particular, the tip of the intussuscepted bowel (i.e., the intussusceptum) should be examined for a mass lesion (e.g., tumor) that could have served as a focus and helped the intussusception occur. Additional diagnostic tests may be warranted depending on the history, physical examination findings, and results of clinical pathologic evaluation.

Treatment

Intussusceptions are treated surgically. Acute ones may be reduced or resected, whereas chronic ones usually must be resected. Recurrence (in the same or a different site) is reasonably common. Surgical plication might prevent recurrence.

Prognosis

The prognosis is often good if septic peritonitis has not occurred and the intestines do not reintussuscept.

CECOCOLIC INTUSSUSCEPTION

Etiology

Cecocolic intussusception, in which the cecum intussuscepts into the colon, is rare. The cause is unknown, although some suggest that whipworm-induced typhlitis may be responsible.

Clinical Features

Primarily occurring in dogs, intussuscepted cecums can bleed sufficiently to cause anemia. Hematochezia is the major sign. It does not lead to intestinal obstruction and infrequently causes diarrhea.

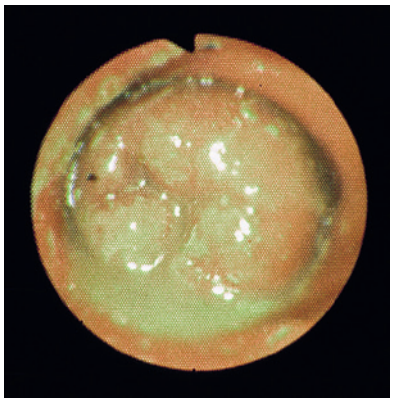


FIG 31.13
Endoscopic view of the ascending colon of a dog with an ileocolic intussusception. Note the large "hot dog"–like mass in the colonic lumen, which is the intussusception.

Diagnosis

Flexible colonoscopy and ultrasonography are the primary ways it is diagnosed.

Treatment

Typhlectomy is curative, and the prognosis is good.

MISCELLANEOUS INTESTINAL DISEASES

SHORT BOWEL SYNDROME

Etiology

Short bowel syndrome occurs when massive resection of small intestines results in the need for special nutritional therapy until the intestines are able to adapt. This is caused by resection of more than 75% to 90% of the small intestine so that the remaining intestine is unable to adequately digest and absorb nutrients. Large numbers of bacteria may reach the upper small intestines, especially if the ileocolic valve is removed. Not all animals with substantial small intestinal resections develop this syndrome. Dogs and cats tolerate loss of large amounts of small intestine better than people do.

Clinical Features

Affected animals usually have severe weight loss and intractable diarrhea (typically without mucus or blood), which often occurs shortly after eating.

Diagnosis

A history of substantial resection in conjunction with the clinical signs is sufficient for diagnosis.

Treatment

The best treatment is prevention. Avoid massive resections if at all possible, even if it means doing a "second-look" surgery 24 to 48 hours later. If massive resection occurs and the animal cannot maintain its body weight with oral feedings alone, total parenteral nutrition is necessary until intestinal adaptation has occurred and treatments have become effective in controlling clinical signs. It is important to continue oral feedings to stimulate intestinal mucosal hypertrophy. The diet should be highly digestible (e.g., low-fat cottage cheese, potato) and should be fed in small amounts at least three to four times a day. Opiate antidiarrheals (e.g., loperamide) and proton pump inhibitors may help lessen diarrhea. Antibiotics might be required to control the large bacterial populations that occur in the small intestine (see pp. 442-443).

Prognosis

If intestinal adaptation occurs, the animal may eventually be fed a near-normal diet. However, some animals will never be able to resume regular diets, and others die despite all efforts. Animals that are initially malnourished seem to have a worse prognosis than those that are initially well nourished.

NEOPLASMS OF THE SMALL INTESTINE

ALIMENTARY LYMPHOMA

Etiology

Lymphoma is a neoplastic proliferation of lymphocytes (see Chapter 79). Alimentary lymphoma must often be considered in patients with severe malabsorptive disease or protein-losing enteropathies. The cause is uncertain; FeLV might be involved in cats (even those that are ELISA negative). LPE has been suggested to be prelymphomatous (especially in cats), but this is uncertain. Lymphoma often affects the intestines, although extraintestinal forms (e.g., lymph nodes, liver, spleen) are more common in dogs. Alimentary lymphoma appears to be more common in cats than in dogs. There are different forms of alimentary lymphoma. Lymphoblastic lymphoma (LL) is found in dogs and cats; well-differentiated SCL is primarily found in cats. Large granular lymphocyte lymphoma is a rare, very severe form found in cats.

Clinical Features

Alimentary LL tends to produce dramatic signs (i.e., chronic progressive weight loss, hyporexia, small intestinal diarrhea, vomiting). Nodules, masses, diffuse intestinal thickening resulting from infiltrative disease, dilated sections of intestine that are not obstructed, and/or focal constrictions are possible, although it may also be present in grossly normal-appearing intestine. PLE may occur. Mesenteric lymphadenopathy (i.e., enlargement) is typical but not invariable. Remember that feline IBD can cause mild to moderate mesenteric lymphadenopathy. Extraintestinal abnormalities (e.g., peripheral lymphadenopathy) are inconsistently found in dogs and cats with alimentary LL.

Alimentary SCL in cats often has a much less aggressive course with relatively mild signs of weight loss, vomiting, and/or diarrhea.

Diagnosis

Diagnosis of LL requires demonstration of neoplastic lymphocytes, which may be obtained by fine-needle aspiration, imprint, or squash cytologic preparations. Paraneoplastic hypercalcemia is neither sensitive nor specific for alimentary lymphoma. Histopathology of intestinal tissue is the most reliable diagnostic method. Some have suggested that full-thickness tissue samples obtained surgically or laparoscopically are preferred over endoscopy. Although such samples are sometimes necessary, the majority of dogs and many cats can be successfully diagnosed endoscopically if the endoscopist obtains good-quality tissue samples and biopsies duodenum and ileum. Occasionally, neoplastic lymphocytes are found only in the serosal layer and full-thickness surgical biopsy specimens are necessary.

Diagnosis of LL tends to be relatively easy in the dog and cat (finding a few obviously malignant lymphocytes confirms it), but diagnosis of feline SCL remains difficult. Poor-quality endoscopic biopsy samples (i.e., too superficial,

having excessive artifact) are notorious for resulting in an erroneous diagnosis of LPE instead of SCL. Finding lymphocytes in the submucosa is not specific for lymphoma. In some cases, finding lymphocytes in organs where they should not be found (e.g., liver) allows diagnosis of SCL.

SCL of the feline intestines tends to be T-cell lymphoma and sometimes has obvious epitheliotrophism. Routine hematoxylin and eosin (H&E) staining does not allow reliable differentiation of SCL from LPE. Immunohistochemistry (i.e., staining for CD3 and CD79a) has been used to help distinguish SCL from LPE. Clonality testing with PCR appears necessary to accurately diagnose SCL in some cases. Clonality testing requires submitting samples to specialized laboratories and takes time and resources.

Treatment

Chemotherapy may palliate some patients with LL, but many become quite ill if given aggressive chemotherapy. In distinction, cats with SCL treated with prednisolone and chlorambucil usually respond well, comparable to cats with IBD that receive the same therapy. Treatment protocols are outlined in Chapter 79.

Prognosis

The long-term prognosis is very poor with LL. Many cats with SCL will have a high quality of life for years with therapy.

INTESTINAL ADENOCARCINOMA

Intestinal adenocarcinoma is more common in dogs than in cats. It typically causes diffuse intestinal thickening or focal circumferential mass lesions. Primary clinical signs are weight loss and vomiting caused by intestinal obstruction. Diagnosis requires demonstrating neoplastic epithelial cells. Endoscopy, surgery, and ultrasound-guided fine-needle aspiration may be diagnostic. Scirrhous carcinomas have very dense fibrous connective tissue that often cannot be adequately biopsied with fine-needle aspiration or a flexible endoscope, so surgery is sometimes required to obtain diagnostic biopsies. The prognosis is good if complete surgical excision is possible, but metastases to regional lymph nodes are common by the time of diagnosis. Postoperative adjuvant chemotherapy does not appear to substantially affect survival time.

INTESTINAL LEIOMYOMA/ LEIOMYOSARCOMA/STROMAL TUMOR

Intestinal leiomyomas and leiomyosarcomas, and stromal tumors are connective tissue tumors that usually form a distinct mass and are primarily found in the small intestine and stomach of older dogs. Primary clinical signs are intestinal hemorrhage, iron deficiency anemia, and obstruction. They can also cause hypoglycemia as a paraneoplastic effect. Diagnosis requires demonstration of neoplastic cells. Evaluation of ultrasound-guided fine-needle aspirates may be diagnostic, but these tumors do not exfoliate as readily as many carcinomas or lymphomas, and incisional or excisional biopsy is often necessary. Surgical excision may be curative if there are no metastases. Metastases make the prognosis poor, although some animals are palliated by chemotherapy.

NEOPLASMS OF THE LARGE INTESTINE

ADENOCARCINOMA

Etiology

Very few canine colonic adenocarcinomas arise from polyps. These tumors can extend into the lumen or be infiltrative and produce a circumferential narrowing.

Clinical Features

Principally found in dogs, colonic and rectal adenocarcinomas are more common in older animals. Hematochezia is common. Infiltrative tumors are likely to cause tenesmus and/or constipation secondary to obstruction.

Diagnosis

Finding carcinoma cells is necessary for a diagnosis. Histopathologic evaluation is often preferable to cytologic analysis because epithelial dysplasia may be present in benign lesions, causing a false-positive cytologic diagnosis of carcinoma. Relatively deep biopsies obtained with rigid biopsy forceps are best for distinguishing carcinomas from benign polyps because invasion of the submucosa is an important feature of rectal adenocarcinomas. Because most colonic neoplasms arise in or near the rectum, digital examination is the best screening test. Colonoscopy is required for masses farther orad. Imaging is used to detect sublumbar lymph node or pulmonary metastases.

Treatment

Complete surgical excision is curative. Transanal pull-through rectal amputation is beneficial in selected cases. There are transabdominal approaches to the distal colon, but long-term outcome is uncertain. However, many patients with rectal adenocarcinoma do not respond as well owing to late diagnosis and extensive local invasion plus distant metastasis to regional lymph nodes.

Prognosis

Timely diagnosis and surgery may give survival times up to 4 years for some patients. The prognosis for unresectable adenocarcinoma is poor. Preoperative and intraoperative radiotherapy may be palliative for some dogs with nonresectable colorectal adenocarcinomas.

RECTAL POLYPS

Etiology

The cause of rectal polyps is unknown.

Clinical Features

Principally found in dogs, hematochezia (which may be considerable) and tenesmus are the primary clinical signs. Obstruction is rare.

Diagnosis

Usually detected during rectal examination, many adenomatous polyps resemble sessile adenocarcinomas because they are so large. Histopathologic analysis is required for diagnosis and to distinguish polyps from malignancies.

Treatment

Complete excision via surgery (everting the rectal mucosa) or endoscopy (using a polypectomy snare) is curative. Although a thorough endoscopic or imaging evaluation of the colon should be done before surgery to ensure that additional polyps are not present, it is rare that there are more. If they are incompletely excised, polyps return and must be excised again (which is common with endoscopically removed polyps).

Prognosis

Most canine rectal and colonic polyps do not result in carcinoma *in situ*, possibly because they are diagnosed relatively sooner than colonic polyps in people. The prognosis is good.

DISEASES OF THE PERINEAL AREA AND ANUS

ACUTE PROCTITIS

Etiology

Acute colitis has many causes (e.g., bacteria, diet, parasites). The underlying cause is seldom diagnosed because this problem tends to be self-limiting. Acute proctitis probably has similar causes but may also be secondary to passage of a rough foreign object that traumatizes the rectal mucosa.

Clinical Features

Animals with acute colitis often feel good despite large bowel diarrhea (i.e., hematochezia, fecal mucus, tenesmus). Vomiting occurs infrequently. The major clinical signs of acute proctitis are constipation, tenesmus, hematochezia, dyschezia, and/or depression.

Diagnosis

Rectal examination is important; animals with acute colitis may have rectal discomfort and/or hematochezia. Eliminating obvious causes (e.g., diet, parasites) and resolving the problem with symptomatic therapy allow presumptive diagnosis. Rectal examination of animals with acute proctitis may reveal roughened, thick, and/or obviously ulcerated mucosa, or it may appear normal. Endoscopy/biopsy are definitive but seldom necessary unless the clinical signs are unduly severe or prolonged.

Treatment

Symptomatic therapy is typically sufficient because acute proctitis and colitis are usually idiopathic. Withholding food for 24 to 36 hours lessens severity of clinical signs. The animal should then be fed small amounts of an easily digested diet (e.g., cottage cheese and rice) with or without fiber. After resolution of clinical signs, the animal may be gradually returned to its original diet. Areas of anal excoriation should be cleansed, and an antibiotic-corticosteroid ointment should be applied. Most animals recover within 1 to 3 days. For proctitis, stool softeners are often helpful. Broad-spectrum antimicrobial therapy is not indicated.

Prognosis

The prognosis for idiopathic disease is good.

RECTAL PROLAPSE

Etiology

Rectal prolapse usually occurs secondary to enteritis or colitis in young animals. They begin to strain because of rectal irritation, and eventually some or all of the rectal mucosa prolapses. Mucosal exposure increases irritation and perpetuates straining, which promotes prolapse. Hence a positive feedback cycle is initiated. Manx cats appear to be predisposed to rectal prolapse.

Clinical Features

Dogs and cats (especially juveniles) are affected. The presence of colonic or rectal mucosa extending from the anus is obvious during the physical examination.

Diagnosis

The diagnosis is based on physical examination. Rectal examination is necessary to differentiate rectal prolapse from an intussusception protruding from the rectum (see p. 501).

Treatment

Treatment consists of resolving the original cause of straining if possible, repositioning the rectal mucosa, and preventing additional straining/prolapse. A well-lubricated finger is used to reposition the mucosa. If it readily prolapses after being replaced, a purse-string suture in the anus is used for 1 to 3 days to hold it in position. The subsequent rectal opening must be large enough so that the animal can defecate. Occasionally, an epidural anesthetic is required to prevent repeated prolapse. If the everted mucosa is so irritated that straining continues, retention enemas with kaolin or barium may provide relief. If a massive prolapse is present or the rectal mucosa is irreversibly damaged, resection may be necessary.

Prognosis

The prognosis is usually good, but some cases tend to recur.

PERINEAL HERNIA

Etiology

Perineal hernia occurs when the pelvic diaphragm (i.e., coccygeus and levator ani muscles) weakens and the rectal canal deviates laterally.

Clinical Features

This condition is principally found in older, small-breed, intact male dogs (especially Boston Terriers, Cardigan Welsh Corgis, Pekingeses, and Boxers); cats are rarely affected. Most animals have dyschezia, constipation, or perineal swelling, but urinary bladder herniation into this defect may cause a potentially fatal postrenal uremia with depression and vomiting.

Diagnosis

Digital rectal examination should be diagnostic (i.e., rectal deviation, lack of muscular support, rectal diverticulum). The clinician should check for retroflexion of the urinary bladder into the hernia. If such herniation is suspected, it can be confirmed by ultrasonography, radiographs, catheterizing the bladder, or aspirating the swelling (after imaging) to see if urine is present.

Treatment

Animals with postrenal uremia constitute an emergency; the bladder should be emptied and repositioned, and IV fluids should be administered. Preferred treatment is surgical reconstruction of the muscular support, but surgery may fail, and clients should be prepared for repeated reconstructive procedures.

Prognosis

The prognosis is fair to guarded.

PERIANAL FISTULAE

Etiology

Impacted anal crypts and/or anal sacs have been hypothesized to become infected and rupture into deep tissues. An immune-mediated mechanism is likely.

Clinical Features

Perianal fistulae occur in dogs and are more common in breeds with a sloping conformation and/or a broad base to the tail head (e.g., German Shepherds). There are typically one or more painful draining tracts around the anus, and constipation (caused by the pain), odor, rectal pain, and/or rectal discharge are typically present.

Diagnosis

Diagnosis is made by physical and rectal examination. Care should be taken when examining the patient, because the rectal area can be very painful. Draining tracts are sometimes absent, but granulomas and abscesses can be palpated via the rectum. Rectal pythiosis rarely mimics perianal fistulae.

Treatment

Most affected dogs are cured with immunosuppressive therapy (e.g., cyclosporine, 3-6 mg/kg PO q12h or topical 0.1% tacrolimus q24h to q12h) with or without antibacterial drugs (e.g., metronidazole, erythromycin). Administering oral ketoconazole (5 mg/kg PO q12h) may allow a lower dose of cyclosporine to be effective, thus decreasing the client's cost. If cyclosporine is used, therapeutic blood monitoring of cyclosporine levels may be needed if the patient is not responding or has signs consistent with toxicity (e.g., hyporexia). Hypoallergenic diets may also be beneficial. Rarely, animals not responding to medical therapy will require surgery. Surgery may cause fecal incontinence. Postoperative care is important and consists of keeping the area clean. Fecal softeners are sometimes useful.

Prognosis

Many patients are treated successfully, but the prognosis is guarded, and repeated medical care or surgeries may be required.

ANAL SACCULITIS

Etiology

In anal sacculitis the anal sac becomes infected, resulting in an abscess or cellulitis.

Clinical Features

Anal sacculitis is relatively common in dogs and occasionally occurs in cats. Small dogs (e.g., Poodles, Chihuahuas) probably have a higher incidence of this disorder than other breeds. Mild cases cause irritation (i.e., scooting, licking, or biting the area). Anal sacs occasionally bleed onto the feces. Severe cases may be associated with obvious pain, swelling, and/or draining tracts. Dyschezia or constipation may develop because the animal refuses to defecate. Fever may occur in dogs and cats with severe anal sacculitis.

Diagnosis

Physical and rectal examinations are usually diagnostic. The anal sacs are often painful, and sac contents may appear purulent, bloody, or normal but increased in volume. In severe cases it may be impossible to express the affected sac. If the sac ruptures, the fistulous tract is usually in a 4 o'clock or 7 o'clock position relative to the anus. Occasionally there is an obvious abscess.

Treatment

Mild cases require only that the anal sac be expressed and an antibiotic-corticosteroid preparation be infused. Infusion with saline solution may aid in expressing impacted sacs. If clients express the anal sacs at home, they can often prevent impaction and reduce the likelihood of severe complications.

Abscesses should be lanced, drained, flushed, and treated with a hot pack; systemic antibiotics should also be administered. Hot packs also help soft spots form in early abscesses. If the problem recurs, is severe, or is nonresponsive to medical therapy, affected sacs can be resected.

Prognosis

The prognosis is usually good.

PERIANAL NEOPLASMS

ANAL SAC (APOCRINE GLAND) ADENOCARCINOMA

Etiology

Anal sac adenocarcinomas are derived from the apocrine glands and are usually found in older female dogs.

Clinical Features

An anal sac or pararectal mass can often be palpated, but some are not obvious. Paraneoplastic hypercalcemia causing hyporexia, weight loss, vomiting, and polyuria-polydipsia is common. Occasionally, constipation due to hypercalcemia or perineal mass occurs. Metastasis to sublumbar lymph nodes occurs early, but metastases to other organs are rare.

Diagnosis

Cytologic and/or histopathologic evaluation is necessary to establish a diagnosis. Hypercalcemia in an older female dog should lead to careful examination of both anal sacs and pararectal structures. Abdominal ultrasonography may reveal sublumbar lymphadenopathy.

Treatment

Hypercalcemia, if present, must be treated (see Chapter 53). The tumor should be removed, but these tumors have often metastasized to regional lymph nodes by the time of diagnosis. Palliative chemotherapy (see Chapter 76) may be transiently beneficial in some dogs.

Prognosis

The prognosis is guarded.

PERIANAL GLAND TUMORS

Etiology

Perianal gland tumors arise from modified sebaceous glands. Perianal gland adenomas have testosterone receptors.

Clinical Features

Perianal gland adenomas are often sharply demarcated, raised, and red, and they may be pruritic. Commonly found around the anus and base of the tail, they may be solitary or multiple and can occur over the back half of the dog. Male hormones appear to stimulate their growth, and they are often found in older intact male dogs (especially Cocker Spaniels, Beagles, and German Shepherds). Pruritus may lead to licking and ulceration of the tumor. Perianal gland adenocarcinomas are rare; they are usually large, infiltrative, ulcerated masses with a high metastatic potential.

Diagnosis

Cytologic and/or histopathologic evaluation is required for diagnosis, but neither reliably distinguishes malignant from benign masses. Finding metastases (e.g., regional lymph nodes, lungs) is the most definitive method of determining malignancy.

Treatment

Surgical excision is preferred for benign or solitary tumors that have not metastasized. Neutering is recommended for dogs with adenomas. Radiation is recommended for multicentric and some malignant tumors. Chemotherapy is helpful in some dogs with adenocarcinomas (see Chapter 76).

Prognosis

The prognosis is good for benign lesions but guarded for malignant lesions.

CONSTIPATION

Constipation may be caused by any perineal or perianal disease already discussed that causes pain (e.g., perianal fistulae, perineal hernia, anal sacculitis) or obstruction as well as anything causing colonic weakness. It may also be caused by other disorders (see Box 26.15).

PELVIC CANAL OBSTRUCTION CAUSED BY MALALIGNED HEALING OF OLD PELVIC FRACTURES

Etiology

Prior trauma (e.g., automobile-associated injuries) is a common cause of pelvic canal obstruction in cats because they frequently sustain pelvic trauma that heals if they are allowed to rest. Cats appear clinically normal once the fractures heal, but diminution of the pelvic canal can produce megacolon and/or dystocia.

Diagnosis

Digital rectal examination should be diagnostic. Radiographs will further define the extent of the problem.

Treatment

Constipation caused by minimal pelvic narrowing may be controlled with stool softeners, but orthopedic surgery may be necessary. The prognosis depends in part on how severely the colon has been distended. Unless the colon is massively stretched out of shape, it can often resume function if it is kept empty and allowed to regain its normal diameter. Prokinetic drugs such as cisapride (0.25 mg/kg PO q8-12h) may stimulate peristalsis but must *not* be used if there is residual obstruction.

Prognosis

The prognosis depends on the severity and chronicity of colonic distention and surgical success in widening the pelvic canal.

BENIGN RECTAL STRICTURE

Etiology

The cause is uncertain but may be congenital.

Clinical Features

Constipation and tenesmus are the principal clinical signs.

Diagnosis

Digital rectal examination should detect the stricture, although it can be missed if a large dog is palpated carelessly or if the stricture is beyond reach. Proctoscopy and evaluation of a deep biopsy specimen (i.e., including submucosa) of the stricture are required to confirm that the lesion is benign and fibrous as opposed to neoplastic or fungal.

Treatment

Simple dilation via balloon or retractor will sometimes tear the stricture and allow normal defecation; other patients require surgery. Owners should be warned that strictures may re-form during healing, and surgery can cause incontinence in rare cases. Prednisolone (1.1 mg/kg/day PO) administered after dilatation might impede stricture reformation.

Prognosis

The prognosis is guarded to good.

DIETARY INDISCRETION LEADING TO CONSTIPATION

Etiology

Dogs often eat inappropriate foods or other materials (e.g., paper, popcorn, hair, bones). Excessive dietary fiber supplements can cause constipation if the animal becomes dehydrated.

Diagnosis

Dietary causes are common in dogs that eat trash. Dietary indiscretion is best diagnosed by examining fecal matter retrieved from the colon.

Treatment

Controlling the pet's eating habits, adding appropriate amounts of fiber to the diet, and feeding a moist diet (especially in cats) help prevent constipation. Repeated retention and cleansing (*not* hypertonic) enemas may be needed to remove retained feces. Manual disruption of hard feces should be avoided, but can be done. The animal should be anesthetized to help prevent colonic trauma during the procedure. Sponge forceps or curved hemostats can be used to mechanically break apart the feces. It often helps to insert a rigid colonoscope up to the fecal mass and then insert a tube with a vigorous stream of running water at body temperature issuing from the tip. This will soften the fecal mass and wash away debris that break off.

Prognosis

The prognosis is usually good. The colon should function normally after cleansing unless the distention has been prolonged and severe.

IDIOPATHIC MEGACOLON

Etiology

The cause is unknown but may involve behavior (i.e., refusal to defecate) or altered colonic neurotransmitters.

Clinical Features

Idiopathic megacolon is principally a feline disease, although dogs are occasionally afflicted. Affected patients may be depressed and hyporectic and are often presented because of infrequent defecation.

Diagnosis

Diagnosis is based upon palpating a massively dilated colon (not one just filled to normal capacity) plus elimination of dietary, behavioral, metabolic, and anatomic causes. Abdominal radiographs should be performed to look for potential causes (e.g., masses pressing on the colon).

Treatment

Impacted feces must be removed. Multiple warm water retention and cleansing enemas over 2 to 4 days usually work. Future fecal impaction is prevented by adding fiber to a moist diet (e.g., Metamucil, pumpkin pie filling) although some cats do better with a low-residue diet. Making sure clean litter is always available, using osmotic laxatives (e.g., lactulose) and/or prokinetic drugs (e.g., cisapride) are sometimes necessary. Lubricants are not as helpful because they do not change fecal consistency. If this conservative therapy fails or is refused by the client, subtotal colectomy helps some cats (dogs seldom tolerate this procedure well). Cats typically have soft stools for a few weeks postoperatively before regaining normal consistency, but some have soft stools for the rest of their lives.

Prognosis

The prognosis is fair to guarded. Many cats respond well to conservative therapy if treated early.

Suggested Readings

Allenspach K, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid-refractory inflammatory bowel disease. *J Vet Intern Med*. 2006;20:239.

Allenspach K, et al. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J Vet Intern Med*. 2007;21:700.

Arslan HH, et al. Therapeutic effects of probiotic bacteria in parvoviral enteritis in dogs. *Rev Med Vet (Toulouse)*. 2012;163:55.

Arranz-Solis D, et al. Tritrichomonas foetus infection in cats with diarrhea from densely housed origins. *Vet Parasit*. 2016;221:118.

Awayshes A, et al. Evaluation of supervised machine-learning algorithms to distinguish between inflammatory bowel disease and alimentary lymphoma in cats. *J Vet Diagn Invest*. 2016;28:679.

Berryessa NA, et al. Gastrointestinal pythiosis in 10 dogs from California. *J Vet Intern Med*. 2008;22:1065.

Bouzid M, et al. The prevalence of *Giardia* infection in dogs and cats, a systematic review and meta-analysis of prevalence studies from stool samples. *Vet Parasit*. 2015;207:181.

Briscoe KA, et al. Histopathological and immunohistochemical evaluation of 53 cases of feline lymphoplasmacytic enteritis and low-grade alimentary lymphoma. *J Comp Pathol*. 2011;145: 187.

Casamian-Sorrosal D, et al. Comparison of histopathologic findings in biopsies from the duodenum and ileum of dogs with enteropathy. *J Vet Intern Med*. 2010;24:80.

Costa M, et al. Diagnostic accuracy of two point-of-care kits for the diagnosis of *Giardia* species infection in dogs. *J Small Anim Pract*. 2016;57:318.

Dandrieux JRS. Inflammatory bowel disease versus chronic enteropathy in dogs: are they one and the same? *J Small Anim Pract*. 2016;57:589.

Danlaux LA, et al. Ultrasonographic thickening of the muscularis propria in feline small intestinal small cell T-cell lymphoma and inflammatory bowel disease. *J Fel Med Surg*. 2014;16: 89.

Dossin O, et al. Protein-losing enteropathies in dogs. *Vet Clin N Am*. 2011;41:399.

Dye TL, et al. Randomized, controlled trial of budesonide and prednisone for the treatment of idiopathic inflammatory bowel disease in dogs. *J Vet Inter Med*. 2013;27:1385.

Foy DS, et al. Endoscopic polypectomy using endocautery in three dogs and one cat. *J Am Anim Hosp Assoc*. 2010;46:168.

Fragkou FC, et al. Prevalence and clinicopathological features of triaditis in a prospective case series of symptomatic and asymptomatic cats. *J Vet Intern Med*. 2016;30:1031.

Garcio-Sancho M, et al. Evaluation of clinical, macroscopic, and histopathologic response to treatment in nonhypoproteinemic dogs with lymphocytic-plasmacytic enteritis. *J Vet Intern Med*. 2007;21:11.

Gaschen FP, et al. Adverse food reaction in dogs and cats. *Vet Clin N Am*. 2011;41:361.

Geiger T. Alimentary lymphoma in cats and dogs. *Vet Clin N Am*. 2011;41:419.

Goodwin LV, et al. Hypercoagulability in dogs with protein-losing enteropathy. *J Vet Intern Med*. 2011;25:273.

Gras L, et al. Increased risk for Campylobacter jejuni and C. coli infection of pet origin in dog owners and evidence for genetic association between strains causing infection in humans and their pets. *Epidem Infect*. 2013;141:2526.

Gruffydd-Jones T, et al. Giardiasis in cats: ABCD guidelines on prevention and management. *J Fel Med Surg*. 2013;15:650.

Hall EJ. Antibiotic-responsive diarrhea in small animals. *Vet Clin N Am*. 2011;41:273.

Han-Slang H, et al. High detection rate of dog circovirus in diarrheal dogs. *BMC Vet Res*. 2016;12:116.

Jergens AE, et al. Comparison of oral prednisone and prednisone combined with metronidazole for induction therapy of canine inflammatory bowel disease: a randomized-controlled trial. *J Vet Intern Med*. 2010;24:269.

Jergens AE, et al. Feline idiopathic inflammatory bowel disease: what we know and what remains to be unraveled. *J Fel Med Surg*. 2012;14:445.

Kawano K, et al. Prevalence of food-responsive enteropathy among dogs with chronic enteropathy in Japan. *J Vet Med Sci*. 2016;78:1377.

Kilpinen S, et al. Oral tylosin administration is associated with an increase of faecal enterococci and lactic acid bacteria in dogs with tylosin-responsive diarrhoea. *Vet J*. 2015;205:369.

Kilpinen S, et al. Efficacy of two low-dose oral tylosin regimens in controlling the relapse of diarrhea in dogs with tylosin-responsive diarrhea: a prospective, single-blinded, two-arm parallel, clinical field trial. *Acta Vet Scand*. 2014;56:43.

Kiupel M, et al. Diagnostic algorithm to differentiate lymphoma from inflammation in feline small intestinal biopsy samples. *Vet Pathol*. 2011;48:212.

Kruse BD, et al. Prognostic factors in cats with feline panleukopenia. *J Vet Intern Med*. 2010;24:1271.

LaFlamme DP, et al. Effect of diets differing in fat content on chronic diarrhea in cats. *J Vet Intern Med*. 2011;25:230.

Leahy AM, et al. Evaluation of faecal Salmonella shedding among dogs at seven animal shelters across Texas. *Zoonoses Pub Healt*. 2016;63:515.

Litster AL, et al. Use of ponazuril paste to treat coccidiosis in shelter-housed cats and dogs. *Vet Parasit*. 2014;202:319.

Lecoindre A, et al. Focal intestinal lipogranulomatous lymphangitis in 10 dogs. *J Small Anim Pract*. 2016;57:465.

Loyd JA, et al. Retrospective evaluation of the administration of 25% human albumin to dogs with protein-losing enteropathy: 21 cases (2003-2013). *J Vet Emer Crit Care*. 2016;26:587.

Manchester AC, et al. Association between granulomatous colitis in French bulldogs and invasive Escherichia coli and response to fluoroquinolone antimicrobials. *J Vet Intern Med*. 2013;27:55.

Mandigers PJJ, et al. A randomized, open label, positively-conducted field trial of a hydrolyzed protein diet in dogs with chronic small bowel enteropathy. *J Vet Intern Med*. 2010;24: 1350.

Marks SL, et al. Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. *J Vet Intern Med*. 2011;25:1195.

Maunder CL, et al. Campylobacter species and neutrophilic inflammatory bowel disease in cats. *J Vet Intern Med*. 2016;30:996.

Menozzi A, et al. Rifaximin is an effective alternative to metronidazole for the treatment of chronic enteropathy in dogs: a randomized trial. *BMC Vet Res*. 2016;12:217.

Moore PF, et al. Feline gastrointestinal lymphoma: mucosal architecture, immunophenotype, and molecular clonality. *Vet Path*. 2012;49:658.

Mortier F, et al. Acute haemorrhagic diarrhoea syndrome in dogs: 108 cases. *Vet Rec*. 2015;176:627.

Nakashima K, et al. Prognostic factors in dogs with protein-losing enteropathy. *Vet J*. 2015;205:28.

Norsworthy G, et al. Prevalence and underlying causes of histologic abnormalities in cats suspected to have chronic small bowel disease: 300 cases (2008-2013). *J Amer Vet Med Assoc*. 2015;247:629.

Ohmi A, et al. A retrospective study in 21 Shiba dogs with chronic enteropathy. *J Vet Med Sci*. 2011;73:1.

Payne PA, et al. The biology and control of *Giardia* spp and *Tritrichomonas foetus*. *Vet Clin N Am*. 2009;39:993.

Procter TD, et al. A cross-sectional study examining Campylobacter and other zoonotic enteric pathogens in dogs that frequent dog parks in three cities in South-Western Ontario and risk factors for shedding of Campylobacter spp. *Zoonoses Publ Health*. 2014;61:208.

Procoli F, et al. Comparison of histopathologic findings in duodenal and ileal endoscopic biopsies in dogs with chronic small intestinal enteropathies. *J Vet Intern Med*. 2013;27:268.

Renne R, et al. Palatability and clinical effects of an oral recuperation fluid during the recovery of dogs with suspected parvoviral enteritis. *Topics Compan An Med*. 2016;31:68.

Rodriguez JY, et al. Distribution and characterization of Heterobilharzia americana in dogs in Texas. *Vet Parasito*. 2014;203:35.

Sabattini S, et al. Differentiating feline inflammatory bowel disease from alimentary lymphoma in duodenal endoscopic biopsies. *J Small Anim Pract*. 2016;57:396.

Schmitz S, et al. Comparison of three rapid commercial canine parvovirus antigen detection tests with electron microscopy and polymerase chain reaction. *J Vet Diagn Invest*. 2009;21:344.

Schorza V, et al. Cryptosporidium felis in faeces from cats in the UK. *Vet Rec*. 2014;174:609.

Schulz BS, et al. Comparison of the prevalence of enteric viruses in healthy dogs and those with acute haemorrhagic diarrhoea by electron microscopy. *J Small Anim Pract*. 2008;49:84.

Silva ROS, et al. Clostridium perfringens: a review of enteric diseases in dogs, cat and wild animals. *Anaerobe*. 2015;33:14.

Simpson KW, et al. Pitfalls and progress in the diagnosis and management of canine inflammatory bowel disease. *Vet Clin N Am*. 2011;41:381.

Stavisky J, et al. A case-control study of pathogen and life style risk factors for diarrhoea in dogs. *Prevent Vet Med*. 2011;99:185.

Streit S, et al. Ultrasonographic findings for selected gastrointestinal tract diseases. *Tieraerztliche Praxis Ausgabe Kleintiere Heimtiere*. 2014;42:281.

Sutherland-Smith J, et al. Ultrasonographic intestinal hyperechoic mucosal striations in dogs are associated with lacteal dilation. *Vet Radiol Ultrasound*. 2007;48:51.

Washabau R, et al. Endoscopic, biopsy, and histopathologic guidelines for the evaluation of gastrointestinal inflammation in companion animals. *J Vet Intern Med*. 2010;24:10.

Willard MD, et al. Effect of tissue processing on assessment of endoscopic intestinal biopsies in dogs and cats. *J Vet Intern Med*. 2010;24:84.

Woldemeskel M, et al. Canine parvovirus-2b-associated erythema multiforme in a litter of English setter dogs. *J Vet Diagn Invest*. 2011;23:576.

Xenoulis PG, et al. Feline exocrine pancreatic insufficiency: a retrospective study of 150 cases. *J Vet Intern Med*. 2016;30:1790.

Yao C, et al. Tritrichomonas foetus infection, a cause of chronic diarrhea in the domestic cat. *Vet Res*. 2015;46:35.

Zwingenberger AL, et al. Ultrasonographic evaluation of the muscularis propria in cats with diffuse small intestinal lymphoma or inflammatory bowel disease. *J Vet Intern Med*. 2010;24:289.

CHAPTER 32

Disorders of the Peritoneum



INFLAMMATORY DISEASES

SEPTIC PERITONITIS

Etiology

Septic peritonitis is usually *secondary peritonitis*, caused by leakage from the gastrointestinal (GI) or biliary tract or pyometras. In the dog, GI tract perforation or devitalization is usually caused by neoplasia, ulceration (especially nonsteroidal antiinflammatory drug or steroid induced), intussusception, foreign objects, or dehiscence of suture lines. In cats, GI perforation due to lymphosarcoma is an important cause. Biliary tract leakage is typically from a ruptured gallbladder secondary to necrotizing cholecystitis (i.e., mucocele or chronic bacterial infection). Septic peritonitis can also develop after surgery or hematogenous spread from elsewhere. Trauma (i.e., gunshot, car accident, bite wounds) is a more common cause in cats than in dogs. Barium sulfate can leak from a GI perforation after a radiographic contrast procedure and produces particularly severe peritonitis.

Occasionally dogs and cats develop primary (also called *spontaneous*) bacterial peritonitis (PBP) in which there is no identifiable source of the infection. Oral bacteria are suspected to be the source in cats with PBP, but translocation from the intestines might be responsible. Gram-positive organisms tend to be more common in PBP.

Clinical Features

Septic peritonitis secondary to intestinal suture line dehiscence classically manifests 3 to 6 days postoperatively. Dogs with two or more of the following have been reported to be at increased risk for dehiscence of intestinal suture lines: serum albumin < 2.5 g/dL, intestinal foreign body, and preoperative peritonitis. Dogs with secondary septic peritonitis due to leakage from the GI tract, biliary tract, or a pyometra are usually severely depressed, febrile (or hypothermic), nauseated, and may have abdominal pain (if they are not too depressed to respond). Abdominal effusion is usually mild to modest in amount. Signs usually progress rapidly until systemic inflammatory response syndrome (SIRS; formerly known as *septic shock*) occurs. However, some animals with septic peritonitis may have mild vomiting, slight fever, and copious volumes of abdominal fluid and feel relatively well for days or longer. Cats with SIRS due to septic peritonitis tend to present differently than dogs; sometimes they only show bradycardia, hypothermia, and hypotension.

Dogs with PBP tend to have larger abdominal fluid accumulations than dogs with secondary septic peritonitis. Clinical signs in dogs (especially those with PBP associated with severe hepatic disease) can sometimes be much less severe than is usually seen in secondary peritonitis. Cats with PBP do not necessarily present differently than those with sepsis due to GI tract leakage.

Diagnosis

Most animals with septic peritonitis due to GI or biliary tract perforation have small amounts of abdominal fluid that are difficult to detect by physical examination but which decrease serosal detail on plain abdominal radiographs. Ultrasonography is more sensitive than radiography for detecting small amounts of abdominal fluid. Free peritoneal gas not related to recent abdominal surgery strongly suggests GI tract leakage (Fig. 32.1) or peritoneal infection with gas-forming bacteria. Ultrasonography may detect masses (e.g., tumors), biliary mucocele, cholecystitis, or pyometra. Neutrophilia is common but nonspecific in dogs and cats with septic peritonitis. Neutropenia and/or hypoglycemia may occur with severe septicemia.

Abdominocentesis is indicated if free abdominal fluid is detected. Ultrasound guidance should allow clinicians to sample effusions even when only modest amounts are present. Retrieved fluid is examined cytologically and cultured. Abdominal fluid is expected to be an exudate (i.e., high protein, large numbers of nucleated cells with toxic or degenerating neutrophils predominating); however, this finding does not diagnose septic peritonitis. Bacteria (especially if phagocytized by white blood cells) or fecal contents in abdominal fluid are necessary to definitively diagnose septic peritonitis (Fig. 32.2). Unfortunately, fecal contents and bacteria are sometimes difficult to find. Prior antibiotic use in particular may suppress bacterial numbers and the percentage of neutrophils demonstrating degenerative

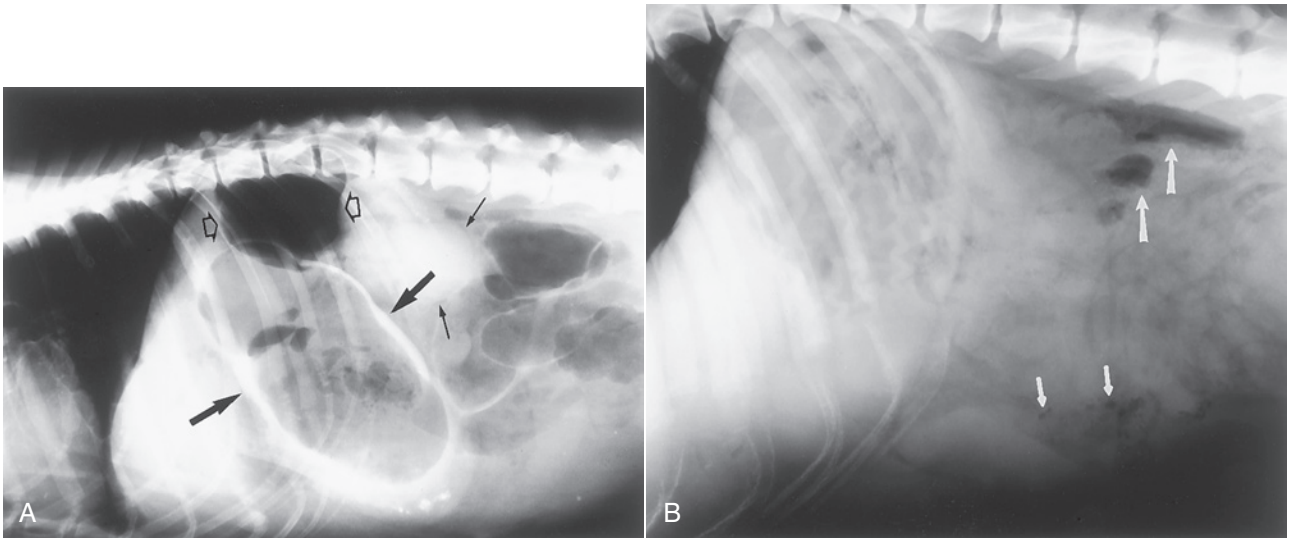


FIG 32.1
(A) Plain lateral abdominal radiograph of a dog. Visceral margins of kidney *(small solid arrows)* and stomach *(large solid arrows)* are outlined by negative contrast (i.e., air). In addition, there are pockets of free air in the abdomen *(open arrows)*. This dog had a gastric ulcer that spontaneously perforated. **(B)** Plain lateral radiograph of a dog with a splenic abscess. There are air bubbles in the region of the spleen *(short arrows)* and free gas in the dorsal peritoneal cavity *(long arrows)*.

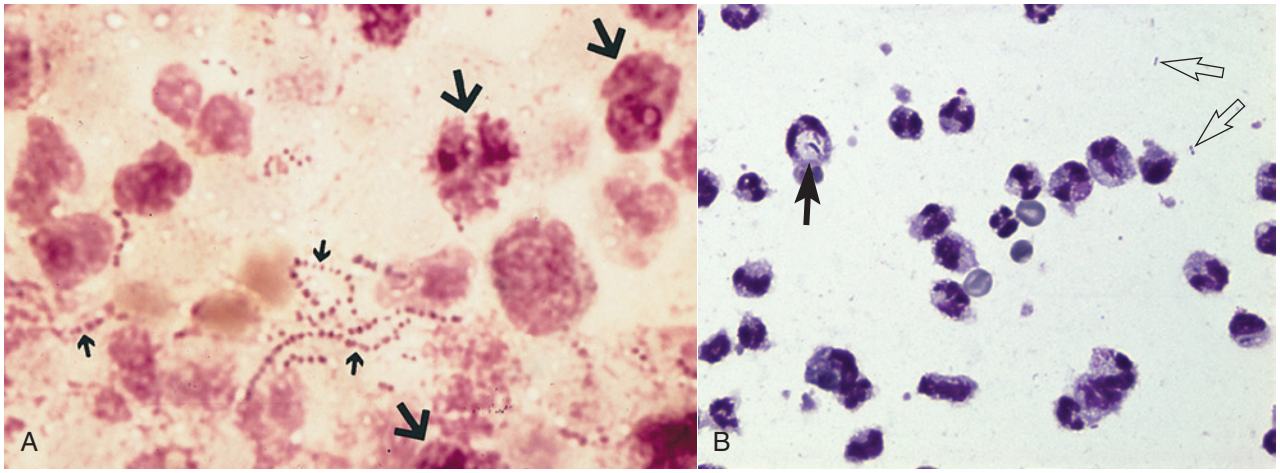


FIG 32.2
(A) Photomicrograph of peritoneal exudate from a dog with septic peritonitis. Note bacteria *(small arrows)* and neutrophils that have degenerated so much that it is difficult to identify them as neutrophils *(large arrows)* (Wright's stain; ×1000). **(B)** Photomicrograph of septic peritoneal fluid. There is one intracellular bacterium *(large arrow)* and two things *(clear arrows)* that may or may not be bacteria. The neutrophils are not nearly as degenerated as in **A.** (**A** courtesy Dr. Claudia Barton, Texas A&M University.)

changes. Furthermore, mildly degenerative neutrophils are common in effusions after recent abdominal surgery.

If bacteria or plant material cannot be found in the abdominal effusion, it can be difficult to quickly distinguish septic peritonitis from sterile abdominal diseases that mimic septic peritonitis (e.g., severe acute pancreatitis). Both can cause SIRS, and ultrasound is not as sensitive in detecting pancreatitis as desired. Degenerative neutrophils in the abdominal fluid are suggestive of septic peritonitis, but severe sterile pancreatitis can produce degenerative changes identical to those seen with infection. Comparing lactate levels in blood and effusion is not always accurate in distinguishing septic from nonseptic effusions. Finding a plasma (not whole blood) glucose concentration that is > 38 mg/dL more than the peritoneal fluid or the peritoneal fluid supernatant glucose concentration strongly suggests septic

peritonitis, but the test is not perfect.[1] In patients in which septic peritonitis is strongly suspected but unproven, the clinician may need to proceed with exploratory laparotomy before abdominal fluid culture results are available.

Canine pancreatic lipase immunoreactivity (cPLI) is very sensitive for acute pancreatitis, but specificity for clinically important pancreatic disease is uncertain. High values have been found in patients that do not clearly have pancreatitis as an important clinical problem, and dogs with septic peritonitis may have inflammation of the pancreas secondary to generalized abdominal sepsis. The clients need to understand that in some cases there is no quick, simple, reliable way to distinguish septic from nonseptic peritonitis before surgery.

A potentially important distinction is PBP versus secondary septic peritonitis. Dogs with PBP may be more difficult to diagnose based upon abdominal fluid analysis because they may have exudates, modified transudates, or pure transudates. They can have relatively few bacteria in the effusion, and concentration techniques (e.g., cytospin) may be required to demonstrate bacteria in the effusion. Some dogs with PBP are clinically less ill than expected for patients with secondary peritonitis.

Treatment

Animals with septic peritonitis usually have leakage from the alimentary tract or biliary tract, or a pyometra; they should be surgically explored as soon as they are acceptable anesthetic risks. In contrast, dogs with PBP do not usually benefit from surgery. If there is a good reason to strongly suspect PBP (e.g., low-grade peritonitis with gram-positive cocci in a modestly ill dog with hepatic cirrhosis and no evidence or reason to suspect GI or biliary perforation), conservative medical management plus close observation might be a reasonable initial plan.

If secondary peritonitis (which is much more common than PBP) is suspected, then surgery is almost always indicated. Preanesthetic complete blood count (CBC), serum biochemistry profile, and urinalysis are desirable, but surgery usually should not be inappropriately delayed while waiting for laboratory results. During surgery a careful search should be made for GI tract defects. Tissue surrounding a perforation should be submitted for histopathology to search for underlying disease (especially neoplasia). Serosal patch grafting has not been shown to be advantageous when closing such defects. After the defect is corrected, the abdomen should be repeatedly lavaged with large volumes of warm crystalloid solutions to dilute and remove debris and bacteria. The abdomen cannot be adequately lavaged via a drain tube or even a peritoneal dialysis catheter except in the mildest cases. Adhesions re-form quickly; they should not be broken down unless necessary to examine the intestines. If barium sulfate is present, as much as possible should be mechanically removed, even if it requires omentectomy. Intestines should be resected only if they are truly devitalized; excessive resection may produce short bowel syndrome (see p. 502).

Many consider substantial abdominal contamination an indication for postoperative abdominal drainage. Closed suction drains have been used postoperatively with success and are much preferred to Penrose drains. Open abdominal drainage is very time and labor intensive and seldom necessary. At this time, there is no good evidence that abdominal drainage significantly impacts outcome.

Systemic antimicrobial therapy should initially consist of broad-spectrum parenteral antibiotics. For very ill patients (e.g., SIRS), a combination of a β-lactam drug (e.g., ampicillin plus sulbactam), metronidazole, and an aminoglycoside (e.g., amikacin) or a fluoronated quinolone is usually an excellent choice (see the discussion of antibacterial drugs used in GI disorders, pp. 442-443). Remember that when enrofloxacin is given parenterally, it must be administered over 30 to 40 minutes in a diluted form. Aminoglycosides and quinolones are dose-dependent drugs; administration of the entire daily dose in one injection is safer and as or more effective than administering smaller doses two to three times daily. For patients less severely ill, the clinician may elect to use less-aggressive antibiotic therapy (e.g., Cefoxitin [30 mg/kg IV q6-8h]). Dogs with PBP can often be treated with oral antibiotics (e.g., Clavamox or enrofloxacin).

Fluid and electrolyte support helps prevent aminoglycoside-induced nephrotoxicity. Hypoalbuminemia is common. Administration of colloids (e.g., hetastarch, pentastarch) can increase plasma oncotic pressure and improve peripheral perfusion, but close observation is indicated because sometimes the colloid leaks into the extravascular space, worsening perfusion. The clinician may administer human or canine albumin to improve plasma oncotic pressure, but human albumin sometimes causes anaphylactoid reactions in dogs. Fresh-frozen plasma (with or without heparin) seems indicated if disseminated intravascular coagulation (DIC) is present, but (1) this is a very inefficient way to increase serum albumin concentrations, and (2) one should monitor AT III concentrations and coagulation times. Early nutritional support seems to shorten hospitalization time.[2]

Prognosis

The prognosis depends on the cause. Prognosis in patients with GI leakage depends on the cause of the leakage (e.g., perforations may be caused by malignancies) and the animal's condition when it is diagnosed. Hypotension, long surgery time, glucocorticoid administration, and postoperative hypoalbuminemia worsen the prognosis after small intestinal surgery. Glucocorticoid administration after colonic surgery is a major risk factor for death. High blood lactate levels on admission and failure to lower blood lactate levels within 6 hours of admission are bad prognostic signs.[3]

Patients with leakage of infected bile into the abdomen can decompensate and die very quickly and precipitously. Dogs with SBP usually have a relatively good prognosis.

HEMOABDOMEN

Most red effusions are blood-tinged transudates, not hemoabdomen. Hemoabdomen is usually indicated by an abdominal fluid with a hematocrit of > 10% to 15%. Blood in the abdominal cavity can be iatrogenic (i.e., caused by abdominocentesis), traumatic (e.g., automobile-associated trauma, splenic torsion, splenic hematoma), due to coagulopathy (e.g., ingestion of vitamin K antagonist), or caused by malignancy (e.g., hemangiosarcoma). Clots or platelets in the fluid sample mean the bleeding is iatrogenic or currently occurring near the site of abdominocentesis. History, physical examination, coagulation studies, and/or abdominal ultrasonography usually establish the diagnosis. Spontaneous hemoabdomen in older dogs is often caused by a bleeding hemangiosarcoma or hepatocellular carcinoma, and these tumors are typically easy to find ultrasonographically. Thrombocytopenia can be confusing; it may be the cause of abdominal bleeding or may be caused by vigorous abdominal bleeding. Even when a coagulopathy is secondary to the original cause of the hemoabdomen (e.g., tumor), it may become severe enough to promote bleeding by itself. In cats, the causes of hemoabdomen are more evenly divided between neoplastic (i.e., hemangiosarcoma and hepatocellular carcinoma) and nonneoplastic (e.g., coagulopathy, hepatic disease, ruptured urinary bladder) diseases. The prognosis depends upon the cause.

ABDOMINAL HEMANGIOSARCOMA

Etiology

Abdominal hemangiosarcoma often originates in the spleen or liver (see Chapter 81). It can spread throughout the abdomen by implantation, causing widespread peritoneal seepage of blood, or it can metastasize to distant sites (e.g., liver, lungs, heart).

Clinical Features

Abdominal hemangiosarcoma is principally found in older dogs, especially German Shepherd Dogs, Labrador Retrievers, and Golden Retrievers. Anemia, abdominal effusion, and periodic weakness or collapse from poor peripheral perfusion are common presenting complaints. Some animals have bicavity hemorrhagic effusion.

Diagnosis

Ultrasonography is the most sensitive test for splenic and hepatic masses, especially when there is copious abdominal effusion. Radiographs may reveal a mass if there is minimal free peritoneal fluid. Splenic hematoma, hemangioma, and widespread accessory splenic tissue masquerade as hemangiosarcoma but have a much better prognosis; therefore a definitive diagnosis is important. Definitive diagnosis requires cytology or histopathology because fluid analysis rarely reveals neoplastic cells. Fine-needle biopsy (especially fine-needle core biopsy) is sometimes diagnostic, but there is a risk of life-threatening hemorrhage; the patient must be watched closely for hypovolemia after the procedure. Two or more large tissue samples from the resected mass should be submitted, and the clinician should be prepared to request recuts; hemangiosarcoma may be difficult to find histologically because there is often hematoma surrounding the tumor.

Treatment

Solitary masses should be excised. Chemotherapy may be palliative for some animals with multiple masses; chemotherapy may also be used as an adjuvant postoperative treatment modality (see Chapter 81).

Prognosis

The prognosis is poor because the tumor metastasizes early.

MISCELLANEOUS PERITONEAL DISORDERS

ABDOMINAL CARCINOMATOSIS

Etiology

Abdominal carcinomatosis involves widespread miliary peritoneal carcinomas that can originate from various sites. Intestinal and pancreatic adenocarcinomas are common causes of carcinomatosis.

Clinical Features

Weight loss may be the predominant complaint, although some animals are presented because of obvious abdominal effusion.

Diagnosis

Physical examination and radiography are inadequate for diagnosis. Ultrasonography may reveal larger masses or infiltrates, but small miliary lesions are typically missed by ultrasound. Fluid analysis reveals a nonseptic exudate or a modified transudate; epithelial neoplastic cells are occasionally found (see Chapter 34) but must be differentiated from reactive mesothelial cells. Laparoscopy or abdominal exploratory surgery with histologic examination of tissue specimens is usually needed for diagnosis.

Treatment

Intracavitary chemotherapy has been palliative for some animals, although generally there is no effective treatment for this disorder. An oncologist should be consulted.

Prognosis

The prognosis is grim.

MESOTHELIOMA

Etiology

The cause of mesothelioma in dogs and cats is unknown.

Clinical Features

Mesothelioma often causes bicavity effusion. The tumor may appear as fragile clots adhering to the peritoneal surface of various organs.

Diagnosis

Imaging reveals only fluid accumulations. Fluid cytology rarely is diagnostic because reactive mesothelial cells are notorious for mimicking malignancy. Laparoscopy or laparotomy is typically required for a definitive diagnosis.

Treatment

Intracavity chemotherapy may be attempted. An oncologist should be consulted.

Prognosis

The prognosis is grim, but chemotherapy sometimes prolongs survival.

FELINE INFECTIOUS PERITONITIS

Feline infectious peritonitis (FIP) is a viral disease of cats and is discussed in detail in Chapter 96. Only the abdominal effusion of FIP is discussed here. Although a major cause of feline abdominal effusion, FIP is not generally a common disease (unless one is involved with catteries), and it is not the only cause of feline abdominal effusions. Furthermore, not all cats with FIP have effusions. FIP effusions are classically pyogranulomatous (i.e., macrophages and nondegenerate neutrophils) with a relatively low nucleated cell count (i.e., ≤10,000/μL). However, some cats with FIP have effusions that primarily contain neutrophils. A nonseptic exudate in a nonazotemic cat suggests FIP until proven otherwise.

Suggested Readings

Adams RJ, et al. Closed suction drainage for treatment of septic peritonitis of confirmed gastrointestinal origin in 20 dogs. *Vet Surg*. 2014;43:843.

Aronsohn MG, et al. Prognosis for acute nontraumatic hemoperitoneum in the dog: a retrospective analysis of 60 cases (2003-2006). *J Am Anim Hosp Assoc*. 2009;45:72.

Bernardine F, et al. Spontaneous gastrointestinal perforation in cats: a retrospective study of 13 cases. *J Fel Med Surg*. 2015;17:873.

Costello MF, et al. Underlying cause, pathophysiologic abnormalities, and response to treatment in cats with septic peritonitis: 51 cases (1990-2001). *J Am Vet Med Assoc*. 2004;225:897.

Culp WTN, et al. Primary bacterial peritonitis in dogs and cats: 24 cases (1990-2006). *J Am Vet Med Assoc*. 2009;234:906.

Culp WTN, et al. Spontaneous hemoperitoneum in cats: 65 cases (1994-2006). *J Am Vet Med Assoc*. 2010;236:978.

Dayer T, et al. Septic peritonitis from pyloric and non-pyloric gastrointestinal perforation: prognostic factors in 44 dogs and 11 cats. *J Small Anim Pract*. 2013;54:625.

Grimes JA, et al. Identification of risk factors for septic peritonitis and failure to survive following gastrointestinal surgery in dogs. *J Am Vet Med Assoc*. 2011;238:486.

Horowitz FB, et al. A retrospective analysis of 25% human albumin supplementation in hypoalbuminemic dogs with septic peritonitis. *Can Vet J*. 2015;56:591.

Jitpean S, et al. Outcome of pyometra in female dogs and predictors of peritonitis and prolonged postoperative hospitalization in surgically treated cases. *BMC Vet Res*. 2014;10(6).

Ko JJ, et al. Barium peritonitis in small animals. *J Vet Med Sci*. 2014;76:621.

Mueller MG, et al. Use of closed-suction drains to treat generalized peritonitis in dogs and cats: 40 cases (1997-1999). *J Am Vet Med Assoc*. 2001;219:789.

Parsons KJ, et al. A retrospective study of surgically treated cases of septic peritonitis in the cat (2000-2007). *J Small Anim Pract*. 2009;50:518.

Ralphs SC, et al. Risk factors for leakage following intestinal anastomosis in dogs and cats: 115 cases (1991-2000). *J Am Vet Med Assoc*. 2003;223:73.

Ruthrauff CM, et al. Primary bacterial septic peritonitis in cats: 13 cases. *J Am Anim Hosp Assoc*. 2009;45:268.

Shales CJ, et al. Complications following full-thickness small intestinal biopsy in 66 dogs: a retrospective study. *J Small Anim Pract*. 2005;46:317.

Smelstoys JA, et al. Outcome of and prognostic indicators for dogs and cats with pneumoperitoneum and no history of penetrating trauma: 54 cases (1988-2002). *J Am Vet Med Assoc*. 2004;225:251.

Wong C, et al. The colloid controversy: are colloids bad and what are the options. *Vet Clin N Amer*. 2017;47:411.

References

1. Koenig A, et al. Usefulness of whole blood, plasma, peritoneal fluid, and peritoneal fluid supernatant glucose concentrations obtained by a veterinary point-of-care glucometer to identify septic peritonitis in dogs with peritoneal effusion. *J Amer Vet Med Assoc*. 2015;247:1027.
2. Liu DT, et al. Early nutritional support is associated with decreased hospitalization in dogs with septic peritonitis: a retrospective study of 45 cases (2000-2009). *J Vet Emerg Crit Care*. 2012;22:453.
3. Cortellini S, et al. Plasma lactate concentrations in septic peritonitis: a retrospective study of 83 dogs (2007-2012). *J Vet Emerg Crit Care*. 2015;25:388.



Selected Drugs Used in Gastrointestinal Disorders

GENERIC NAME	TRADE NAME	DOSE FOR DOGS	DOSE FOR CATS
Aluminum hydroxide	Amphojel	10-30 mg/kg PO q6-8h	10-30 mg/kg PO q6-8h
Amikacin	Amiglyde	20-25 mg/kg IV, SC q24h	10-15 mg/kg IV, SC q24h
Amoxicillin		22 mg/kg PO, IM, SC, q8-12h	Same
Amphotericin B, lipid complex or liposomal	Abelcet AmBisome	1.1-3.3 mg/kg/treatment IV; watch for nephrotoxicity	0.5-2.2 mg/kg/treatment IV (not approved); watch for nephrotoxicity
Ampicillin		22 mg/kg IV q6-8h	Same
Apomorphine		0.02-0.04 mg/kg IV; 0.04-0.1 mg/kg SC	Do not use
Atropine		0.02-0.04 mg/kg IV, SC q6-8h; 0.2-0.5 mg/kg IV, IM for organophosphate toxicity	Same
Azathioprine	Imuran	50 mg/m^2 PO q24-48h (not approved)	Do not use
Azithromycin	Zithromax	5-10 mg/kg PO q24h for 5-7 days (not approved)	5-15 mg/kg PO q24h for 7 days (not approved)
Bethanechol	Urecholine	2.5-15 mg/dog PO q8h	1.2-5 mg/cat PO q8h
Bisacodyl	Dulcolax	5-10 mg/dog PO as needed	5 mg/cat PO q24h
Bismuth subsalicylate	Pepto-Bismol	1 mL/kg/day PO divided q8-12h for 1-2 days	Do not use
Budesonide	Entocort	0.125 mg/kg PO q24-48h (not approved)	0.5-0.75 mg/cat PO q24-72h (not approved)
Butorphanol	Torbutrol, Torbugesic	0.2-0.4 mg/kg IV, SC, IM q2-3h as needed	0.2 mg/kg IV, SC as needed
Cefazolin	Ancef	20-25 mg/kg IV, IM, SC q6-8h	Same
Cefoxitin	Mefoxin	30 mg/kg IV, IM, SC q6-8h (not approved)	Same as dogs (not approved)
Chlorambucil	Leukeran	2-6 mg/m^2 PO q24-48h (not approved)	1 mg twice weekly < 3.5 kg; 2 mg twice weekly > 3.5 kg (not approved)
Chloramphenicol		50 mg/kg PO q8h	20 mg/kg PO q12h
Cisapride	Propulsid	0.1-0.5 mg/kg PO q8-12h	2.5-5 mg total dose PO q8-12h (1 mg/kg maximum dose)
Clindamycin	Antirobe	11-33 mg/kg PO q12h	Same
Cyclosporine	Atopica	3-7 mg/kg PO q12h, adjust based upon therapeutic drug monitoring	5 mg/kg PO q24h
Cyproheptadine	Periactin	Not used for anorexia in dogs	2 mg/cat PO
Dexamethasone	Azium	0.05-0.1 mg/kg IV, SC, PO q24-48h for inflammation	Same
Dioctyl sodium sulfosuccinate	Colace	10-200 mg/dog PO, depending on weight, q8-12h	10-50 mg/cat PO q12-24h
Diphenhydramine	Benadryl	2-4 mg/kg PO; 1-2 mg/kg IV, IM q8-12h	Same
Doxycycline	Vibramycin	10 mg/kg PO q24h or 5 mg/kg PO q12h	Same
Enrofloxacin	Baytril	5-20 mg/kg, PO or IV (diluted), q24h	5 mg/kg PO q24h (high doses can be associated with blindness)
Epsiprantel	Cestex	5.5 mg/kg PO once	2.75 mg/kg PO once

Continued

Selected Drugs Used in Gastrointestinal Disorders—cont'd

GENERIC NAME	TRADE NAME	DOSE FOR DOGS	DOSE FOR CATS
Erythromycin		11-22 mg/kg PO q8h (for antimicrobial action); 0.5-1 mg/kg PO q8-12h (for prokinetic activity)	Same
Esomeprazole	Nexium	1 mg/kg PO, IV q24h (not approved)	1 mg/kg PO q24h (not approved)
Famotidine	Pepcid	0.1-0.2 mg/kg PO, IV q12-24h	Same (not approved)
Febantel plus pyrantel plus praziquantel	Drontal Plus	See manufacturer's recommendations; also see Table 28.7	Adults: 10 mg/kg q24h for 3 days Kittens receive 15 mg/kg (not approved)
Fenbendazole	Panacur	50 mg/kg PO q24h for 3-5 days	Not approved, but probably the same as for dogs for 3 days
Hetastarch		10-20 mg/kg/day (consult critical care literature for safety concerns)	10-15 mg/kg/day
Interferon omega (IFN-ω)	Virbagen, Omega	2,500,000 units/kg IV, SC q24h for 3 days	1,000,000 units/kg SC q24h for 5 days
Itraconazole	Sporanox	5 mg/kg PO q12h (not approved)	5 mg/kg PO q24h (not approved)
Ivermectin		200 µg/kg PO once (not in Collies or other sensitive breeds) for intestinal parasites	250 µg/kg PO once
Kaolin-pectin	Kaopectate	1-2 mL/kg PO q8-12h	Not recommended
Ketamine		Not recommended for restraint	1-2 mg/kg IV for 5-10 minutes of restraint
Ketoconazole	Nizoral	5 mg/kg PO q12h to suppress cyclosporine metabolism (not approved)	Not recommended
Lactulose	Cephulac	0.2 mL/kg PO q8-12h, then adjust dose to achieve soft stools (not approved)	1-5 mL/cat PO q8h for constipation (not approved)
Loperamide	Imodium	0.1 mg/kg PO q8-12h (not approved)	0.08-0.16 mg/kg PO q12h (not approved)
Magnesium hydroxide	Milk of Magnesia	5-10 mL/dog PO q6-8h (antacid)	5-10 mL/cat PO q8-12h (antacid)
Maropitant	Cerenia	1 mg/kg SC or 2 mg/kg PO q24h (dogs 2-7 months old—only use for 5 days); 8 mg/kg PO q24h for 2 days for motion sickness	1 mg/kg, IV, SC or PO, q24h
Mesalamine	Pentasa	5-10 mg/kg PO q8-12h (not approved)	Not recommended
Methylprednisolone acetate	Depo-Medrol	1 mg/kg IM q1-3 wk	10-20 mg/cat IM q1-3 wk
Metoclopramide	Reglan	0.25-0.5 mg/kg IV, PO, IM q8-24h; 0.3-1.0 mg/kg/hr, CRI	Same (not approved)
Metronidazole	Flagyl	12-15 mg/kg PO q12h for 7-8 days for giardiasis; 10-15 mg/kg PO q24h for ARE	12-15 mg/kg PO q24h for 8 days for giardiasis; 10-15 mg/kg PO q24h for ARE
Milbemycin	Sentinel	0.5 mg/kg PO monthly	Not approved
Mirtazapine	Remeron	0.5 mg/kg (approx. 3.75 to 7.5 mg/dog) PO daily (not approved)	1.9 mg/cat PO q24-48h (doses have been used up to 3.75-7.5 mg/cat) (not approved)
Misoprostol	Cytotec	2-5 µg/kg PO q8-12h (not approved)	Not recommended
Neomycin	Biosol	10-15 mg/kg PO q6-12h	Same



Selected Drugs Used in Gastrointestinal Disorders—cont'd

GENERIC NAME	TRADE NAME	DOSE FOR DOGS	DOSE FOR CATS
Olsalazine	Dipentum	5-10 mg/kg PO q12h (not approved)	Not recommended
Omeprazole	Prilosec	1-2 mg/kg PO q12h (not approved)	Same (not approved)
Ondansetron	Zofran	0.5-1 mg/kg PO; 0.1-0.2 mg/kg IV q8-24h (not approved)	0.5 mg/kg q12h PO, SQ (not approved)
Orbifloxacin	Orbax	2.5-7.5 mg/kg PO q24h	7.5 mg/kg PO q24h
Pancreatic enzymes	Viokase V, Pancreazyme	1-3 tsp/454 g of food	Same
Pantoprazole	Protonix	1 mg/kg IV q24h (not approved)	Unknown
Praziquantel	Droncit	See manufacturer's recommendations; also see Table 28.7	See manufacturer's recommendations; also see Table 28.7
Prednisolone		1.1-2.2 mg/kg PO, q24h or divided, for antiinflammatory effects	Same
Prochlorperazine	Compazine	0.1-0.5 mg/kg IM q8-12h	0.13 mg/kg IM q12h (not approved)
Psyllium hydrocolloid	Metamucil	1-2 tsp/10 kg	Same
Pyrantel pamoate	Nemex	5 mg/kg PO once, repeat in 7-10 days	20 mg/kg PO once
Pyridostigmine	Mestinon	0.5-2 mg/kg PO q8-12h	Not used
Ranitidine	Zantac	1-2 mg/kg PO, IV q8-12h (not approved)	2.5 mg/kg IV; 3.5 mg/kg PO q12h
Ronidazole		Unknown	20-30 mg/kg q24h PO for 10 days (not approved)
Sucralfate	Carafate	0.5-1 g PO q6-12h, depending on size (use suspension)	0.25 g PO q6-24h
Sulfadimethoxine	Albon	50 mg/kg PO first day, then 27.5 mg/kg PO q12h for 9 days	Same
Sulfasalazine	Azulfidine	10-20 mg/kg PO q8-12h, not to exceed 3 g/day	Not recommended, but 7.5-20 mg/kg PO q12h has been anecdotally reported
Thiabendazole	Omnizole	50 mg/kg PO q24h for 3 days (not approved)	125 mg/kg PO q24h for 3 days
Trimethoprim-sulfadiazine	Tribrissen, Bactrim	30 mg/kg PO q24h for 10 days	Same as for dogs
Tylosin	Tylan	10-20 mg/kg PO q12-24h in food (may decrease to 5 mg/kg once control is established)	Same
Vitamin B_{12} (cobalamin)		100-200 µg/dog PO q24h or 250-500 µg/dog IM, SC q24d	50-100 µg/cat PO q24h or 250 µg IM, SC q7d
Xylazine	Rompun	1.1 mg/kg IV; 2.2 mg/kg SC, IM	0.4-0.5 mg/kg, IM or IV, for emesis

ARE, Antibiotic-responsive enteropathy; *CRI,* constant-rate infusion; *IBD,* inflammatory bowel disease; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *SC,* subcutaneously.

PART FOUR ▪ Hepatobiliary and Exocrine Pancreatic Disorders

Penny J. Watson

CHAPTER 33

Clinical Manifestations of Hepatobiliary and Pancreatic Disease



GENERAL CONSIDERATIONS

Clinical signs of hepatobiliary and pancreatic diseases in dogs and cats are very variable with considerable overlap in signs. Dogs or cats with disease of either the liver or pancreas can present with nonspecific signs such as anorexia, lethargy, and vomiting, or more specific signs such as jaundice (which can be hepatic in origin in liver disease or posthepatic in pancreatic disease due to extrahepatic biliary obstruction) or cranial abdominal pain, which is more common in pancreatitis and biliary tract disease than in hepatic parenchymal disease. Clinical signs of pancreatitis in dogs and cats show a spectrum from mild abdominal pain and anorexia to "acute abdomen" and potential multiorgan failure and diffuse intravascular coagulation (DIC). Clinical presentation is even more challenging in cats because pancreatic and liver disease often occur concurrently in this species, but cats also tend to hide their pain. Clinical signs of hepatobiliary and pancreatic disease are listed in Box 33.1. It is important to remember that none of these signs are pathognomonic of hepatobiliary or pancreatic disease, and they must be distinguished from identical signs caused by disease of other organ systems. Cause of death in severe, acute pancreatitis and acute hepatitis is usually multiorgan failure and DIC. In lower-grade chronic liver disease, death may eventually occur as a result of loss of function, whereas prolonged survival is possible with chronic pancreatitis in spite of functional loss, provided this is recognized and treated with enzyme supplementation and/or insulin. Dogs and cats with acute pancreatitis, more severe clinical signs, and compromise of more organ systems at presentation are more likely to die. In chronic liver disease, the severity of clinical signs does not necessarily correlate with the prognosis or with degree of liver injury, although several of these signs are often seen together, particularly in dogs with end-stage hepatic disease (e.g., ascites, metabolic encephalopathy from hepatocellular dysfunction, acquired portosystemic venous shunting with gastrointestinal [GI] bleeding). Both ascites and jaundice have been shown to be significant negative prognostic indicators in dogs with chronic hepatitis. The presence of cirrhosis is also a negative prognostic indicator in dogs, and these cases are more likely to present with ascites, acquired portosystemic shunts (PSS), and hepatic encephalopathy (HE). It is important to appreciate that any prognostic data is on a population basis, and that individual dogs with chronic hepatitis and ascites can have a good prognosis. At the opposite end of the spectrum of hepatobiliary and pancreatic disease, because of the tremendous reserve capacity of both the liver and the pancreas, there may be no clues for the presence of a hepatic disorder or low-grade chronic pancreatitis except for abnormal screening blood test results obtained before an elective anesthetic procedure. However, it is important to investigate persistent elevation of liver enzymes even if there are no clinical signs, because treatment is likely to be much more effective if instituted early.

GASTROINTESTINAL SIGNS

Vomiting, diarrhea, and anorexia are common clinical signs associated with both pancreas and liver disease. Vomiting in dogs and cats with liver disease can be as a result of local inflammation, portal hypertension, or HE. Animals with portal hypertension may have hematemesis and melena as a result of upper GI ulceration.

Vomiting is a prominent sign in acute and chronic pancreatitis in dogs and cats, and is due to focal or more generalized peritonitis, and also delayed gastric emptying and duodenal hypomotility due to the proximity of pancreatic inflammation. Dogs with severe acute pancreatitis usually present with acute onset of vomiting, anorexia, marked abdominal pain, and varying degrees of dehydration, collapse, and shock. Differential diagnoses in these cases include other causes of acute abdomen. Signs in cats overlap the signs of cholangitis and inflammatory bowel disease (IBD), which often occur concurrently in cats, with anorexia and

BOX 33.1

Clinical Signs and Physical Examination Findings in Cats and Dogs With Hepatobiliary and Pancreatic Disease*

General, Nonspecific, Both Hepatobiliary and Pancreatic Disease

Anorexia
Depression
Lethargy
Weight loss
Poor or unkempt haircoat
Nausea, vomiting
Diarrhea
Dehydration
Polydipsia, polyuria

More Specific but Not Pathognomonic
Hepatobiliary disease

Abdominal enlargement (organomegaly, effusion, or muscular hypotonia)
Jaundice, bilirubinuria, acholic feces
Metabolic encephalopathy
Coagulopathies

Pancreatic disease

Severe intractable vomiting
Cranial abdominal pain
Steathorrea

*Individual animals will show some but not all of these signs, and many animals with hepatobiliary disease will show no clinical signs at all.

lethargy being most common. Vomiting and abdominal pain occur in fewer than half reported cases of pancreatitis in cats.

Dogs and cats with milder acute or chronic pancreatitis present with mild GI signs—typically anorexia and sometimes some mild vomiting, followed by the passage of some colitis-like feces (e.g., tenesmus, hematochezia, frequent bowel movements), accompanied by some fresh blood resulting from local peritonitis in the area of the transverse colon.

ABDOMINAL PAIN

Abdominal pain is a prominent clinical sign of acute and chronic pancreatitis in dogs. It undoubtedly also occurs in cats with acute pancreatitis but is much more challenging to recognize in this species because of their propensity to hide their pain in the consulting room, even in the face of severe peritonitis. Subtle signs of pain in cats should be taken seriously, as should reports by the owner that their cat is in pain. Some forms of liver disease also cause abdominal pain; the liver parenchyma is poorly supplied with pain fibers, but the liver capsule and biliary tract are well innervated. Biliary tract disease is particularly painful in dogs and cats; gallstones in cats, gallbladder mucoceles in dogs, and extrahepatic biliary obstruction in both species are particularly painful. Dogs and cats with hepatomegaly of any cause often show pain on cranial abdominal palpation, presumably due to stretching of the liver capsule.

POLYURIA AND POLYDIPSIA

Increased thirst and volume of urination can be clinical signs of serious hepatocellular dysfunction and also of PSS both congenital and acquired. The underlying mechanisms are poorly understood, but several factors are suspected to contribute to polydipsia (PD) and polyuria (PU), which are seen primarily in dogs and rarely in cats. Altered sense of thirst may be a manifestation of HE. Early studies suggested that dogs with congenital and acquired PSS have hypercortisolemia associated with a reduced metabolism of cortisol in the liver and decreased cortisol-binding protein concentration in the plasma. However, more recent studies have failed to support this. Changes in the function of portal vein osmoreceptors that stimulate renal water loss early after drinking, before a change in systemic osmolality, may also be partly responsible for PU in patients with liver disease, although studies have been published only for rodents and humans. Loss of the renal medullary-concentrating gradient for urea because of the inability to produce urea from ammonia may also be involved and would first cause PU and then compensatory PD.

PD/PU is an unusual finding in pancreatitis but is sometimes reported in chronic pancreatitis in dogs, perhaps in response to nausea or abdominal pain. It is important to rule out diabetes mellitus (DM) in any dog or cat with chronic pancreatitis that shows PD/PU, because DM can develop due to endocrine tissue destruction in end-stage chronic pancreatitis.

ABDOMINAL EFFUSION

Abdominal effusion occurs in both liver and pancreas disease in both dogs and cats. It is much more common in dogs than in cats with liver disease. With the exception of liver disease associated with feline infectious peritonitis (FIP) or congenital ductal plate abnormalities, cats with liver disease rarely have ascites, whereas ascites are seen in about a third of dogs with chronic hepatitis. A small amount of effusion is suspected when abdominal palpation yields a slippery sensation during physical examination. Moderate- to large-volume effusion is frequently conspicuous but may distend the abdomen so much that details of abdominal organs are obscured during palpation. With acute pancreatitis in either species, abdominal effusion is common although it is usually a much smaller volume than the ascites of liver disease and may only be visible on ultrasound.

PATHOGENESIS OF TRANSUDATES

Whether there is small- or large-volume effusion, the general pathogeneses of third-space fluid accumulation (excessive formation by increased venous hydrostatic pressure,

decreased intravascular oncotic pressure, or altered vascular permeability and insufficient resorption), singly or in combination, apply to cats and dogs with hepatobiliary diseases. In parenchymal liver disease, the commonest cause of ascites formation is portal hypertension, which is a sustained increase in pressure in the portal system, with or without a contribution from reduced serum albumin concentration (Fig. 33.1). The fluid is typically a relatively high protein-modified transudate. A low protein transudate is occasionally seen in animals with liver disease and concurrent hypoalbuminemia. It is very rare to have an albumin concentration low enough to cause ascites alone. Portal hypertension is common in dogs with end-stage liver disease but rare in cats. It is also recognized in some cases of acute liver disease. Typically, it results in the triad of ascites, HE, and GI congestion, and propensity to ulceration. It is caused by the increased resistance to blood flow through the sinusoids of the liver or, less commonly, by more direct obstructions to the portal vein or caudal vena cava, such as those caused by thromboemboli. The presence of a large arteriovenous fistula in the liver can also result in portal hypertension. Early in chronic liver disease, portal hypertension can be the result of multiplication and phenotypic transformation of hepatic Ito (stellate) cells, which become contractile myofibroblasts that surround the sinusoids and cause constriction. In the longer term, fibrous tissue laid down by these transformed

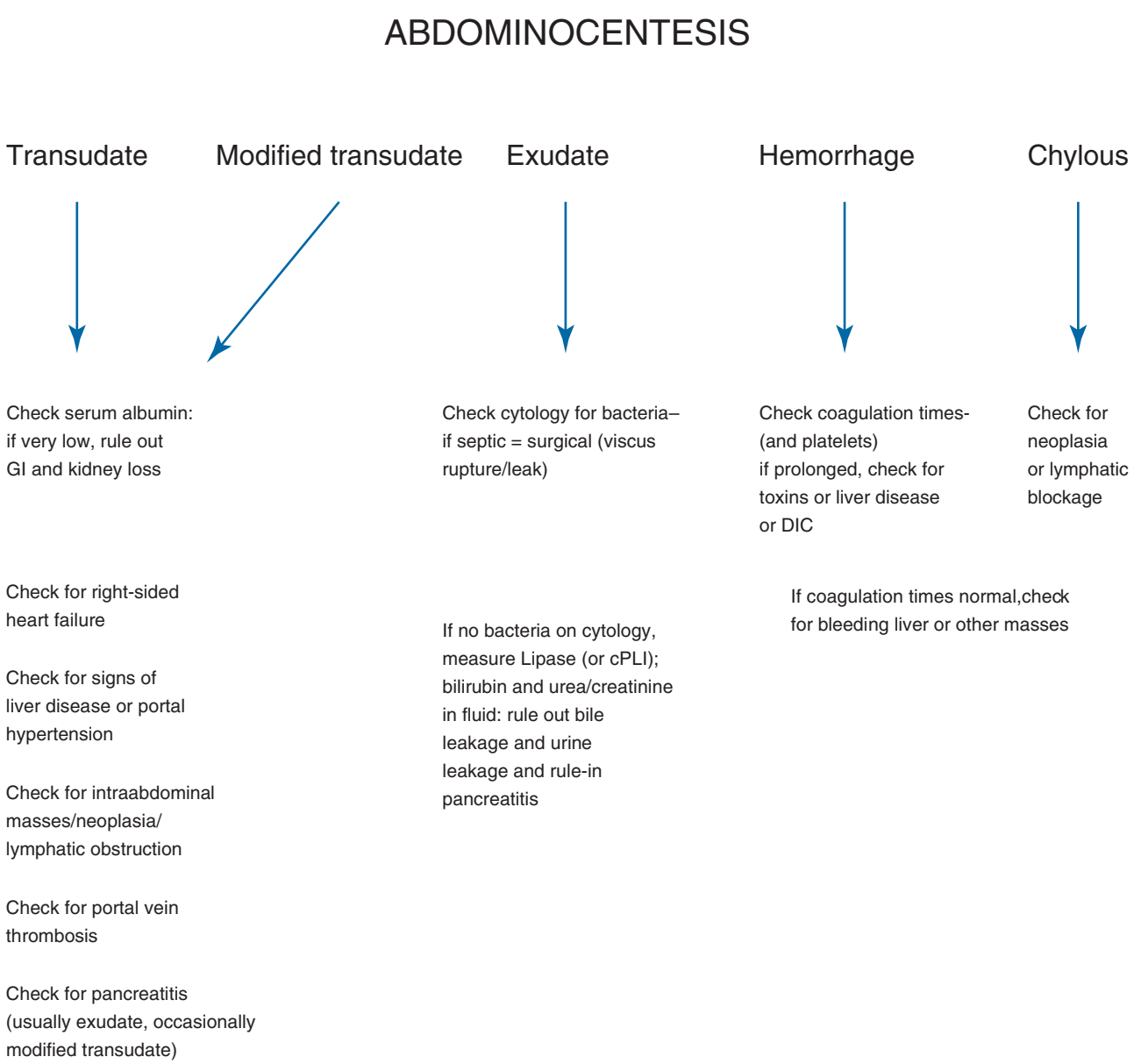


FIG 33.1
Algorithm for initial evaluation of a dog with abdominal effusion and suspected liver or pancreas disease.

stellate cells results in more irreversible sinusoidal obstruction. Thus the most common cause of portal hypertension is chronic hepatitis progressing to cirrhosis in dogs (Fig. 33.2). It can also occur in association with hepatic neoplasia or in acute liver disease as a result of diffuse hepatic swelling. In one study of acute liver disease, 41% of dogs had ascites.

The pathogenesis of the development of ascites in portal hypertension is complex and has really been studied only in humans; it is assumed that the mechanisms of ascites are similar in dogs. One way in which dogs differ from humans is that dogs do not develop the "spontaneous" infection of ascites of liver origin by extension of gut bacteria into the fluid that results in peritonitis, which is commonly reported in people. The presence of ascites is a poor prognostic indicator in humans with chronic hepatitis, and the same appears to be true in dogs. Sodium retention by the kidneys is an important mechanism in the development of ascites in liver disease. As demonstrated in Fig. 33.2, portal hypertension results in congestion of splanchnic vessels with pooling of blood in the splanchnic circulation. This results in a drop in systemic circulating blood volume and thus blood pressure that leads to increased renal sodium retention, partly as a result of reduced glomerular filtration rate and decreased sodium delivery to the tubules and partly as a result of increased release of renin-angiotensin-aldosterone (RAAS) that results in increased sodium retention in the distal tubules. This leads to an increase in circulating fluid volume, which precipitates the formation of ascites, which in turn reduces venous return because of increased pressure on the caudal vena cava and initiates a vicious cycle of renal sodium retention and ascites. This is the "over-fill" theory of ascites formation in liver disease. Therefore aldosterone antagonists (e.g., spironolactone) are usually most effective in dogs with ascites secondary to portal hypertension, whereas loop diuretics, such as furosemide used alone, can be ineffective or even, in some cases, actually increase the volume of effusion by causing a further decrease in systemic blood pressure as a result of hemoconcentration and secondary increases in RAAS activation.

Ascites will also occur as a result of venous congestion from disease of the major hepatic veins and/or distally (i.e., thoracic caudal vena cava, heart; posthepatic venous congestion). This is not as a result of portal hypertension, but rather this increases the formation of hepatic lymph, which exudes from superficial hepatic lymphatics. Because the endothelial cell-lined sinusoids are highly permeable, hepatic lymph is of high protein content.

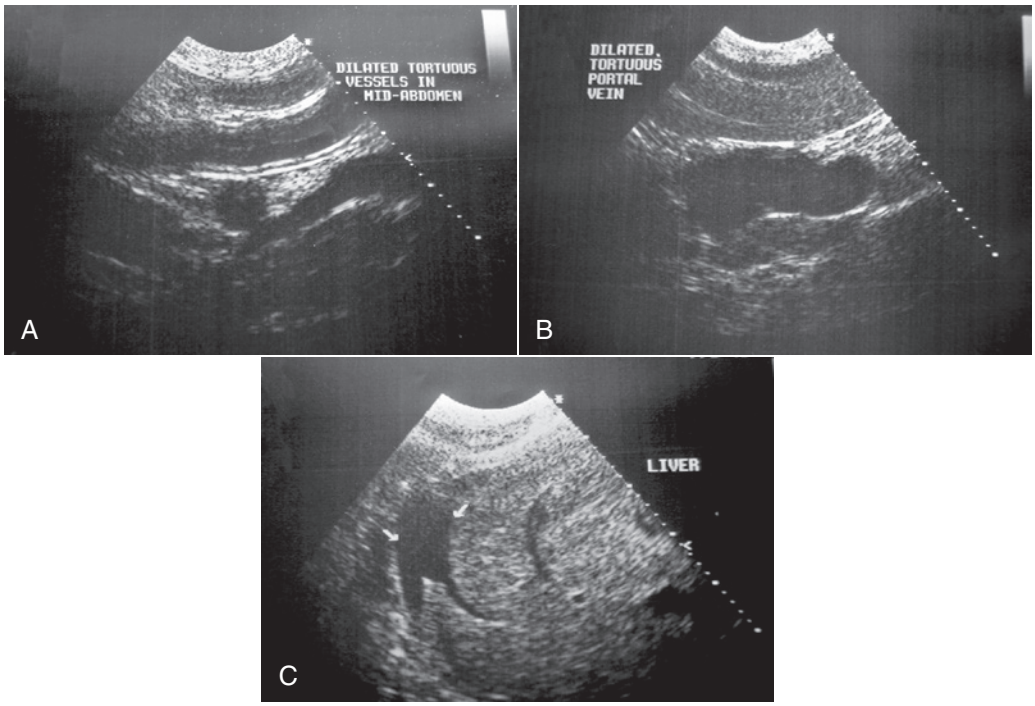


FIG 33.2
Ultrasonographic images demonstrating the progressive development of ascites with portal hypertension in a dog with cirrhosis. **(A)** Ultrasonography on the first visit showed no evidence of free abdominal fluid but revealed dilated vessels in the midabdomen (including splenic congestion) and also a dilated portal vein **(B). (C)** When the dog returned for a liver biopsy 2 weeks later, ultrasonography now revealed the development of mild early ascites. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

PATHOGENESIS OF EXUDATES

In pancreatitis, the cause of abdominal fluid accumulation is usually increased vascular permeability due to peritonitis, which in most cases results in serosanguinous sterile exudates with high protein and cell contents, although modified transudates and chylous effusions are occasionally reported. Pancreatitis can also occasionally result in a more generalized vasculitis and bicavitary effusions. Demonstrating a sterile exudate on cytology should trigger investigations to differentiate bile peritonitis, pancreatitis, or urinary tract leakage as the causes, as detailed in Fig. 33.1. Urea, creatinine, bilirubin, lipase, or cPLI concentrations can be measured in the fluid and be very helpful diagnostically. Extravasation of bile from a ruptured biliary tract elicits a strong inflammatory response and stimulates the transudation of lymph by serosal surfaces. In experimental animal models, the damaging component of bile has been identified as bile acids. Unlike with most other causes of abdominal effusion associated with hepatobiliary disease, there may be evidence of cranial abdominal or diffuse abdominal pain identified during physical examination in cats and dogs with bile peritonitis. The fluid appears characteristically dark orange, yellow, or green and has a high bilirubin content on analysis, which is higher than the serum bilirubin concentration, and the predominant cell type is the healthy neutrophil, except when the biliary tract is infected. Because normal bile is sterile, the initial phase of bile peritonitis is nonseptic, but unless treatment is initiated rapidly, secondary infection, usually with anaerobes of gut origin, may become life-threatening.

Perivenular pyogranulomatous infiltrates in the visceral and parietal peritoneum of cats with the effusive form of FIP increase vascular permeability and promote the exudation of straw-colored, protein-rich fluid into the peritoneal space. Typically, the fluid is of low to moderate cellularity, with a mixed cell population of neutrophils and macrophages, and with a moderate to high protein concentration. It is usually classified as an exudate but occasionally is a modified transudate.

Hepatobiliary or pancreatic malignancies or other intra-abdominal carcinomas that have disseminated to the peritoneum can elicit an inflammatory reaction, with subsequent exudation of lymph and fibrin. The fluid may be serosanguineous, hemorrhagic, or chylous in appearance. Regardless of the gross appearance of the fluid, the protein content is variable, and the fluid may contain exfoliated malignant cells if the primary neoplasm is a carcinoma, mesothelioma, or lymphoma, although often it does not, in which case further investigation is required to diagnose the neoplasm.

HEPATIC ENCEPHALOPATHY

PATHOGENESIS

HE describes neurologic dysfunction in patients with liver disease as a result of exposure of the cerebral cortex to toxins. It is most commonly reported in dogs and cats with congenital portosystemic shunts (CPSS) but is also recognized in dogs with cirrhosis and acquired PSS secondary to portal hypertension, in dogs and cats with acute liver failure, and in cats with hepatic lipidosis (which is in effect a reversible acute liver failure). In a study of dogs with acute liver failure, 57% showed signs of HE, and reports of chronic hepatitis in dogs suggest HE in about 7% of cases.

The most important toxin implicated is ammonia (NH_3), which crosses the blood-brain barrier. The brain is very sensitive to the toxic effects of NH_3 but does not possess a urea cycle, so the NH_3 is detoxified by conversion to glutamine by astrocytes. Excessive NH_3 and thus glutamine buildup results in osmotic stress of astrocytes with cell swelling and cerebral edema. Recent studies in dogs with congenital PSS have confirmed increases in arterial, venous, and CSF NH_3 when compared with normal dogs. Sophisticated imaging techniques (single photon emission tomography) have also demonstrated reduced perfusion in the temporal lobes and increased perfusion in the subcortical regions of dogs with congenital PSS and HE, which are similar to the findings in humans with acquired PSS and HE. Other toxins implicated in HE historically such as mercaptans and aromatic amino acids have little evidence in humans or animals, although both manganese and neurosteroids have been implicated in both species recently. Serum manganese concentrations are high in dogs with congenital PSS, although the clinical relevance of this finding is unclear because ligation of congenital PSS in dogs resolves HE while hypermagnesemia persists.

Buildup of NH_3 in the systemic circulation occurs as a result of diversion of portal flow from the liver by the development of PSS or as a result of a marked reduction in functional hepatic mass. In most cases of acquired portosystemic shunting, there is a combination of vascular and functional mechanisms leading to HE (Fig. 33.3). Rarely, if congenital

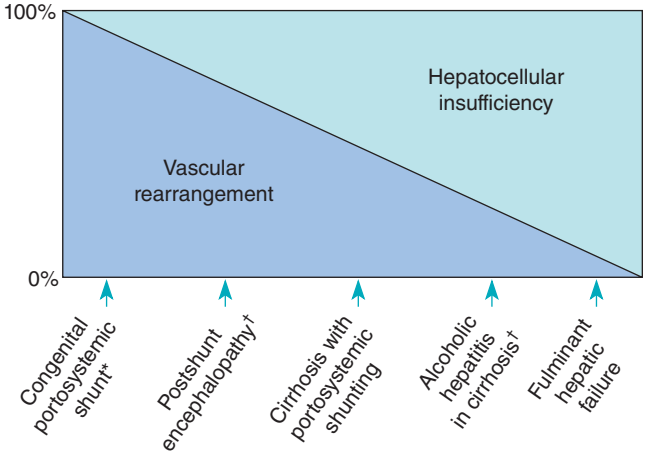


FIG 33.3
Spectrum of hepatic encephalopathy in cats and dogs ranging from pure vascular to pure hepatocellular causes. *, Clinically relevant only in dogs and cats; †, clinically relevant only in human patients. (Modified from Schafer DF et al: Hepatic encephalopathy. In Zakim D, Boyer TD, editors: *Hepatology: a textbook of liver disease,* Philadelphia, 1990, WB Saunders.)

portovascular anomalies and severe primary hepatobiliary disease with acquired shunting have been ruled out, congenital urea enzyme cycle deficiencies and organic acidemias, in which NH_3 cannot be degraded to urea, are considered. HE has also been reported in congenital cobalamin deficiency in dogs. Animals with systemic diseases having hepatic manifestations do not undergo sufficient loss of hepatic mass or change in hepatic blood flow to develop signs of HE.

The sources of increased blood ammonia levels in animals with liver disease are outlined in Fig. 33.4 and include the following:

- Small intestinal enterocyte catabolism of glutamine as their main energy source
- Endogenous hepatic protein metabolism from excess dietary protein, GI bleeding, or breakdown of lean body mass
- Bacterial breakdown of undigested amino acids and purines that reach the colon
- Bacterial and intestinal urease action on urea, which freely diffuses into the colon from the blood

It is very important to realize that the traditional view that the toxins causing HE are predominantly of dietary origin is misleading; although the gut is an important source of NH_3 in animals on high-protein diets, in many animals, particularly those with protein-calorie malnutrition, endogenous sources of NH_3 may be more important, and further dietary protein restriction just worsens the hyperammonemia in these cases. Certain conditions are known to accentuate or precipitate HE and should be avoided or treated aggressively when detected (Box 33.2). In fact, in many cases it is the precipitating factors (rather than the diet) that are most important in triggering HE. It is particularly important to identify and treat any concurrent inflammatory disease that can trigger HE episodes in susceptible individuals. Recent work in humans, experimental animals, and dogs with spontaneous disease has highlighted the importance of inflammation and inflammatory cytokines in triggering HE. It is known that clinically relevant episodes of HE in dogs and cats with congenital or acquired PSS are often precipitated not just by feeding but also by stress and infections, emphasizing the role of hypermetabolism, inflammation, and breakdown of body protein in the development of HE. A

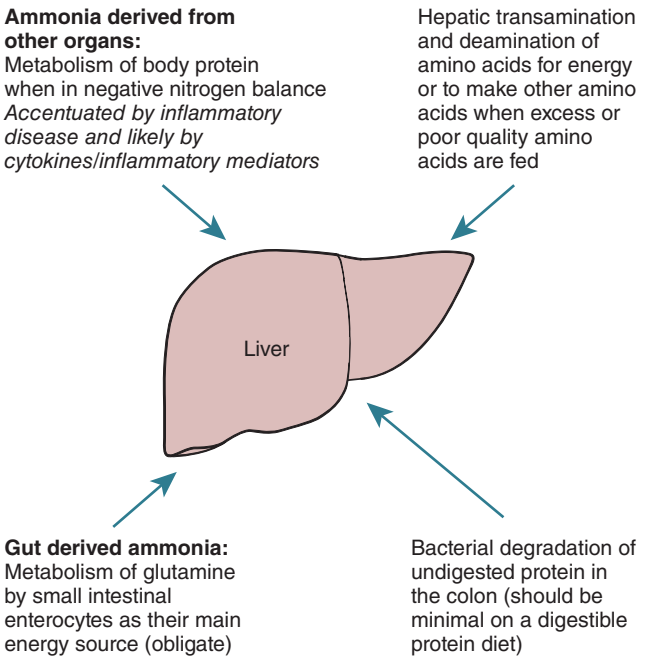


FIG 33.4
Sources of ammonia that can contribute to hepatic encephalopathy. Note that it is now believed that bacterial degradation of undigested protein in the colon is not the most important factor in dogs fed a normal diet.

BOX 33.2

Precipitating Factors for Hepatic Encephalopathy in Susceptible Individual

Increased Generation of Ammonia in the Intestine

- High-protein meal (e.g., puppy or kitten food)
- Very poorly digestible protein reaching the colon and allowing bacterial metabolism to ammonia
- Increased glutamine metabolism in small intestine as energy source from large meal or increased energy requirements for digestion
- GI bleeding (e.g., bleeding ulcer in acquired shunts with portal hypertension) or ingestion of blood
- Constipation (increases contact time between colonic bacteria and feces and therefore increases ammonia production)
- Azotemia (urea freely diffuses across colonic membrane and is split by bacteria to ammonia)

Increased Generation of Ammonia Systemically

- Transfusion of stored blood
- Catabolism, hypermetabolism, protein-calorie malnutrition (increases breakdown of lean body mass with release of NH_3)
- Feeding a poor-quality protein (excessive deamination as protein is used for energy)

Effects on Uptake, Metabolism, and Action of Ammonia in the Brain

- Metabolic alkalosis (increases amount of nonionized NH_3 in circulation, which increases passage across blood-brain barrier)
- Hypokalemia (results in alkalosis with consequences previously outlined)
- Sedatives or anesthetics (direct interaction with various neurotransmitters)
- Estrus (may be caused by production of neurosteroids with neurologic effects)
- Inflammation (inflammatory cytokines have been implicated in having a direct central effect)

recent study in dogs confirmed that animals with congenital PSS and symptomatic HE had higher serum C-reactive protein concentrations than dogs with congenital PSS and no HE. C-reactive protein, an acute-phase protein, is a sensitive nonspecific marker of inflammation in dogs, so this study adds support to the theory that inflammation may trigger symptomatic HE in dogs with PSS. Furthermore, successful ligation of congenital PSS resulted in the reduction of inflammatory indicators in the blood as well as resolution of HE. In the author's experience, it is often initially undetected infections in the urinary tract, particularly pyelonephritis or cystitis, which trigger HE in susceptible dogs. These may be acting in two ways: partly through production of inflammatory cytokines but also partly through absorption of ammonia produced by urease-producing bacteria in the urinary tract.

CLINICAL SIGNS

HE in humans is described as overt HE when there are obvious clinical signs and covert HE when signs are only picked up on neuropyschometric testing. Such testing is not undertaken in dogs and cats, so only the more severe, overt HE is recognized. Subtle, nonspecific signs of HE in cats and dogs that could be noted at any time and that represent chronic or subclinical HE include anorexia, depression, weight loss, lethargy, nausea, fever, hypersalivation (particularly in cats), intermittent vomiting, and diarrhea. Almost any central nervous system (CNS) sign may be observed in cats and dogs with HE, although typical signs tend to be nonlocalizing, suggesting generalized brain involvement—trembling, ataxia, hysteria, dementia, marked personality change (usually toward aggressiveness), circling, head pressing, cortical blindness, or seizures (Box 33.3; Fig. 33.5). Occasionally, animals with hyperammonemia have asymmetric, localizing neurologic signs that regress with appropriate treatment for HE. Acute HE is a true medical emergency. Fortunately, it is much less common than chronic, waxing and waning HE. Animals may present in status epilepticus or comatose, and although HE initially causes no permanent brain damage, prolonged seizures, status epilepticus, or coma will; prolonged severe HE by itself may lead to serious cerebral edema as a result of accumulation of the osmolyte glutamine (from ammonia detoxification) in astrocytes. In addition, the systemic effects of acute HE, particularly hypoglycemia, can be fatal if not recognized and treated.

BOX 33.3

Typical Clinical Signs of Hepatic Encephalopathy in Dogs and Cats

Lethargy
Depression
Behavioral changes
Head pressing
Circling
Pacing
Central blindness
Seizures (uncommon)
Coma (uncommon)
Hypersalivation (especially cats)

CHANGE IN LIVER SIZE

In normal cats and dogs, the liver is palpable just caudal to the costal arch along the ventral body wall, but it may not be palpable at all. Inability to palpate the liver, especially in dogs, does not automatically mean that the liver is small. In lean cats, it is usually possible to palpate the diaphragmatic surface of the liver. In cats or dogs with pleural effusion or other diseases that expand thoracic volume, the liver may be displaced caudally and give the false appearance of being enlarged.

Liver enlargement (hepatomegaly) is much more common in cats than in dogs with liver disease. Dogs more often have a reduced liver size because of chronic hepatitis with fibrosis but can show hepatomegaly particularly in association with tumors. The pattern of liver enlargement may be generalized or focal, depending on the cause. Infiltrative and congestive disease processes, or those that stimulate hepatocellular hypertrophy or mononuclear-phagocytic system (MPS)



FIG 33.5
Head-pressing is one manifestation of hepatic encephalopathy (Courtesy Georgina Harris).

hyperplasia, tend to result in smooth or slightly irregular, firm, diffuse hepatomegaly. Focal or asymmetrical hepatic enlargement is often seen with proliferative or expansive diseases that form solid or cystic mass lesions. Examples of diseases that cause a change in liver size are listed in Table 33.1.

Smooth generalized hepatosplenomegaly may be associated with nonhepatic causes, such as increased intravascular hydrostatic pressure (passive congestion) secondary to right-sided congestive heart failure or pericardial disease. In rare cases, hepatic vein occlusion (Budd-Chiari syndrome) results in similar findings. Hepatosplenomegaly in icteric dogs or cats may be attributable to benign MPS hyperplasia and extramedullary hematopoiesis secondary to immune-mediated hemolytic anemia. Hepatosplenomegaly may also occur due to infiltrative processes such as lymphoma, systemic mast cell disease, malignant histiocytosis, or leukemias.

Another cause of hepatosplenomegaly is primary hepatic parenchymal disease with sustained intrahepatic portal hypertension. In dogs and cats with this syndrome, the liver is usually firm and irregular on palpation, and often the liver itself is reduced in size as a result of fibrosis. However, the spleen can be enlarged and congested as a result of portal hypertension. For conditions that involve primarily the spleen, see Chapter 88.

JAUNDICE, BILIRUBINURIA, AND CHANGE IN FECAL COLOR

By definition, jaundice in cats and dogs is the yellow staining of serum or tissues by an excessive amount of bile pigment or bilirubin (Fig. 33.6); the terms *jaundice* and *icterus* are used interchangeably. Jaundice may be prehepatic, due to very marked red cell breakdown; hepatic, due to primary liver disease; or posthepatic, due to biliary tract obstruction or rupture. Because the normal liver has the ability to take up and excrete a large amount of bilirubin, there must be either a large, persistent increase in the production of bile pigment (hyperbilirubinemia) or a major impairment in bile excretion (cholestasis with hyperbilirubinemia) before jaundice is detectable as yellow-stained tissues (serum bilirubin concentration ≥2 mg/dL) or serum (serum bilirubin concentration ≥1.5 mg/dL).

In normal animals, bilirubin is a waste product of heme protein degradation. The primary source of heme proteins is senescent erythrocytes, with a small contribution by myoglobin and heme-containing enzyme systems in the liver. After phagocytosis by cells of the MPS, primarily in the bone marrow and spleen, heme oxygenase opens the protoporphyrin ring of the hemoglobin molecule, forming biliverdin. Biliverdin reductase then converts biliverdin to fat-soluble bilirubin IXa, which is released into the circulation, where it is bound to albumin for transport to hepatic sinusoidal membranes. After uptake, transhepatocellular movement, and conjugation to various carbohydrates, conjugated bilirubin, now water-soluble, is excreted into the bile

TABLE 33.1

Differential Diagnoses for Changes in Hepatic Size

DIAGNOSIS	SPECIES
Hepatomegaly	
Generalized	
Infiltration	
Primary or metastatic neoplasia	C, D
Cholangitis	C
Extramedullary hematopoiesis*	C, D
Mononuclear-phagocytic cell hyperplasia*	C, D
Amyloidosis (rare)	C, D
Passive congestion	
Right-sided heart failure	C, D
Pericardial disease	D
Caudal vena cava obstruction	D
Caval syndrome	D
Budd-Chiari syndrome (rare)	C, D
Hepatocyte swelling	
Lipidosis	C (moderate to marked), D (mild)
Hypercortisolism (steroid hepatopathy)	D
Anticonvulsant drug therapy	D
Acute extrahepatic bile duct obstruction	C, D
Acute hepatotoxicity	C, D
Focal or asymmetric	
Primary or metastatic neoplasia	C, D
Nodular hyperplasia	D
Chronic hepatic disease with fibrosis and nodular regeneration	D
Abscess(es) (rare)	C, D
Cysts (rare)	C, D
Microhepatia (Generalized Only)	
Reduced hepatic mass	
Chronic hepatic disease with progressive loss of hepatocytes and fibrosis	D
Decreased portal blood flow with hepatocellular atrophy	
Congenital portosystemic shunt	C, D
Intrahepatic portal vein hypoplasia	D
Chronic portal vein thrombosis	D
Hypovolemia	
Shock?	?
Addison's disease	D

C, Primarily cats; *D*, primarily dogs; *C, D*, cats and dogs.
*Concurrent splenomegaly likely.

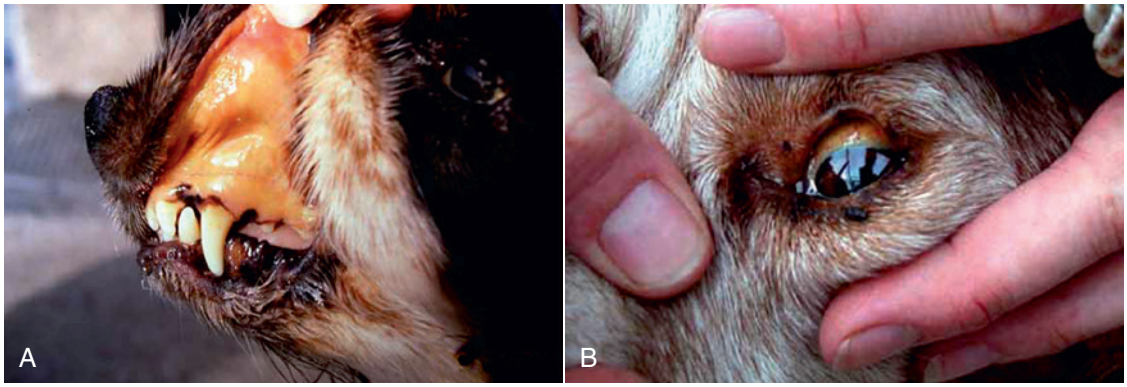


FIG 33.6
Jaundiced mucous membranes in a dog (**A,** gum; **B,** sclera). Note that this dog had jaundice because of immune-mediated hemolytic anemia and not liver disease—hence, the mucous membranes are pale and yellow, which makes them more easily photographed. (Courtesy Sara Gould.)

canaliculi. Conjugated bilirubin is then incorporated into micelles and stored with other bile constituents in the gallbladder until it is discharged into the duodenum. However, in dogs, only 29% to 53% of bile produced is stored in the gallbladder; the rest is secreted directly into the duodenum. After arrival in the intestine, conjugated bilirubin undergoes bacterial deconjugation and then reduction to urobilinogen, with most urobilinogen being resorbed into the enterohepatic circulation. A small fraction of urobilinogen is then excreted in the urine, and a small portion remains in the intestinal tract to be converted to stercobilin, which imparts normal fecal color.

Inherited abnormalities of bilirubin metabolism have not been identified in cats and dogs, so in the absence of massive increases in bile pigment production by hemolysis, jaundice is attributable to impaired excretion of bilirubin, and usually other constituents of bile, by diffuse intrahepatic hepatocellular or biliary disease or by interrupted delivery of bile to the duodenum. The inability to take up, process intracellularly, or excrete bilirubin into the bile canaliculi (the rate-limiting step) is the mechanism of cholestasis believed to be operational in many primary hepatocellular diseases. Jaundice is more likely to be a clinical feature if the liver disorder primarily involves the periportal (zone 1) hepatocytes (Fig. 33.7) than if the lesion involves centrilobular (zone 3) hepatocytes. Inflammation and swelling of larger intrahepatic biliary structures could similarly delay bile excretion.

Extrahepatic biliary duct obstruction (EBDO) occurs as a result of intraluminal or extraluminal obstruction of the bile duct at any point along its length. This may be obstruction of the cystic duct by a gallbladder mucocele in dogs or obstruction of the common bile duct in dogs and cats by choleliths, neoplasia of occasionally foreign bodies. Jaundice can develop in both cats and dogs as a result of acute flare-up of a chronic pancreatitis causing transient extrahepatic biliary obstruction. Indeed, an acute flare-up of chronic pancreatitis is the commonest cause of EBDO in dogs.

Obstruction of the bile duct near the duodenum results in increased intraluminal biliary tract pressure, interhepatocellular regurgitation of bile constituents into the circulation, and jaundice. If only one of the hepatic bile ducts exiting the liver is blocked, or if only the cystic duct exiting the gallbladder is obstructed for some reason, there may be biochemical clues for localized cholestasis, such as high serum alkaline phosphatase activity; however, the liver's overall ability to excrete is preserved, and jaundice may not ensue.

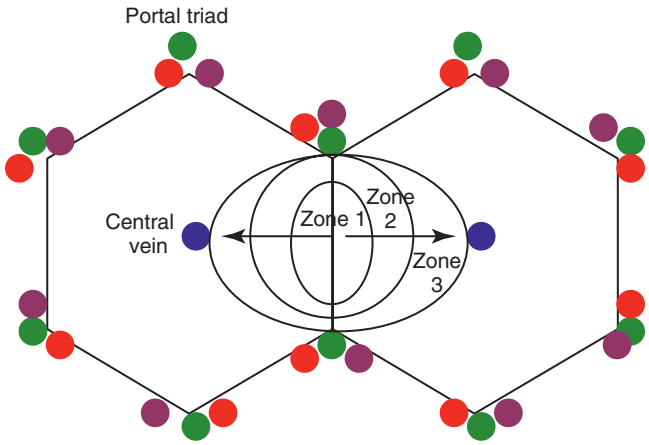


FIG 33.7
Rappaport scheme of the hepatic functional lobule (acinus), organized according to biochemical considerations (1958). This is centered on a line connecting two portal triads and describes functional zones radiating from the triad to the central vein. For example, zone 1 cells are responsible for protein synthesis, urea and cholesterol production, gluconeogenesis, bile formation, and β oxidation of fatty acids; zone 2 cells also produce albumin and are actively involved in glycolysis and pigment formation; and zone 3 cells are the major site of liponeogenesis, ketogenesis, and drug metabolism. Zone 3 hepatocytes, being farther from the hepatic artery and hepatic portal veins, also have the lowest oxygen supply and are therefore most susceptible to hypoxic damage. *Arrows* show direction of blood flow. The portal triad comprises one or more branches of bile duct *(green),* hepatic artery *(red),* and hepatic portal vein *(violet).*

Traumatic or pathologic biliary tract rupture allows leakage of bile into the peritoneal space and some absorption of bile components. Depending on the underlying cause and the time elapsed between biliary rupture and diagnosis, the degree of jaundice may be mild to moderate. If biliary rupture has occurred, the total bilirubin content of the abdominal effusion is higher than that of serum.

Reference ranges for serum total bilirubin concentrations in dogs and cats may vary among laboratories, but most published resources agree that concentrations over 0.3 mg/dL in cats and 0.6 mg/dL in dogs are abnormal. When results of laboratory tests are assessed, species differences in the formation and renal processing of bilirubin between cats and dogs must be taken into account. Canine renal tubules have a low resorptive threshold for bilirubin. Dogs (males to a greater extent than females) have the necessary renal enzyme systems to process bilirubin to a limited extent; therefore bilirubinuria (up to 2+ to 3+ reaction by dipstick analysis) may be a normal finding in canine urine specimens with a specific gravity greater than 1.025. Cats do not have this ability, and they have a ninefold higher tubular absorptive capacity for bilirubin than dogs. Bilirubinuria in cats is associated with hyperbilirubinemia and is always pathologic (Fig. 33.8). Because unconjugated and most conjugated bilirubin is albumin-bound in the circulation, only a small amount of non–protein-bound conjugated bilirubin is expected to appear in the urine in physiologic and pathologic states. In dogs with hepatobiliary disease, increasing bilirubinuria often precedes the development of hyperbilirubinemia, and clinical jaundice and may be the first sign of illness detected by owners.

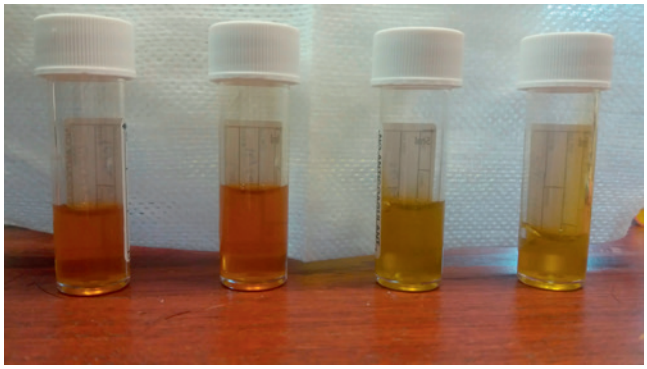


FIG 33.8
Samples of urine (two pots on the left) and gallbladder bile (two pots on the right) from a cat with chronic biliary tract obstruction due to a stricture of the common bile duct. Note the grossly abnormal pale appearance of the bile due to reduced excretion of bilirubin into bile. This is not unusual in cats with chronic biliary obstruction. The serum and urine contained a large amount of bilirubin, so it is assumed that the bilirubin transporters in this case had moved from the luminal surface of the bile ducts to the hepatic side. (Reproduced with permission from Watson P. Liver and biliary tract: hepatocellular disorders. In: Hall EJ, Williams DA, Kathrani A, eds. BSAVA Manual of Canine and Feline Gastroenterology 3rd edition. Gloucester: British Small Animal Veterinary Association, 2019. © BSAVA.)

Several nonhepatobiliary disorders impede bilirubin excretion by poorly understood means. Jaundice with evidence of hepatocellular dysfunction but minimal histopathologic changes in the liver has been described in septic human, feline, and canine patients. Certain products released by bacteria, such as endotoxin, are known to interfere with bile flow reversibly. As yet unexplained mild hyperbilirubinemia (≤2.5 mg/dL) may also be detected in approximately 20% of hyperthyroid cats. Experimental investigations of thyrotoxicosis in laboratory animals have demonstrated increased production of bilirubin, which has been proposed to be associated with increased degradation of hepatic heme proteins. There is no histologic evidence of cholestasis at the light microscopic level in affected cats, and the hyperbilirubinemia resolves with return to euthyroidism. Guidelines for initial evaluation of the icteric cat or dog are given in Fig. 33.9. Finally, lipemia is a common cause of pseudohyperbilirubinemia in dogs as a result of lipid interference with the colorimetric laboratory methods.

Acholic feces result from the total absence of bile pigment in the intestine (Fig. 33.10). Only a small amount of bile pigment is needed to be changed to stercobilin and yield a normal fecal color; therefore bile flow into the intestine must be completely discontinued to result in acholic feces, and this is very rare in dogs and cats. In addition to appearing pale from lack of stercobilin and other pigments, acholic feces are pale because of steatorrhea resulting from the lack of bile acids to facilitate fat absorption. Mechanical diseases of the extrahepatic biliary tract (e.g., unremitting complete EBDO, traumatic bile duct avulsion from the duodenum) are the most common causes of acholic feces in cats and dogs.

Feces also become pale as a result of exocrine pancreatic insufficiency in dogs and cats, either as a result of pancreatic acinar atrophy of end-stage chronic pancreatitis and marked loss of pancreatic tissue mass. Fat maldigestion caused by a lack of pancreatic lipase result in pale yellow, voluminous, and smelly feces. Pancreatic enzyme lack can also be transient for example in an acute flare-up of chronic pancreatitis, which may also cause biliary obstruction resulting in two mechanisms for pale feces (see Fig. 33.10).

COAGULOPATHIES

Coagulopathies can be recognized in dogs and cats with liver disease and with acute pancreatitis. In acute pancreatitis in dogs and cats, coagulopathies most commonly occur in association with severe disease as a result of DIC. However, particularly in cats, they can also occur in more low grade and chronic disease as a result of acquired vitamin K deficiency due to fat maldigestion, particularly in cats with concurrent IBD and biliary tract disease.

Because of the integral role of the liver in hemostasis, hemorrhagic tendencies can be a presenting sign in cats and dogs with severe hepatobiliary disease: either end-stage chronic disease, particularly in dogs, or severe acute disease in both species. Despite the fact that most coagulation proteins and

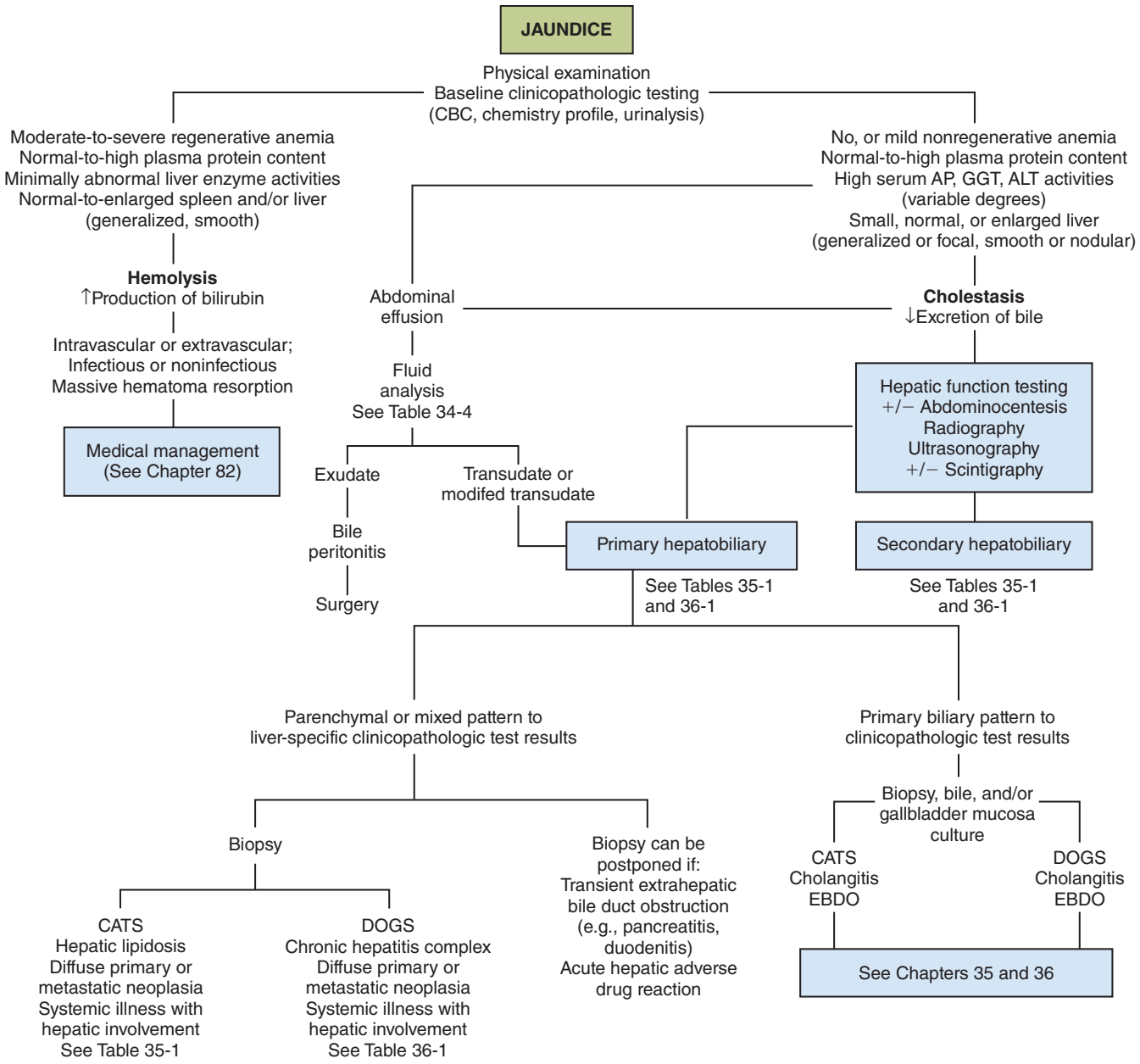


FIG 33.9
Algorithm for preliminary evaluation of the icteric cat or dog. *AP,* Alkaline phosphatase; *ALT,* alanine transaminase; *EBDO,* extrahepatic bile duct obstruction; *GGT,* γ-glutamyltransferase.

inhibitors, except for von Willebrand factor (vWF) and possibly factor VIII, are synthesized in the liver (Box 33.4), the overall frequency of clinical sequelae of disturbances in hemostasis is low. A recent study using thromboelastography in dogs with chronic hepatitis showed some dogs were hypocoagulable, some were hypercoagulable, and some had normal TEG results. Dogs with portal hypertension and more end-stage liver disease were more likely to be hypocoagulable. Similar results were reported in dogs with acute liver disease, with a more common occurrence of a hypocoagulable state in dogs with more severe disease. The inability to synthesize vitamin K–dependent factors (II, VII, IX, and X) because of the absence of bile acid–dependent fat absorption secondary to complete EBDO or a transected bile duct from abdominal trauma can cause clinically apparent bleeding. This is likely more important in cats than dogs because of the high prevalence of biliary tract disease in cats, and because concurrent pancreatic and/or intestinal disease in cats further compromises the absorption of fat-soluble vitamins. Subclinical and clinical coagulopathies are also noted in animals with severe diseases of the hepatic parenchyma. In early studies of the mechanism of impaired coagulation after partial hepatectomy in dogs, after surgical removal of 70% of the hepatic mass, dogs developed significant alterations



FIG 33.10
Acholic feces from a 7-year-old spayed female Collie dog with a strictured bile duct and complete bile duct obstruction 3 weeks after recovery from severe pancreatitis.

BOX 33.4

Coagulation Proteins and Inhibitors Synthesized by the Liver

Proteins C and S
Antithrombin
Fibrinogen
Plasminogen
Vitamin K–dependent factors
- II (prothrombin)
- VII
- IX
- X

Factor V
Factor XI
Factor XII
Factor XIII

in plasma clotting factor concentrations without spontaneous hemorrhage. Having severe hepatic parenchymal disease predisposes a dog or cat not only to changes in coagulation factor activity from hepatocellular dysfunction but also to DIC, particularly in those with acute disease. In dogs with acute hepatic necrosis, some clinicians have observed thrombocytopenia, thought to be associated with increased platelet use or sequestration. Splenic sequestration of platelets is common in humans with chronic liver disease and portal hypertension but has not been not reported in dogs and cats.

Other than noticeable imbalances in coagulation factor activity, the only other mechanism whereby bleeding might occur in a cat or dog with severe hepatic disease is portal hypertension–induced vascular congestion and fragility. In such cases, which are expected considerably more often in dogs than in cats because of the types of hepatobiliary diseases that they acquire, the common site affected is the upper GI tract (stomach, duodenum); therefore hematemesis and melena are common bleeding presentations and a common cause of death in dogs with chronic liver disease. In contrast to human patients, in whom fragile esophageal varices develop and can burst, causing severe and often fatal hemorrhage, the mechanism of GI hemorrhage in companion animals is unknown but is suspected to be related to poor mucosal perfusion and reduced epithelial cell turnover associated with portal hypertension and splanchnic pooling of blood.



FIG 33.11
English Cocker Spaniel with chronic pancreatitis showing loss of body weight and poor coat as a result of developing exocrine deficiency. Weight loss is slow and insidious, and often not recognized initially by owner or vet.

PROTEIN-CALORIE MALNUTRITION

Pathogenesis

Protein-calorie malnutrition is very common in dogs with chronic hepatitis and dogs and cats with chronic pancreatitis as a result of reduced intake caused by anorexia, vomiting, and diarrhea, and increased loss/wastage of calories caused by hypermetabolism and poor liver function or (in the case of chronic pancreatitis) lack of digestive enzymes. In chronic pancreatitis, the development of exocrine pancreatic insufficiency is progressive and insidious, and it may not be initially recognized (Fig. 33.11). In human medicine, anyone with confirmed chronic pancreatitis is assumed already to have some degree of exocrine insufficiency and is given enzyme supplementation. A more proactive approach to supplementation would also be wise in dogs and cats because protein-calorie malnutrition in both liver and pancreatic

disease is likely to have a serious effect on both longevity and quality of life. There are no studies specifically addressing the effect of malnutrition on survival and infections of dogs with liver disease, but in other canine diseases it is known to increase the risk of septic complications. This is true in humans with portal hypertension and also likely in dogs. In humans with portal hypertension, malnutrition also predisposes to gut ulceration. In addition, negative nitrogen balance and reduced muscle mass predispose to HE. Breakdown of body protein results in more ammonia production, and also in a normal individual up to 50% of arterial ammonia is metabolized in skeletal muscle by conversion of glutamate to glutamine, so loss of muscle mass will reduce the ability to detoxify ammonia. What gives the most cause for concern regarding protein-calorie malnutrition in the small animal patient is that it is often partly caused by well-meaning but unhelpful manipulations by the clinician or even by a lack of recognition and attention. For this reason, it is very important that clinicians treating dogs with chronic liver disease or cats and dogs with chronic pancreatic disease remain alert to the possibility of protein-calorie malnutrition.

Malnutrition can also be seen in dogs and cats with congenital PSS, either as a result of reduced liver synthetic capability or as a result of inappropriately severe protein restriction by the attending clinician. Cats with chronic liver disease may have negative energy balance, often as a result of the effects of concurrent intestinal and pancreatic disease reducing digestion and absorption of food. In addition, cats in negative nitrogen balance are at a particular risk of developing acute hepatic lipidosis (see Chapter 35), so protein-calorie malnutrition in this species requires particularly aggressive management.

Clinical Signs and Diagnosis

When suffering from severe malnutrition, dogs and cats appear cachectic, with reduced muscle mass (see Fig. 33.11). However, loss of muscle mass occurs relatively late in the process, and in the earlier stages of protein-calorie malnutrition the animal's body condition score may be normal and yet many potentially deleterious effects on the immune system and gut wall will already be underway. There is no simple blood test that allows diagnosis of malnutrition. The most effective means to do this is by taking a careful history as well as performing a clinical examination. Any animal with chronic liver or pancreatic disease should be considered as being at risk of protein-calorie malnutrition, and in this context an older animal that was previously overweight and has recently lost weight should be considered seriously for nutritional and (if appropriate) pancreatic enzyme support. A history of partial or complete anorexia for more than 3 days or recent weight loss of >10% not associated with fluid shifts should trigger rapid and aggressive nutritional management.

Suggested Readings

Brioschi V, et al. Imaging diagnosis–extrahepatic biliary tract obstruction secondary to a biliary foreign body in a cat. *Vet Radiol Ultrasound*. 2014;55:628.

Fry W, et al. Thromboelastography in dogs with chronic hepatopathies. *J Vet Intern Med*. 2017;31:419.

Gow AG, et al. Surgical attenuation of spontaneous congenital portosystemic shunts in dogs resolves hepatic encephalopathy but not hypermanganesemia. *Metab Brain Dis*. 2015;30:1285.

Kelley D, et al. Thromboelastographic evaluation of dogs with acute liver disease. *J Vet Intern Med*. 2015;29:1053.

Lester C, et al. Retrospective evaluation of acute liver failure in dogs (1995–2012): 49 cases. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:559.

Lidbury JA, et al. Hepatic encephalopathy in dogs and cats. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:471.

Or M, et al. Ammonia concentrations in arterial blood, venous blood, and cerebrospinal fluid of dogs with and without congenital extrahepatic portosystemic shunts. *Am J Vet Res*. 2017;78:1313.

Or M, et al. Short communication: regional cerebral blood flow assessed by single photon emission computed tomography (SPECT) in dogs with congenital portosystemic shunt and hepatic encephalopathy. *Vet J*. 2017;220:40.

Tivers MS, et al. Attenuation of congenital portosystemic shunt reduces inflammation in dogs. *PLoS ONE*. 2015;10(2):e0117557.

CHAPTER 34

Diagnostic Tests for the Hepatobiliary and Pancreatic System



DIAGNOSTIC APPROACH

The diagnosis of either liver or pancreatic disease is challenging and relies on a combination of clinicopathologic tests, diagnostic imaging, and often also some form of biopsy, particularly for the liver. Hepatic involvement is common in cats and dogs with pancreatitis, either because of concurrent disease in both organs (particularly in cats) or because of reactive hepatopathy or extrahepatic biliary obstruction in some cases of pancreatitis (particularly in dogs), further complicating interpretation of diagnostic test results. Many of these tests point to liver or pancreatic involvement but do not give an indication of the type of disease present or of organ function or prognosis. Only a limited number of tests give functional information. It is important to remember that both the liver and pancreas have large structural and functional reserves, particularly in chronic disease. In dogs with chronic hepatitis, signs of functional impairment may not be evident until 75% of the hepatic mass has been lost, and in chronic pancreatitis in dogs and cats, endocrine and exocrine insufficiency will not be apparent until about 90% of islet or acinar tissue have been lost, respectively.

DIAGNOSTIC APPROACH TO LIVER DISEASE

Because the liver is physiologically and anatomically diverse and because of the high prevalence of secondary (reactive) liver disease, no single test adequately identifies liver disease or its underlying cause. For this reason, a battery of tests must be used to assess the hepatobiliary system. A reasonable package of screening tests recommended for an animal suspected of having hepatobiliary disease includes a complete blood count (CBC), serum biochemical profile, urinalysis, fecal analysis, and survey abdominal radiography or ultrasonography (US). Results of these tests may suggest evidence of hepatobiliary disease that can be confirmed by other, more specific tests, which would usually be some form of tissue sample. It is important at this stage to rule out secondary hepatopathy as much as possible because, with hepatopathies secondary to other diseases, time and resources should be devoted as soon as possible to identify and treat the underlying cause rather than investigate the liver.

Box 34.1 lists common diagnostic tests for liver disease and indicates which can give functional or prognostic information. It is important to remember that some hepatobiliary diseases are characterized by subtle changes in enzyme activity in association with severe functional disturbance, and some have high enzyme activities and normal functional indices. In addition, secondary hepatopathies can result in very high hepatic enzyme activities but no functional impairment, so the degree of enzyme activity elevation is in no way prognostic. Diseases that cause acute hepatocyte loss result in evidence of functional impairment more quickly than diseases with chronic hepatocyte loss, in which the remaining hepatocytes have time to compensate.

By using a combination of history, physical examination findings, and results of screening and hepatobiliary-specific laboratory tests, the clinician may be able to do the following: describe the disorder as primary or secondary (reactive) hepatopathy, active or quiescent; characterize the pattern of hepatobiliary disease as primarily hepatocellular, primarily biliary, or mixed hepatobiliary; and estimate the degree of hepatobiliary dysfunction. However, without the results of a liver biopsy, the clinician should be aware that this pattern recognition may be misleading. For example, a dog with apparently predominantly biliary disease on clinical pathology may have severe hepatocellular disease on biopsy, and a dog suspected of having secondary (reactive) hepatopathy may have primary hepatic disease. Without histologic confirmation, conclusions drawn from other diagnostic tests remain speculative. However, once a definitive diagnosis of hepatic disease has been made, it is also possible to deduce from the results of hepatic function tests whether the dog or cat has hepatic failure, in which there is a state of multiple function loss. Some primary hepatic diseases may progress to failure; most secondary hepatic diseases do not (see Tables 35.1 and 36.1). Often, use of the term *failure* inappropriately connotes a poor prognosis; if the underlying cause can be removed, full recovery is possible.

BOX 34.1

Summary of Biochemical Tests for the Hepatobiliary System and Their Relevance to Assess Function

Tests for liver involvement (primary or secondary)	Tests for liver function
Liver enzymes: predominantly hepatocellular (but overlap with hepatobiliary—see text) • Alanine aminotransferase • Aspartate aminotransferase	Nonspecific: • Total protein and albumin/globulin ratio* • Coagulation tests* • Urea • Glucose • Cholesterol†
Liver enzymes: predominantly hepatobiliary (but overlap with hepatocellular—see text) • Alkaline phosphatase • Gamma-glutamyltransferase	More specific tests of function and/or portosystemic shunting • Bile acids pre- and poststimulation† • Ammonia
Bilirubin	Relatively specific tests of function only and not portosystemic shunting • Bilirubin*,†

*Also prognostic indicators when interpreted correctly—see text.
†Only useful tests of function in an animal with no evidence of cholestasis.

Most importantly, before an accurate prognosis can be given, a complete evaluation must be conducted, including, for most primary hepatobiliary diseases in dogs and cats, a liver biopsy.

DIAGNOSTIC APPROACH TO PANCREATIC DISEASE

The use of appropriate clinicopathologic tests in a dog or cat with typical clinical signs can help in the diagnosis of pancreatitis, but some form of diagnostic imaging is advisable to confirm this. Secondary causes of enzyme elevation are less common in the pancreas than in the liver. Nonetheless, pancreatitis may not be the most clinically significant disease in an individual sick animal, and diagnostic imaging is important to rule out other causes of acute abdomen with secondary pancreatic involvement such as gastrointestinal (GI) obstruction or gallbladder rupture. More general clinicopathologic tests also allow assessment of the degree of concurrent systemic inflammatory response and evidence of multiorgan failure in severe acute pancreatitis (Box 34.2). In more chronic pancreatitis, exocrine and/or endocrine functional impairment can occur and are assessed as indicated in Box 34.2 in addition to clinical signs. Exocrine function is also impaired in pancreatic acinar atrophy (PAA). A fecal sample is an important addition to the diagnostic panel in dogs with diarrhea associated with pancreatic disease to rule out infectious causes of the clinical signs, particularly as dogs with PAA tend to be younger animals also more predisposed to GI parasites.

BOX 34.2

Summary of Biochemical Tests for the Pancreatitis and to Assess the Associated Systemic Inflammatory Response or Pancreatic Function

Tests for pancreatitis	Tests for pancreatic function
Relatively specific • Pancreatic lipase immunoreactivity (species specific tests) • Lipase and DGGR lipase* • Trypsin-like immunoreactivity (elevated) (species specific—Poorly sensitive; more specific for pancreatitis in dog than cat) • Serum elastase— rarely used • Amylase—poor sensitivity and specificity	Tests for exocrine function: • Trypsin-like immunoreactivity (reduced)—species specific • Fecal elastase (rarely used) • Cobalamin (reduced due to lack of pancreatic intrinsic factor)
Nonspecific tests which assess systemic inflammatory response and associated organ failure (see text) • Complete blood count—particularly neutrophil and platelet counts • Urea and creatinine with concurrent urine SG • Electrolytes: particularly potassium; sodium; calcium • Liver enzymes • Bilirubin	Tests for endocrine function • Blood glucose • Urine glucose and ketones • Fructosamine

*DGGR lipase more specific than traditional lipase—see text

DIAGNOSTIC TESTS PREDOMINANTLY TO ASSESS THE STATUS OF THE HEPATOBILIARY SYSTEM

A summary of laboratory tests for cats and dogs with hepatobiliary disease and interpretation of the results are given in Table 34.1.

Serum Liver Enzyme Activities

Liver-specific serum enzyme activities are included routinely in screening serum biochemistry panels and are regarded as markers of hepatocellular and biliary injury and reactivity. However, this can be due to primary liver disease or secondary to other disease particularly in the splanchnic bed. Hepatocellular enzymes are increased in more than 60% of dogs and cats with acute pancreatitis, and cholestatic markers are increased in more than 60% of dogs and cats with acute pancreatitis.

Because marked hepatic disease can be present in patients with normal serum enzyme activity, finding normal values should not preclude further investigation, especially if there are clinical signs or other laboratory test results that suggest

TABLE 34.1

First- and Second-Line Clinicopathologic Tests Useful in the Diagnosis of Hepatobiliary Disease

SCREENING TEST	PARAMETER EXAMINED	COMMENTS
Serum ALT, AST activities	Integrity of liver cell membranes, escape from cells	Degree of increase roughly correlates with number of hepatocytes involved but not severity of disease
Serum AP, GGT activities	Reactivity of biliary epithelium to various stimuli, increased synthesis and release	Increase associated with intrahepatic or extrahepatic cholestasis or drug effect (dogs only)—corticosteroids, anticonvulsants (AP only, not GGT)
Serum albumin concentration	Protein synthesis	Rule out other causes of low concentration (glomerular or intestinal loss); low value indicates ≥80% overall hepatic function loss or negative acute phase response
Serum urea concentration	Protein degradation and detoxification	With low values, rule out prolonged anorexia, dietary protein restriction, severe PU-PD, urea cycle enzyme deficiency (rare), congenital PSS, severe acquired chronic hepatobiliary disease
Serum bilirubin concentration	Uptake and excretion of bilirubin	Rule out marked hemolysis first; if PCV is normal, intrahepatic or extrahepatic cholestasis is present
Serum cholesterol concentration	Biliary excretion, intestinal absorption, integrity of the enterohepatic circulation	High values compatible with severe cholestasis of any type; low values suggest congenital PSS, anticonvulsant drug–induced change, severe acquired chronic hepatobiliary disease, or severe intestinal malassimilation
Serum glucose concentration	Hepatocellular gluconeogenic or glycolytic ability, insulin and other hormone metabolism	Low values indicate severe hepatocellular dysfunction, PSS, presence of primary liver tumor
Plasma ammonia concentration	Integrity of the enterohepatic circulation, hepatic function and mass	High fasting or postprandial values suggest congenital or acquired PSS or acute hepatocellular inability to detoxify ammonia to urea (massive necrosis)
Serum bile acid concentrations	Integrity of the enterohepatic circulation, hepatic function and mass	High fasting or postprandial values compatible with hepatocellular dysfunction, congenital PSS, or loss of hepatic mass; elevated in cholestasis independent of hepatocellular dysfunction or shunting, so rule out first
Coagulation profile	Hepatocellular function, adequacy of vitamin K absorption and stores	Abnormal values may indicate marked hepatocellular dysfunction, acute or chronic DIC, complete EBDO

ALT, Alanine aminotransferase; *AP,* alkaline phosphatase; *AST,* aspartate aminotransferase; *DIC,* disseminated intravascular coagulation; *EBDO,* extrahepatic bile duct obstruction; *GGT,* γ-glutamyltransferase; *PCV,* packed cell volume; *PSS,* portosystemic shunt; *PU-PD,* polyuria-polydipsia.

hepatobiliary disease. In these cases, a function test such as a bile acid stimulation test should be performed. If this is also normal, it is very unlikely that the animal has hepatic disease. Increased serum activity of enzymes normally located in hepatocyte cytosol in high concentration reflects structural or functional cell membrane injury that would allow these enzymes to escape or leak into the blood. Two hepatocellular enzymes found to be of most diagnostic use in cats and dogs are alanine transaminase (ALT; also, glutamic pyruvic transaminase [GPT]) and aspartate transaminase (AST; also, glutamic oxaloacetic transaminase [GOT]). Because ALT is found principally in hepatocytes and AST (also located within hepatocyte mitochondria) has a wider tissue distribution (e.g., in muscle), ALT is the enzyme selected to reflect hepatocellular injury most accurately. Less is known about the behavior of AST in various hepatobiliary diseases in companion animals, although some studies have indicated that AST is a more reliable indicator of liver injury in cats. The AST level is also elevated in muscle injury, so it should always be interpreted along with serum concentrations of the muscle-specific enzyme creatine kinase. In dogs with skeletal muscle necrosis, several studies have also demonstrated mild to moderately high serum ALT activity, without histologic or biochemical evidence of liver injury, in addition to expected high serum activities of muscle-specific creatine kinase and AST.

In general, the magnitude of serum ALT and AST activity elevation approximates the extent, but not the reversibility, of hepatocellular injury. Severe acute hepatocellular necrosis will elevate levels more markedly than chronic hepatic

disease. However, generalized hypoxia, regeneration, and metabolic activity will also cause moderate to marked elevations, which may be higher than those with primary chronic liver disease. The author has seen very marked hepatocellular liver enzyme level elevations in a dog with a liver lobe trapped in a diaphragmatic hernia, with no underlying primary liver disease. The degree of elevation of liver enzyme activities cannot therefore be used as a prognostic indicator. ALT, and to a lesser extent AST, activities are also often increased by glucocorticoids in dogs, although to a lesser extent than alkaline phosphatase.

The activities of serum enzymes that reflect new synthesis and release of enzymes from the biliary tract in response to certain stimuli include the enzymes alkaline phosphatase (AP) and γ-glutamyltransferase (GGT). Bile retention (i.e., cholestasis) is one of the strongest stimuli for accelerated production of these enzymes. Unlike ALT and AST, AP and GGT are in low concentration in the cytoplasm of hepatocytes and biliary epithelium, and are membrane-associated, so the fact that they simply leak out of damaged cells does not account for increased serum activity. Measurable AP activity is also detectable in nonhepatobiliary tissues of cats and dogs, including osteoblasts, intestinal mucosa, renal cortex, and placenta, but serum activity in healthy adult cats and dogs arises only from the liver, with some contribution by the bone isoenzyme in young, rapidly growing dogs and in kittens younger than 15 weeks. The renal form is generally measurable in the urine; the gut form has a very short half-life and is not usually measurable, although the steroid-induced isoenzyme of AP in dogs is believed to be an altered gut isoenzyme with a prolonged half-life. Cats do not have a steroid-induced isoenzyme of AP. The half-life of feline AP is shorter than that of canine AP, so serum activity is relatively lower in cats than in dogs with a similar degree of cholestasis and, conversely, even mild elevations of AP levels in cats are clinically significant. Markedly high serum AP activity of bone origin (mean total serum AP values > fivefold higher than those in nonaffected individuals, with only the bone isoenzyme detected) was identified in certain healthy juvenile members (7 months old) of a family of Siberian Huskies. This change is believed to be benign and familial, and should be considered when results of serum AP activity are interpreted in this breed. A young growing dog of any breed can have a mild increase in serum AP. Increased serum AP activity has also been described in adult Scottish Terriers. This is believed to be associated with a vacuolar hepatopathy and adrenal dysfunction. More details are given in Chapter 36.

Certain drugs, the most common of which are anticonvulsants (specifically phenytoin, phenobarbital, and primidone) and corticosteroids, can elicit striking increases (up to 100-fold) in serum AP activity (and to a lesser extent GGT and ALT activity) in dogs but not in cats. There usually is no other clinicopathologic or microscopic evidence of cholestasis in these cases (i.e., hyperbilirubinemia). Anticonvulsant drugs stimulate the production of AP identical to the normal liver isoenzyme; GGT activity does not change. Pharmacologic levels of corticosteroids administered orally, by injection, or topically reliably provoke a unique AP isoenzyme that is separable from the others by electrophoretic and immunoassay techniques. However, measurement of AP isoenzymes has been shown to be of limited usefulness in dogs treated with phenobarbital or in dogs with hyperadrenocorticism. In the latter, it has a high sensitivity but very low specificity, so finding a low steroid-induced isoenzyme rules out hypercortisolism, but a high concentration of steroid-induced isoenzyme may be found in many diseases other than hypercortisolism. Serum GGT activity rises similarly in response to corticosteroid influence but less spectacularly. Serum AP and GGT activities tend to rise in parallel in cholestatic hepatopathies of cats and dogs, although they are much less dramatic in cats. Simultaneous measurement of serum AP and GGT levels may aid in differentiating seemingly benign drug-induced effects from nonicteric cholestatic hepatic disease in dogs. Assessing serum AP and GGT activities together may also offer clues to the type of hepatic disorder in cats. Both enzymes are in low concentration in feline liver tissue compared with that in the canine liver and have short half-lives, so relatively smaller increases in serum activity, especially of GGT, are important signs of the presence of hepatic disease in cats. In cats, a pattern of high serum AP activity with less strikingly abnormal GGT activity is most consistent with hepatic lipidosis (see Chapter 35), although extrahepatic bile duct obstruction (EBDO) must also be considered.

DIAGNOSTIC TESTS TO ASSESS HEPATOBILIARY SYSTEM FUNCTION

Serum Bilirubin Concentration

Because of the large reserve capacity of the mononuclear-phagocytic system and liver to process bilirubin (e.g., 70% hepatectomy will not cause jaundice), hyperbilirubinemia usually occurs only from greatly increased production or decreased excretion of bile pigment. However, in severe chronic liver disease in dogs, hepatocyte senescence may also play a role because senescent cells are no longer able to process bilirubin (Kortum et al., 2018). Specific inborn errors of bilirubin uptake, conjugation, and excretion have not been documented in cats or dogs. The increased production of bilirubin from red blood cell destruction arises from intravascular or extravascular hemolysis and rarely from resorption of a large hematoma; hyperbilirubinemia also occurs in association with rhabdomyolysis or after diffuse subcutaneus bleeding in Greyhounds and other dog breeds. Under these circumstances, in dogs, serum bilirubin concentrations are usually lower than 10 mg/dL; values rarely exceed 10 mg/dL unless there is a concurrent flaw in bilirubin excretion. This has been observed clinically in studies of dogs with immune-mediated hemolytic anemia in which high liver enzyme activities are observed, even before treatment with corticosteroids, and moderately delayed bilirubin excretion has been documented. It has been proposed that cholestasis results from liver injury associated with

hypoxia and, in some cases, because of early disseminated intravascular coagulation (DIC). Because increased production and decreased excretion of bilirubin occur in dogs with severe hemolysis, serum bilirubin concentrations can therefore be as high as 35 mg/dL. Icterus in cats with pure hemolytic disease is an inconsistent finding and, if present, is mild.

Because almost all diseases associated with hyperbilirubinemia in cats and dogs are characterized by a mixture of conjugated and unconjugated bilirubinemia, quantifying the two fractions by the use of the van den Bergh test achieves little in regard to distinguishing primary hepatic or biliary disease from nonhepatobiliary disease in a clinical setting. This lack of benefit in using the van den Bergh test may relate to the time between onset of illness and examination, which is usually at least several days. Under conditions of acute massive hemolysis, the total serum bilirubin concentration may initially consist primarily of the unconjugated form. As hemolysis continues, the liver is able to take up and conjugate bilirubin, accounting for a combination of unconjugated and conjugated bilirubin.

Hyperbilirubinemia is attributed primarily to hemolysis when there is moderate to marked anemia with strong evidence of regeneration (except in the first 1-3 days, when the response is less regenerative) and minimal changes in serum markers of cholestasis. Most dogs and cats with liver disease are not severely anemic.

Serum Bile Acid Concentration

The validation of rapid, technically simple methods for serum bile acid (SBA) analysis in cats and dogs has provided a sensitive, variably specific test of hepatocellular function and the integrity of the enterohepatic portal circulation. Primary bile acids (e.g., cholic, chenodeoxycholic) are synthesized only in the liver, where they are conjugated with various amino acids (primarily taurine) before secretion into the bile. Bile is stored in the gallbladder, where it is concentrated until it is released into the duodenum under the influence of cholecystokinin. After facilitating fat absorption in the small intestine, the primary bile acids are efficiently absorbed into the portal vein and returned to the liver for reuptake and resecretion into the bile. The stored bile acid pool typically circulates twice in this way after a meal. A small percentage of primary bile acids that escapes resorption is converted by intestinal bacteria to secondary bile acids (e.g., deoxycholic, lithocholic), some of which are also resorbed into the portal circulation. Absorption of bile acids by the intestine is extremely efficient, but hepatic extraction from portal venous blood is not. This accounts for the low concentrations of cholic, chenodeoxycholic, and deoxycholic acids that are released into the peripheral blood of healthy cats and dogs in the fasting state—total, <5 µmol/L by the enzymatic method and 5-10 µmol/L by radioimmunoassay (RIA). During a meal, a large load of bile acids is delivered to the intestine and portal circulation for recycling; postprandial values in normal dogs and cats may increase up to threefold to fourfold over fasting values (15 µmol/L with the enzymatic method for cats and dogs; 25 µmol/L with the RIA method for dogs). Normal values for juvenile animals are similar to adult reference ranges. Abnormally high fasting and/or postprandial SBA concentrations reflect a disturbance in hepatic secretion into the bile or at any point along the path of portal venous return to the liver and hepatocellular uptake.

The standard way to assess SBA concentration is outlined in Box 34.3. Collective experience indicates that the likelihood of precipitating an episode of HE during this part of the test is extremely low, even in predisposed animals. After the serum is harvested, the samples may be refrigerated for several days or frozen almost indefinitely before assay. The stability of the blood sample is one of the major advantages over the much more labile serum ammonia test.

Studies of SBAs have confirmed their value in detecting clinically relevant hepatobiliary disease requiring definitive diagnostic testing in cats and dogs, especially in anicteric animals with equivocal clinical signs and unexplained high liver enzyme activity. There continues to be controversy about whether a fasting or postprandial value alone is sufficient or whether fasting and postprandial measurements are required. If only one sample can be obtained, and the animal will eat or can tolerate being force-fed a small meal, the postprandial value is most useful to determine the presence or absence, but not the type, of clinically relevant hepatobiliary disease in most cats and dogs. Current recommendations state that for animals suspected of having acquired hepatobiliary disease, biopsy is needed when the postprandial SBA concentration using the enzymatic method in animals without icterus exceeds 20 µmol/L in cats and 25 µmol/L in dogs. However, other researchers, particularly in the United Kingdom, have suggested that an SBA concentration of between 20 and 40 µmol/L in dogs represents a gray area (Hall et al., 2005). Elevations in this range have been seen



BOX 34.3

Summary of Techniques for Bile Acid Stimulation Test and Postprandial Ammonia Challenge Test

Bile Acid Stimulation Test

Collect a 3-mL blood sample in a serum tube after the animal was fasted for 12 hours.

Feed a small amount of food that is normal in fat content (≈20% fat [dry matter basis] in dogs).

Collect another 3-mL blood sample in a serum tube 2 hours after the meal.

Postprandial Ammonia Challenge Test

Collect a 3-mL blood sample after the animal was fasted for 12 hours.

Feed an amount of food corresponding to 25% of the dog's daily metabolic energy requirement.

Collect another 3-mL blood sample in a serum tube 6 hours after the meal.

with secondary hepatopathies, particularly hyperadrenocorticism, and with small intestinal bacterial overgrowth because of reduced hepatic clearance of deconjugated bile acids. Therefore the author would recommend a liver biopsy with a higher cut-off value of 40 μmol/L for postprandial bile acids. In patients with PSS, the magnitude of elevation does not correlate with the degree of shunting or severity of clinical signs. The change between the fasting and postprandial values likely corresponds to portosystemic shunting, either microscopic (intrahepatic) or macroscopic. There is so much overlap in fasting and postprandial SBA patterns among primary hepatobiliary diseases that no definitive statement can be made regarding the specific causative hepatobiliary disease. Occasionally, fasting SBA levels are higher than postprandial levels, which signify nothing more than occasional, normal, spontaneous gallbladder contraction in fasting. In general, secondary hepatic diseases cause more modest hepatobiliary dysfunction (SBA level < 100 μmol/L). It is very important to remember that elevation of the SBA level has no functional significance in a dog or cat with jaundice of hepatic or posthepatic origin. In these cases, elevations will purely reflect cholestasis, and measuring the SBA level does not provide any further information.

For the diagnosis of congenital PSS, fasting and postprandial SBA level determinations are recommended to enhance detection ability; this is because it is relatively common for fasting values to be well within normal limits and for postprandial values to be as high as 10- to 20-fold higher than normal postprandial values.

Because the measurement of fasting and postprandial SBA concentrations assesses the same functions as the ammonium chloride (NH_4Cl) tolerance test, but without potentially dangerous consequences, it is the preferred method. As with any specially requested test, the laboratory chosen should use methods verified for clinical use in the target species and be able to provide reference ranges.

Several factors may affect SBA levels and therefore their interpretation. One aspect of the SBA challenge test that has not been standardized is the feeding step. The ideal quantity and composition of the test meal have not been determined. Size of the test meal and therefore consumption of the entire meal or only part of the meal may affect gastric emptying. Delayed gastric emptying could cause the peak SBA concentration to occur more than 2 hours later. Hastened or delayed intestinal transit time or the presence of intestinal disease, especially of the ileum, may also impede and blunt peak absorption of the test meal. It is likely that fat content of the test meal is important because fat is the primary stimulus for the small intestinal mucosa to secrete cholecystokinin, which causes gallbladder contraction. Expulsion of bile during periodic physiologic gallbladder contraction between meals may complicate interpretation of the fasted sample result. Lipemia of the sample can seriously affect the validity of the test, particularly on heparinized blood. For this reason, it is far preferable to use serum, both for the external samples and for the SNAP test. It is possible to use erythromycin at a small fraction of the therapeutic antibiotic dose (1-2.5 mg/kg orally) with a meal to increase the stimulation of gallbladder emptying. The effect of this treatment on gallbladder emptying has been studied but not its effect on the bile acid stimulation test.

Several questions remain to be answered regarding the clinical use of SBA level measurement in cats and dogs. Investigation of individual SBA profiles in cats and dogs with various hepatobiliary diseases has provided interesting information but no clear and specific profile for any one disease. Can sequential SBA levels be used to monitor a cat's or dog's progress more precisely? Until this and other questions are answered, the use of SBA analysis is limited to measuring total serum values, in the absence of cholestasis and jaundice, as a sensitive and relatively specific screening test for the presence or absence of clinically significant hepatobiliary disease and/or congenital or acquired portosystemic shunting. Additional diagnostic testing must always follow to identify the specific cause.

Urinary Bile Acid Concentration

Determination of bile acids accumulating in urine over time can be used to assess hepatobiliary function. Urine bile acids are believed to reflect average SBA concentrations during the interval of urine formation. Expressing urine bile acid concentrations as a ratio with the urine creatinine concentration eliminates the influence of urine concentration and flow. Random urine sampling for bile acid determination does not require attending to the timing of an enterohepatic challenge or obtaining a sample after withholding food. Studies of urinary bile acid concentrations have shown that they were increased in dogs and cats with hepatobiliary disease and portosystemic vascular anomalies compared with dogs and cats with nonhepatic disorders, except for hepatic neoplasia in dogs. The urine nonsulfated bile acid–to–creatinine ratio and the urine sulfated plus nonsulfated bile acid–to–creatinine ratio positively correlated with SBA test results and had similar overall diagnostic performance and substantially higher (dogs) or similar (cats) specificity compared with the SBA test. Therefore these are recommended. The urine sulfated bile acid–to–creatinine ratio had lower sensitivity in dogs and cats compared with the SBA test.

Plasma Ammonia Concentration

One test that is not included in a standard screening battery of tests but is available through reference laboratories is plasma ammonia concentration. Fasting plasma ammonia can be measured in any cat or dog with historic or physical examination findings suggestive of HE. Signs of HE, whether they have a congenital or acquired basis, appear the same (see Box 33.3). Quantifying the plasma ammonia concentration not only can confirm HE, although normal fasting values in animals with hepatobiliary disease are relatively common, but can also provide baseline data and help in evaluating response to treatment. SBA values, particularly postprandial levels, provide similar information in dogs with congenital PSS. A high plasma ammonia concentration usually indicates reduced hepatic mass available to process

ammonia and/or the presence of portosystemic shunting, which disrupts presentation of ammonia to the liver for detoxification. However, ammonia is very labile in the blood sample and can be falsely elevated—for example, if the blood sample is taken in an environment contaminated with urine. Sample handling has to be undertaken with caution, and some benchtop analyzers are inaccurate, particularly in the moderately elevated range. For these reasons, determination of SBA levels is often a preferred test. The exception to this would be an animal with suspected HE and concurrent cholestasis. As outlined in the preceding paragraphs, bile acid concentrations will be high in cholestasis because they are excreted in the bile, independent of any reduction in liver function or shunting. Measuring blood ammonia in these cases will provide useful additional information about potential shunting and HE.

In one study, the 12-hour fasting plasma ammonia concentration had higher sensitivity and specificity than the 12-hour fasting bile acid concentration for detecting portosystemic shunting in a general population of dogs and in dogs with liver disease. However, a bile acid stimulation test (fasting and 2-hour postprandial bile acid) has a much higher sensitivity for detecting a PSS than a single fasting bile acid, and a single postprandial bile acid concentration is likely as sensitive as a fasting ammonia concentration, although the author did not test this.

Although reference ranges vary among laboratories, fasting plasma ammonia values for normal dogs are typically 100 mg/dL or less and 90 mg/dL or less for normal cats. At least 6 hours of fasting should precede sample collection. Samples must be collected into iced ammonia-free heparinized tubes and spun immediately in a refrigerated centrifuge. Plasma must be removed within 30 minutes so that values will not be spuriously elevated by hemolysis because red blood cells contain two to three times the ammonia concentration of plasma. To obtain accurate values, feline plasma can be frozen at –20° C and assayed within 48 hours; canine plasma must be assayed within 30 minutes.

If signs are compatible with HE at the time of sample collection, a single fasting sample will suffice. If there are no signs of HE and results of other tests are equivocal, a postprandial challenge test may be performed (see Box 34.3). The older ammonium chloride challenge tests (oral or rectal) are contraindicated because of the significant potential for either test to trigger a severe encephalopathic crisis in the patient. The postprandial ammonia test is safer, with a 91% sensitivity for portosystemic shunting but only a 31% sensitivity for diffuse hepatocellular disease.

Plasma Protein C Activity

Plasma protein C activity has been evaluated as a marker of hepatobiliary disease in dogs. Protein C is an anticoagulant protein that is synthesized in the liver and circulates as a plasma zymogen. Low protein C activity has been associated with thrombotic disorders in humans and animals. Low protein C activity has also been documented in dogs with acquired and congenital hepatobiliary disorders, and dogs with a PSS appear to have the lowest protein C activity. In a study by Toulza et al. (2006), protein C activity was significantly lower in dogs with a congenital or acquired PSS, compared with dogs without a PSS. Plasma protein C activity improved or normalized after surgery for the shunt. These findings suggest that plasma protein C activity reflects the adequacy of hepatoportal perfusion in dogs and that protein C activity may prove useful as a means to monitor improvement of hepatic-portal perfusion after the ligation of portosystemic vascular anomalies. Plasma protein C activity may also help differentiate dogs with intrahepatic portal vein hypoplasia from those with portal systemic vascular anomaly—plasma protein C activity, ≥70% versus <70%, respectively.

NONSPECIFIC TESTS OF LIVER FUNCTION

Serum Albumin Concentration

The liver is almost the only source of albumin production in the body, so hypoalbuminemia can be a manifestation of hepatic inability to synthesize this protein. Causes other than lack of hepatic synthesis (i.e., marked glomerular or GI loss, or bleeding) must be considered before ascribing hypoalbuminemia to hepatic insufficiency. Renal protein loss can be detected presumptively by routine urinalysis. Consistent identification of positive protein dipstick reactions, especially in dilute urine with inactive sediment, justifies further evaluation by at least the measurement of the random urine protein-to-creatinine ratio (normal ratio, <0.2 in cats and dogs). If proteinuria is ruled out, diseases that cause GI protein loss should be considered; however, these GI diseases usually result in an equivalent loss of globulins and thus panhypoproteinemia. This is not invariably the case in inflammatory GI disease, in which a concurrent increase in gamma globulin levels masks the gut loss. Conversely, although panhypoproteinemia is reportedly not typical of hypoproteinemia of hepatic origin, globulin concentrations can be low in liver disease, particularly portosystemic shunts (PSS), because all plasma globulins except gamma globulins are made in the liver. Globulin concentrations frequently are normal to increased in dogs and cats with chronic inflammatory hepatic disease because they reflect the inflammatory response. The plasma half-life of albumin in cats and dogs is long (8-10 days), and there must be a loss of approximately 80% of functioning hepatocytes before hypoalbuminemia occurs, so the finding of hypoalbuminemia usually indicates severe chronic hepatic insufficiency.

The exception to this is the hypoalbuminemia associated with a negative acute phase response in acute or acute-on-chronic inflammatory liver disease. The serum albumin concentration can decrease when there is an increase in hepatic production of acute phase proteins in animals without hepatic insufficiency. Serum protein electrophoresis can help differentiate this condition from a true lack of hepatic function. Sevelius and Andersson (1995) have shown that a low albumin concentration associated with a low concentration

of acute-phase proteins in electrophoresis indicates severe hepatic dysfunction with a poor prognosis, whereas hypoalbuminemia combined with normal or elevated acute-phase protein levels indicates a good prognosis. Hypoalbuminemia of any cause is unusual in cats, except in those with nephrotic syndrome. When interpreting serum protein concentrations, the clinician should remember that total protein values for young cats and dogs are lower than those for adults, and puppy serum albumin concentration is similar to that in adults, whereas kitten serum albumin concentration is lower than that in adult cats.

Serum Urea Nitrogen Concentration

The formation of urea as a means of detoxifying ammonia derived from intestinal sources takes place only in the liver. Despite this apparent advantage as a specific measure of hepatic function, serum urea concentration is commonly affected by several nonhepatic factors; the capability of the liver to detoxify urea is so great that it is not noticeably reduced until severe, extensive end-stage liver disease has developed. Prolonged, restricted protein intake because of complete anorexia or intentional reduction in protein intake for therapeutic purposes (e.g., chronic kidney disease; urate, cystine, or struvite urolithiasis) is the most common cause of low blood urea nitrogen (BUN) concentration. Prior fluid therapy and/or marked polydipsia or polyuria of nonrenal causes will also result in a decrease in the BUN level. As always, reference ranges should be considered for each species when interpreting BUN values. For example, a BUN concentration of 12 mg/dL is well within normal limits for dogs but is subnormal for cats. If low BUN levels are noted in a cat or dog with normal water intake and a good appetite for a diet with the appropriate protein content for the species (on a dry matter basis, 22% for dogs and 35%-40% for cats), the possibility of hepatic inability to convert ammonia to urea or portosystemic shunting of ammonia away from the liver should be investigated.

Serum Cholesterol Concentration

Total cholesterol concentration is included in serum chemistry profiles by many commercial laboratories but affords useful information for only a limited number of hepatobiliary diseases. High total cholesterol values are observed in cats and dogs with severe intrahepatic cholestasis involving bile ducts or EBDO because of impaired excretion of free cholesterol into the bile and subsequent regurgitation into the blood. Hypocholesterolemia has been documented in dogs with chronic severe hepatocellular disease and frequently in cats and dogs with congenital PSS. It has been speculated that hypocholesterolemia is a sign of markedly altered intestinal absorption of (and increased use of) cholesterol for bile acid synthesis when the enterohepatic recirculation of bile acids is disturbed, as occurs with PSS. In other hepatobiliary diseases of cats and dogs, the total cholesterol values vary considerably. Normal values in 4-week-old kittens are higher than those for adults; 8-week-old puppy reference ranges are the same as those for adults.

Serum Glucose Concentration

Hypoglycemia is an unusual event associated with hepatobiliary disease in dogs and especially in cats. There is a lost ability to maintain normal serum glucose concentrations in animals with acquired chronic progressive hepatobiliary disease when 20% of the functional hepatic mass or less remains. This inability to maintain a normal serum glucose concentration is presumably caused by the loss of hepatocytes with functioning gluconeogenic and glycolytic enzyme systems and impaired hepatic degradation of insulin. Hepatocyte senescence may also play a role. Hypoglycemia is often a near-terminal event in dogs with chronic progressive hepatobiliary disease. In striking contrast is the frequent observation of hypoglycemia in dogs with congenital PSS, particularly small-breed dogs. Hypoglycemia in patients with PSS has been suggested to be the result of an increase in circulating insulin concentration caused by reduced first-pass metabolism in the liver, as observed in humans, but a more recent study showed normal to low insulin concentration in dogs with PSS and hypoglycemia, which did not support this hypothesis, so the cause remains unknown. Hypoglycemia is also common as a paraneoplastic syndrome in dogs with large hepatocellular carcinomas and can be associated with the production of insulin-like growth factor by the tumor. In either case, if hypoglycemia is identified and confirmed by repeating the test using sodium fluoride, if necessary, and if nonhepatic causes (e.g., functional hypoglycemia, sepsis, insulinoma or other neoplasm producing an insulin-like substance, or Addison disease; see Chapter 50) are excluded, a primary hepatic tumor (e.g., hepatocellular carcinoma), PSS, or severe generalized hepatopathy is suspected.

DIAGNOSTIC TESTS TO ASSESS PANCREATIC INFLAMMATION AND FUNCTION

Specific Tests of Pancreatic Inflammation

The most specific tests for the pancreas are the catalytic assays for amylase and lipase and the immunoassays for trypsin-like immunoreactivity (TLI) and pancreatic lipase immunoreactivity (PLI). Catalytic assays rely on the ability of the molecule to catalyze a reaction in vivo and thus rely on the presence of active enzyme; however, they are not species-specific. The sensitivity and specificity of the traditional catalytic assays in dogs are relatively poor, particularly for amylase, and in cats, traditional amylase and lipase are of questionable diagnostic value. However, recently a new lipase assay has been developed, which appears to be more sensitive and specific than the traditional lipase and also shows very good agreement with PLI. This is the 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester (DGGR) lipase assay. The enzyme and substrate interactions in this assay are more selective than with the traditional multistep colorimetric lipase assay that uses 1,2-diglyceride (1,2-DiG) as the substrate. It is proposed that, with the new assay, hydrolysis with other lipases and

esterases is less likely to occur. Recent studies in dogs suggested good agreement between the DGGR lipase assay and PLI (Kook et al., 2014; Goodband et al. (2018)) and two other studies suggests that it may also be useful in cats, unlike the older lipase assay (Oppliger et al., 2013 and 2014).

Immunoassays, however, use an antibody against a part of the enzyme molecule distant from the active site and thus will also measure inactive precursors (e.g., trypsinogen); these tend to be organ- and species-specific. The advantages and disadvantages of the different assays are outlined in Table 34.2. Overall, PLI has the highest sensitivity and likely the highest specificity in both species. Recent studies of PLI for the diagnosis of acute pancreatitis in dogs suggest a sensitivity of between 86.5% and 94.1% and a specificity of 80% to 90% or 66.3% to 77.5%, depending on the cut-off and methodology used in the studies, respectively (Mansfield et al., 2012; McCord et al., 2012). The positive predictive value is high in animals with a high likelihood of acute

TABLE 34.2

Catalytic Enzyme Tests and Immunoassays in the Diagnosis of Acute and Chronic Pancreatitis in Dogs and Cats

ASSAY	ADVANTAGES	DISADVANTAGES
Catalytic Assays		
Dogs only; of no use in cats except for DGGR lipase (see following and text for more details)		May be normal in severe ± chronic pancreatitis caused by enzyme depletion ± loss of tissue; degree of elevation of no prognostic value, except where stated; both renally excreted and elevated two or three times in azotemia
Amylase	Widely available on in-house analyzers; steroids do not elevate it, so can help diagnose pancreatitis in dog with hyperadrenocorticism	Low sensitivity and specificity because of high background level from other sources, including small intestine
Lipase	Widely available on practice analyzers; more sensitive than amylase; degree of elevation may have prognostic significance New DGGR lipase has higher sensitivity and specificity than older assays and correlates well with PLI in both dogs and cats (see details in text)	Extrapancreatic sources so high background level Steroids elevate up to five times
Immunoassays		
Canine TLI	Elevations—high specificity for pancreatitis	Low sensitivity for diagnosis of pancreatitis (but high sensitivity for EPI); said to rise and fall more quickly than lipase or amylase; renally excreted: elevated two or three times in azotemia May be inappropriately low in severe ± chronic cases caused by pancreatic depletion ± loss of tissue mass; no clear prognostic significance
Feline TLI	No advantages for diagnosis of pancreatitis— reserve for diagnosis of EPI	Lower sensitivity and specificity than canine TLI, better used for diagnosis of EPI; renally excreted so elevated in azotemia
Canine PLI	Most sensitive and specific test for canine pancreatitis together with DGGR lipase (see text for figures); organ-specific, so no interference from extrapancreatic sources Available as in-house test (see URL in text)	Increased in renal disease but may not be significantly increased (?) (unclear yet if affected by steroids)
Feline PLI	Most sensitive and specific test available for feline pancreatitis, together with DGGR lipase (see text for figures); available as in-house test (see URL in text)	Very little published data yet available on its use

PLI, Pancreatic lipase immunoreactivity; *TLI*, trypsin-like immunoreactivity.

pancreatitis, but the negative predictive value in this population is unclear, as negative predictive value has only been shown to be high in a population with low prevalence of disease (McCord et al., 2012). In the author's experience, a negative PLI is uncommon in dogs with severe acute pancreatitis but does occur, so pancreatitis should not be completely ruled out by a negative result. A single study in cats showed the test to have 100% sensitivity in moderate to severe acute pancreatitis but only 54% for mild pancreatitis, with a specificity of 91% (Forman et al., 2004). However, the sensitivity is lower in chronic pancreatitis in dogs and cats. SNAP tests for canine and feline PLI are commercially available (see details at https://www.idexx.com/small-animal-health/products-and-services/snap-cpl-test.html for dogs and https://www.idexx.com/small-animal-health/products-and-services/snap-fpl-test.html for cats), which should aid in rapid diagnosis in both species.

Tests of Pancreatic Exocrine Function

Exocrine pancreatic insufficiency (EPI) can develop in dogs and cats as a result of chronic pancreatitis and in dogs with PAA (see Chapter 37 for more details). The diagnosis of EPI in dogs and cats relies on showing consistent clinical signs (weight loss and steatorrhea) combined with demonstrating reduced pancreatic enzyme output. The most sensitive and specific way of doing this is by measuring reduction in circulating enzyme activity. This is achieved by use of the immunoassay TLI, which measures both trypsin and trypsinogen. Measurement of decreased TLI in the blood has a high sensitivity and specificity for the diagnosis of EPI in dogs and cats, and is currently the single test of choice for diagnosis in small animals. It is important to measure it on a fasting sample because the release of pancreatic enzymes associated with feeding can raise the activity in the serum. It is not necessary to stop exogenous pancreatic enzyme supplementation before measuring TLI because exogenous enzymes should not be absorbed from the gut into the circulation; even if they are, the test is an immunoassay that does not cross-react with the trypsin or trypsinogen of other species in the supplement. However, there are some problems in interpreting the results, as shown in Box 37.3. In particular, in a dog with ongoing chronic pancreatitis and EPI, the TLI will be unpredictable because bouts of pancreatic inflammation can raise it in to the normal range.

Unlike in humans, amylase and lipase levels are not consistently low in dogs and cats with EPI because of the high background levels of enzymes from other organs. A low cPLI also has a good sensitivity and specificity for the diagnosis of EPI in dogs (Steiner et al., 2001). However, this test is not superior to TLI. PLI is also likely to be low in cats with EPI.

Fecal tests for EPI are rarely used because of their low sensitivity and specificity compared with serum tests. Measuring fecal trypsin levels has a very low sensitivity and specificity for EPI, as do assessment of fecal proteolytic activity or microscopic examination of feces for undigested fat, starch, and muscle fibers. All these tests have been superseded by the measurement of serum TLI and cPLI. Measurement of fecal elastase may have some usefulness in dogs with EPI as a result of chronic pancreatitis or duct blockage, in which TLI results may be misleading. Elastase testing appears to have higher sensitivity and specificity than the other fecal tests for the diagnosis of EPI in dogs. Elastase is a pancreatic enzyme, and a species-specific ELISA for canine elastase is available for commercial use in dogs (ScheBo Biotech USA Inc, PMB 168, 445 E Cheyenne Mountain Blvd., Suite C, Colorado Springs, CO 80906, USA; Spillmann et al., 2000, 2001). There is also a bed-side elastase ELISA test available now: ScheBo Elastase 1 Quick–Canine rapid (available to vets in the United States through http://catacheminc.com/veterinary-diagnostics/schebo-pancreas-elastase). This test is also being marketed online for owner use.

As with canine TLI, because there is no cross-reaction with elastase from other species, dogs can remain on enzyme supplementation while the test is performed. There is marked variation in elastase levels in normal canine feces compared with humans. The sensitivity and specificity of the test are improved by taking three separate fecal samples on 3 days or using a cut-off value for the diagnosis of EPI, which is below this variation in most dogs.

It is also advisable to measure the serum cobalamin concentration in animals with EPI because it is often decreased due to a deficiency of pancreatic intrinsic factor. Dogs produce most intrinsic factor in the pancreas but a small amount in the stomach, whereas cats produce all their intrinsic factor in the pancreas. Cobalamin bound to intrinsic factor is absorbed in the ileum so concurrent inflammatory bowel disease affecting the ileum will also predispose to deficiency. Cats with EPI as an end stage of chronic pancreatitis should therefore always be cobalamin deficient, particularly if they have concurrent inflammatory bowel disease. However, normal concentrations are often found in affected cats, presumably because of persistence of liver stores.

Tests of Pancreatic Endocrine Function

End-stage chronic pancreatitis in dogs and cats can result in a loss of endocrine function and diabetes mellitus. For details of tests of pancreatic endocrine function, see the chapter on diabetes mellitus (Chapter 49).

NONSPECIFIC TESTS IMPORTANT FOR PROGNOSIS AND SUPPORTIVE CARE IN BOTH LIVER AND PANCREAS DISEASE

Nonspecific changes in serum biochemistry, particularly electrolytes and urea and creatinine, are important for supportive care of dogs and cats with pancreas and liver disease, particularly acute hepatitis and acute pancreatitis, where multiorgan failure is a possible sequela. Likewise, assessment of a CBC, particularly PCV and platelet count, and coagulation status are important to check for significant intestinal bleeding and/or coagulopathy in acute or chronic pancreatitis or hepatitis.

Serum Biochemistry

Alterations in urea, glucose, cholesterol, and albumin as nonspecific indicators of liver function have been considered in the previous section. Azotemia may also occur in acute liver disease as a result of multiorgan failure, although when azotemia occurs in the context of acute liver disease in dogs, leptospirosis is important to rule out (see Chapter 36), particularly if there is concurrent glycosuria and thrombocytopenia.

In acute pancreatitis, azotemia is very common and is usually prerenal due to dehydration or shock, although intrinsic renal damage may also occur. This and other common changes in serum biochemistry in acute pancreatitis in dogs and cats are detailed in Table 34.3. It is particularly important to monitor electrolyte concentrations in animals with acute pancreatitis because hypokalemia is common and potentially life-threatening. Hypokalemia is also relatively common in hepatobiliary disease where it is attributed to a

TABLE 34.3

Typical Clinicopathologic Findings in Dogs and Cats With Acute Pancreatitis

PARAMETER	CHANGES IN DOGS	CHANGES IN CATS	CAUSE AND SIGNIFICANCE
Urea ± creatinine	Increased in 50%-65% of cases	Urea increased in 57% of cases and creatinine in 33%	Usually prerenal because of dehydration and hypotension (urea > creatinine), indicates need for aggressive fluid therapy Often also some intrinsic renal failure (sepsis and immune complexes)
Potassium	Decreased in 20% of cases	Decreased in 56% of cases	Increased loss in vomiting and renal loss with fluid therapy + reduced intake and aldosterone release caused by hypovolemia Requires treatment because it contributes to gastrointestinal atony
Sodium	Can be increased (12%), decreased (33%), or normal	Usually normal or decreased (23%) Increased only in 4% of cases	Increase caused by dehydration; decrease caused by loss in gastrointestinal secretions with vomiting
Chloride	Very commonly decreased (81%)	Unknown	Loss in gastrointestinal secretions with vomiting
Calcium	Increased in ≈9% of cases and decreased in ≈3% of cases	Total calcium reduced in 40% to 45% of cases; ionized calcium reduced in 60% of cases; total calcium increased in 5%	Reduction poor prognostic indicator in cats but of no prognostic significance in dogs; caused by saponification in peripancreatic fat (unproven) and glucagon release, stimulating calcitonin in some Increased calcium likely cause rather than effect of disease in cats, but unproven in dogs
Phosphate	Often increased (55%)	Increased in 27%, decreased in 14%	Increase usually caused by reduced renal excretion secondary to renal compromise; decrease (in cats) caused by treatment for diabetes mellitus
Glucose	Increased in 30%-88%, decreased in up to 40%	Increased in 64%, very rarely decreased	Increased because of decreased insulin and increased glucagon, cortisol, and catecholamines; about 50% return to normal; decreases caused by sepsis and anorexia
Albumin	Increased in 39%-50%, reduced in 17%	Increased in 8%-30%, reduced in 24%	Increase caused by dehydration; decrease caused by gut loss, malnutrition, concurrent liver disease, or renal loss
Hepatocellular enzymes (ALT and AST)	Increased in 61%	Increased in 68%	Hepatic necrosis and vacuolation caused by sepsis, local effects of pancreatic enzymes ± concurrent hepatic disease in cats
Cholestatic enzymes (ALP and GGT)	Increased in 79%	Increased in 50%	Biliary obstruction caused by acute-on-chronic pancreatitis ± concurrent cholangitis ± lipidosis in cats; steroid-induced ALP in dogs

Continued

TABLE 34.3

Typical Clinicopathologic Findings in Dogs and Cats With Acute Pancreatitis—cont'd

PARAMETER	CHANGES IN DOGS	CHANGES IN CATS	CAUSE AND SIGNIFICANCE
Bilirubin	Increased in 53%	Increased in 64%	Same as GGT
Cholesterol	Increased in 48%-80%	Increased in 64%	Can be caused by cholestasis; unclear in others if cause or effect; often caused by concurrent or predisposing disease
Triglycerides	Commonly increased	Rarely measured	Unclear if cause or effect; often caused by concurrent or predisposing disease
Neutrophils	Increased in 55%-60%	Increased in about 30%, decreased in 15%	Increase caused by inflammatory response; decrease in some cats caused by consumption; may be poor prognostic indicator
Hematocrit	Increased in ≈20% and decreased in ≈20%	As dogs	Increase caused by dehydration; decrease caused by anemia of chronic disease; gastrointestinal ulceration
Platelets	Commonly decreased in severe cases (59%)	Usually normal	Decrease caused by circulating proteases ± disseminated intravascular coagulation

ALP, Alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *GGT,* γ-glutamyltranspeptidase.
Data from Schaer M: A clinicopathological survey of acute pancreatitis in 30 dogs and 5 cats, *J Am Anim Hosp Assoc* 15:681, 1979; Hill RC et al: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat: a retrospective study of 40 cases (1976-1989), *J Vet Intern Med* 7:25, 1993; Hess RS et al: Clinicopathological, radiographic and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995), *J Am Vet Med Assoc* 213:665, 1998; Mansfield CS et al: Review of feline pancreatitis. Part 2: clinical signs, diagnosis and treatment, *J Feline Med and Surgery* 3:125, 2001.

combination of excessive renal and GI losses, reduced intake, and secondary hyperaldosteronism in dogs and cats with severe chronic hepatobiliary disease. Metabolic alkalosis, presumptive evidence of which might be an abnormally high serum total carbon dioxide content confirmed by blood gas analysis, is usually caused by overzealous diuretic therapy in dogs with chronic hepatic failure and ascites. Hypokalemia and metabolic alkalosis potentiate each other and may also worsen signs of hepatic encephalopathy (HE) by promoting the persistence of readily membrane-diffusible ammonia (NH_3).

COMPLETE BLOOD COUNT

There are few changes in blood cells that suggest hepatobiliary disease. Most are changes in erythrocytes associated with fragmentation or changes in cell size or membrane composition. Microcytosis (mean corpuscular volume [MCV] < 60 fL in canine breeds other than the Japanese Akita or Shiba Inu), with normochromasia or slight hypochromasia (mean cell hemoglobin concentration, 32-34 g/dL), is a common finding in dogs with congenital PSS (≥60%); it is less common in cats with congenital PSS (≤30%). Most affected animals are not anemic. The cause of microcytosis, which has also been observed with less frequency in dogs with chronic hepatic failure and acquired PSS, is chelation of iron in the liver rather than absolute iron deficiency; therefore iron supplementation does not help. However, the change in the size of red blood cells is reversible upon restoration of portal blood flow. If anemia is also present, microcytosis must be distinguished from anemia of inflammatory disease, which can occasionally cause small red blood cells and relative iron deficiency, or from iron deficiency anemia associated with chronic GI blood loss, which might particularly be seen in a dog with chronic hepatitis and portal hypertension (see Chapter 36). The anemia sometimes seen in association with the microcytosis of PSS is usually mild. A marked microcytic anemia greatly increases the index of suspicion for chronic GI blood loss.

Strongly regenerative anemia, with macrocytosis, high reticulocyte count, and normal to slightly increased serum protein concentration in a jaundiced dog, especially if spherocytes are also identified, indicates hemolytic anemia and increased bilirubin formation as the cause of jaundice. Cats and dogs with hemolytic anemia typically also have high serum liver enzyme and bile acid concentrations, which indicate hepatic consequences developing secondary to the effects of marked hemolysis, such as hypoxia and thromboembolism.

Certain red blood cell morphologic changes are consistent with serious hepatobiliary disease and are related to alterations in lipoprotein metabolism and irregularities in red blood cell membrane structure. Poikilocytes (abnormally shaped red blood cells), such as acanthocytes (spiked red blood cells), leptocytes (elongated, pale staining red blood

cells), and codocytes (target cells) are good examples. Poikilocytosis of unknown pathogenesis is a consistent finding in cats with congenital PSS and occasionally with other hepatobiliary diseases; cats with chronic hepatobiliary disease frequently have Heinz bodies in their red blood cells. Fragmented red blood cells or schistocytes constitute an expected finding in animals with DIC; hemangiosarcoma is considered when an inappropriate number of nucleated red blood cells is also detected. Mild to moderate nonregenerative anemia is common in cats with many different illnesses, including those of the hepatobiliary tract.

Few changes in the leukon are expected in cats or dogs with hepatobiliary disease, except when an infectious agent is present as the initiating event (histoplasmosis, bacterial cholangitis, or leptospirosis in dogs), where there is concurrent pancreatitis, which is particularly common in cats, or when infection has complicated a primary hepatobiliary disorder (e.g., gram-negative sepsis in a dog with cirrhosis, septic bile peritonitis). Neutrophilic leukocytosis is likely in such cases, whereas pancytopenia is typical of disseminated histoplasmosis and severe toxoplasmosis in cats and of early infectious canine hepatitis.

In contrast, neutrophilic leukocytosis is very common in dogs with pancreatitis, reported in 55% to 60% of cases but only 30% of cases in cats (see Table 34.3).

COAGULATION TESTS

Clinically relevant coagulopathies are unusual in cats and dogs with hepatobiliary disease except for those with acute hepatic failure (including acute hepatic lipidosis in cats or hepatic lymphoma in both species), complete EBDO, or active DIC. It is more common to have subtle prolongation of activated partial thromboplastin time (APTT; 1.5 times normal), abnormal fibrin degradation products (10-40 µg/mL or more), and variable fibrinogen concentration (<100-200 mg/dL) in cats and dogs with severe parenchymal hepatic disease. Elevated D-dimers are common in patients with liver disease and do not always indicate DIC in these cases. It has been proposed that nonspecific elevation can occur in liver disease as a result of reduced clearance by the liver. Platelet numbers may be normal or low; mild thrombocytopenia (130,000-150,000 cells/µL) is usually associated with splenic sequestration or chronic DIC. More severe thrombocytopenia (≤100,000 cells/µL) is expected in acute DIC or decompensated chronic DIC.

Primary or metastatic cancer of the liver could also cause coagulopathy unrelated to a loss of hepatocellular ability to make or degrade coagulation proteins. A recent study evaluating thromboelastography (TEG) in dogs with partial or complete extrahepatic biliary obstruction found that all 10 affected dogs were hypercoagulable compared with 19 normal dogs, which was perhaps the opposite of the expected result (Mayhew et al., 2013). In contrast, TEG results in dogs with chronic hepatitis were found to be very variable, with some dogs being hypercoagulable, some normocogulable, and some hypocoagulable, and dogs with negative prognostic indicators tended to be hypocoagulable (Fry et al., 2017). Dogs with acute liver disease also had a variety of TEG results although with a predominance of hypocoagulable and hyperfibrinolytic results, particularly as functional impairment occurred (Kelley et al., 2015).

Abnormal coagulation function and thrombocytopenia are common in dogs with severe acute pancreatitis and suggest the development of DIC, although recent systematic studies of coagulation in dogs and cats with acute pancreatitis are lacking. In one study, pancreatitis was a common diagnosis in dogs with low blood antithrombin activity suggesting an increased risk of hypercoagulability and thrombosis, although there was no significant difference in antithrombin activity between survivors and nonsurvivors with pancreatitis (Kuzi et al., 2010).

ABDOMINOCENTESIS—FLUID ANALYSIS—IN LIVER AND PANCREAS DISEASE

If abdominal fluid is detected during physical examination, abdominal radiography, or US, a sample must always be obtained for analysis. For moderate- to large-volume effusion, simple needle paracentesis is sufficient to obtain 5 to 10 mL of fluid for gross inspection, determination of protein content, cytologic evaluation, and, in selected cases, special biochemical analysis. Pancreatitis is usually associated with small volume effusions whereas liver disease can be associated with large volumes.

Removal of a significant volume of abdominal fluid for clinical reasons should be avoided unless it is absolutely necessary because this often causes a precipitous decrease in serum protein concentrations in animals with liver disease because of the inability of the liver to replace proteins removed in the fluid. It is preferable in cases other than peritonitis to remove fluid gradually, using diuretics. In cases in which large-volume fluid removal is necessary (e.g., in peritonitis), concurrent administration of fresh-frozen plasma or a colloid solution is essential to replace protein lost. In dogs with chronic hepatic failure and sustained intrahepatic portal hypertension, abdominal fluid is usually a modified transudate with a moderate nucleated cell count and protein content (Table 34.4). A pure transudate with a low cell count (<2500 cells/µL) and protein concentration (<2.5 g/dL), and a clear, minimally colored appearance, are noted when the dog is hypoproteinemic. Abdominal fluid in dogs with intrahepatic postsinusoidal venous obstruction (e.g., venoocclusive disease) or posthepatic venous obstruction (e.g., any cause of right-sided heart failure) can be any color but is typically red- or yellow-tinged and is classified as a modified transudate. Feline infectious peritonitis fluid and neoplastic effusions are also commonly classified as modified transudates or nonseptic exudates. Bile peritonitis also results in an exudate, which is initially sterile but can become septic with time. Measuring bilirubin concentration in the fluid helps with diagnosis. With neoplasia, effusions can occasionally be chylous or even hemorrhagic, and the latter can also be seen in amyloidosis as a result of rupture of the liver capsule. Reactive mesothelial cells can be

TABLE 34.4

Characteristics of Abdominal Effusion in Hepatobiliary Disease

TYPE OF EFFUSION	APPEARANCE	NUCLEATED CELL COUNT	PROTEIN CONTENT	SPECIFIC GRAVITY	EXAMPLE(S)
Transudate					
Pure	Clear, colorless	<1500/µL	<2.5 g/dL	<1.016	Chronic hepatic failure with marked hypoalbuminemia
Modified	Serosanguineous, amber	<7000/µL	≥2.5 g/dL	1.010-1.031	Chronic hepatic failure, right-sided heart failure, pericardial disease, caval syndrome, Budd-Chiari–like syndrome, intrahepatic portal vein hypoplasia, chronic portal vein thrombosis, feline infectious peritonitis (some cases), neoplasia (some cases), pancreatitis (some cases)
Exudate					
Septic	Cloudy; red, dark yellow, green	>7000/µL	≥2.5 g/dL	1.020-1.031	Perforated duodenal ulcer, bile peritonitis (fluid bilirubin concentration > serum bilirubin concentration)
Nonseptic	Clear; red, dark yellow, green	>7000/µL	≥2.5 g/dL	1.017-1.031	Feline infectious peritonitis, neoplasia with serosal involvement, ruptured hemangiosarcoma, early bile peritonitis, pancreatitis with EBDO
Effusion					
Chylous	Opaque, white to pink ("strawberry milkshake")	Variable; usually 1000-10,000/µL	Variable; 2.5-6.5 g/dL	1.030-1.032	Neoplasia (some cases), diseases obstructing lymphatic drainage
Hemorrhagic	Red	Variable; usually 1500 to 1000/µL	Usually >3.0 g/dL	<1.013	Neoplasia (some cases), amyloidosis with hepatic capsule rupture, ruptured hemangiosarcoma

EBDO, Extrahepatic bile duct obstruction.

mistaken for neoplastic cells, emphasizing the need for experience in evaluating cytologic specimens. Exudates have a high cell count (>20,000 cells/µL) and protein content (>2.5 g/dL) and, on the basis of whether the inflammatory cells look toxic or contain ingested bacteria, are further classified as septic or nonseptic. Fluid analysis provides additional clues to the origin of the hepatobiliary disease and must not be overlooked. A guide to interpreting fluid analysis results is given in Table 34.4.

Abdominal effusions are common in dogs and cats with pancreatitis but are usually of small volume. Effusions form as a result of peritonitis but also vasculitis, which may explain why some animals with pancreatitis have pleural as well as peritoneal fluid. The effusions are usually serosanguineous exudates, although modified transudates and chylous effusions have been reported, particularly in cats. Lipase, amylase, and PLI concentrations may be elevated in the fluid and may be much higher than the serum, helping the diagnosis of pancreatitis. Importantly, measuring pancreatic enzymes in the fluid helps differentiate the cause of a sterile exudate from the other possibilities of bile peritonitis or urinary tract leakage.

URINALYSIS

In pancreatitis, urinalysis is important to differentiate prerenal from intrinsic renal disease, so ideally a urine sample should be taken before fluid therapy. A high urine specific gravity (SG) with azotaemia suggests acute prerenal failure due to dehydration and shock. However, dogs with severe

pancreatitis often have poorly concentrated or even isosthenuric urine, suggesting concurrent intrinsic renal damage. Proteinuria is reported in up to 78% of dogs with acute pancreatitis (Hess et al., 1998), probably due to a combination of systemic inflammation and tubular damage. In English Cocker Spaniels with chronic and acute-on-chronic pancreatitis, glomerulonephritis is often also recognized as part of a polysystemic immune-mediated disease targeting ducts, and affected dogs should be screened for proteinuria. Finding glucose in the urine in a dog or cat with pancreatitis will raise the suspicion of diabetes mellitus. Glucosuria can be transient during a bout of pancreatitis, presumably due to insulin resistance and stress. This is rare in dogs but anecdotally more common in cats. Diabetes mellitus can be differentiated from stress by concurrent measurement of serum fructosamine, assessment of the urine for ketones and careful monitoring of blood and urine glucose during recovery. The presence of ketones, in addition to glucosuria, in the urine in both dogs and cats with pancreatitis usually indicates diabetic ketoacidosis, which requires immediate and urgent treatment. Ketonuria is occasionally seen in dogs and cats with negative calorie balance that have depleted their hepatic glycogen reserves, but concurrent glucosuria would be very unusual in these circumstances as these animals are usually hypoglycemic.

Common findings in urinalysis consistent with hepatobiliary disease include excessive bilirubinuria in a nonanemic dog (≥2+ in urine of SG ≤1.025), presence of bilirubin in the urine of cats, and ammonium biurate crystalluria in properly processed urine specimens (Fig. 34.1). In dogs, excessive bilirubinuria may precede the onset of hyperbilirubinemia and jaundice. Small numbers of bilirubin crystals may be found in concentrated urine specimens from normal dogs, and ammonium biurate crystals are also occasionally found in normal animals and in Dalmatian dogs with a defect in urate metabolism (see Chapter 43). Therefore these are not pathognomonic for PSS. Hyperammonemia combined with excess uric acidemia from diminished hepatic conversion to allantoin exceeds the renal threshold and favors the precipitation of crystals, especially in alkaline urine. Their presence in the urine may fluctuate, but alkalinizing the urine specimen with a few drops of sodium or potassium hydroxide may increase the likelihood of identifying ammonium biurate crystals during sediment examination.

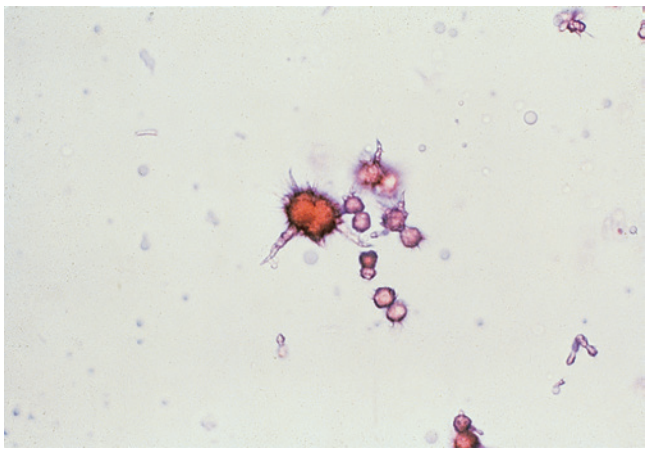


FIG 34.1
Ammonium biurate crystals in the urine of a dog with a congenital portosystemic shunt.

Measurement of urinary urobilinogen by dipstick analysis has traditionally been used to assess the patency of the extrahepatic biliary system. However, the test is now considered to be of minimal value in diagnosing EBDO because so many factors influence the detection of urobilinogen in the urine (e.g., intestinal flora and transit time, renal function, urine pH and specific gravity, exposure of the urine specimen to light). If urine samples are obtained serially and processed properly, repeated absence of urobilinogen suggests but is not diagnostic of complete EBDO.

Consistently dilute urine (SG as low as 1.005) may be a feature of congenital and acquired PSS and severe hepatocellular diseases because of the associated polydipsia and polyuria (see Chapter 33). Urine SG must also be interpreted in light of concurrent drug therapy, such as administration of diuretics, corticosteroids, or anticonvulsants.

Glucosuria in the absence of a significantly increased blood glucose concentration might increase the index of suspicion of hepatic leptospirosis, particularly if there is concurrent azotemia.

FECAL EVALUATION

Fecal specimen analysis rarely provides useful information in the evaluation of a dog or cat with suspected hepatobiliary disease, except for a change in appearance associated with two specific conditions. Absence of fecal pigment (acholic feces; see Fig. 33.10) and steatorrhea are consequences of chronic, complete EBDO, and dark, orange-colored feces reflect increased bilirubin production and excretion after marked hemolysis or rhabdomyolysis. It should also be noted that GI ulceration is a serious and important complication of portal hypertension, particularly in dogs (see Chapter 33), so the clinician should always be alert to the development of melena in a dog with chronic liver disease.

In pancreatitis, it is not uncommon to see some diarrhea and often with signs of colitis with some mucus and fresh blood because the inflamed left limb of the pancreas is adjacent to the transverse colon. Fat malabsorption as a result of exocrine insufficiency produces steatorrhea with yellow, smelly, voluminous feces.

DIAGNOSTIC IMAGING

SURVEY RADIOGRAPHY

In hepatobiliary disease, radiographic evaluation of the abdomen is used to complement physical examination findings and to confirm suspicions regarding the character and location of the hepatobiliary disease suggested by the clinicopathologic examination findings. Survey radiographs provide subjective information regarding the size and shape

of the liver (see Table 33.1). Optimally, the animal should have an empty GI tract when the radiographs are obtained. In the normal dog and cat in right lateral recumbency, the gastric axis is parallel to the ribs at the 10th intercostal space, and the caudoventral border of the liver (the left lateral liver lobe) appears sharp. The image is made possible by the contrasting fat-filled falciform ligament (Fig. 34.2). In dog breeds with narrow, deep chests, the entire liver shadow may be contained within the caudal rib cage. In dogs with a wide, shallow thoracic conformation, the liver may extend slightly beyond the costal arch. In the ventrodorsal view, the borders of the liver are defined by the cranial duodenum and the gastric fundus; in this view, the gastric shadow is perpendicular to the spine. This view is less useful for assessing liver size unless it is markedly and asymmetrically enlarged. The gallbladder and extrahepatic biliary tree are not separately visible radiographically in healthy animals.

Survey radiography is of minimal to no benefit if there is moderate to marked abdominal effusion because the similar radiographic opacities of the liver and fluid preclude distinction of liver size and shape, except by indirect assessment (e.g., malposition of a gas-filled stomach and duodenum; Fig. 34.3). However, because abdominal fluid increases ultrasonographic contrast, this is the imaging modality of choice in animals with ascites. Poor abdominal detail in emaciated or very young animals lacking abdominal fat stores also makes the detection of subtle hepatic changes difficult.

In cats and dogs with generalized hepatomegaly, the liver extends beyond the costal arch; it causes displacement of the gastric axis and pylorus caudally and dorsally in the lateral projection, and shifting of the gastric shadow caudally and to the left in the ventrodorsal view (see Fig. 34.2). In addition, the edges of the liver in the lateral view may appear rounded (see Fig. 34.2). Occasionally, the spleen and liver cannot be differentiated when they are in direct contact, as seen in the right lateral view. A ventrodorsal view would help determine the size, shape, and position of each organ. Increased intrathoracic volume associated with deep inspiration, severe pleural effusion, or overinflation of the lungs

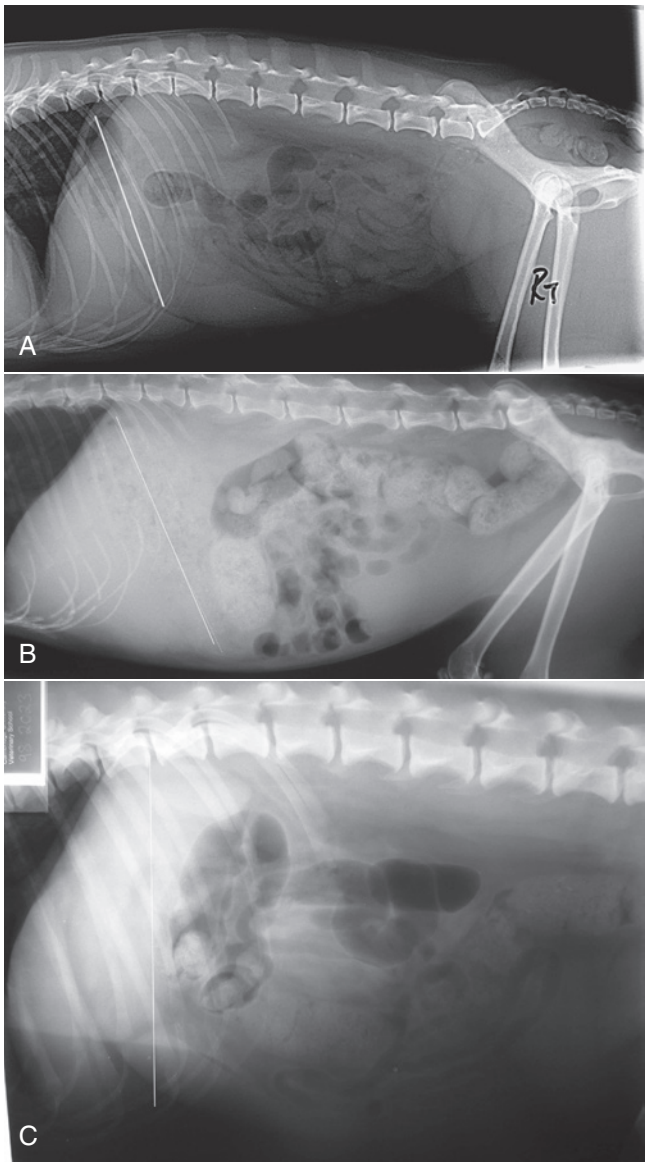


FIG 34.2
Lateral abdominal radiographs demonstrating gastric axis *(white line)* as an indication of liver size. **(A)** Lateral abdominal radiograph of a normal cat with normal liver size. **(B)** Lateral abdominal radiograph of a cat with diffuse hepatic amyloidosis demonstrating hepatomegaly and caudal displacement of the gastric axis. **(C)** Lateral abdominal radiograph of a middle-aged English Springer Spaniel with cirrhosis demonstrating microhepatica and cranial displacement of the gastric axis. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

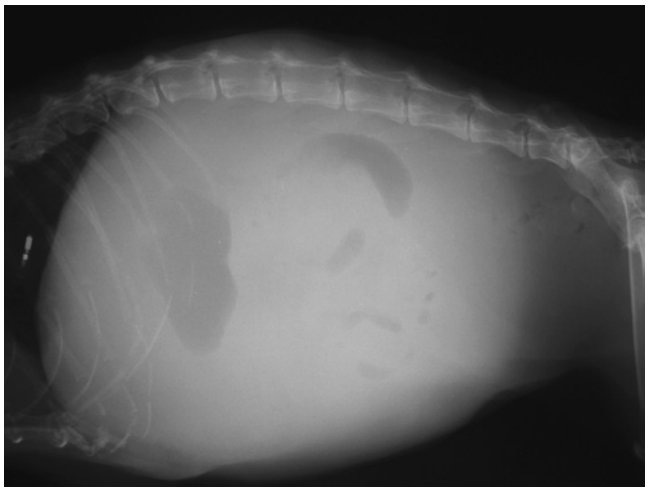


FIG 34.3
Lateral abdominal radiograph of an 8-year-old Bearded Collie with chronic hepatitis, portal hypertension, and ascites demonstrating the loss of abdominal detail associated with free abdominal fluid, which renders radiography unhelpful. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

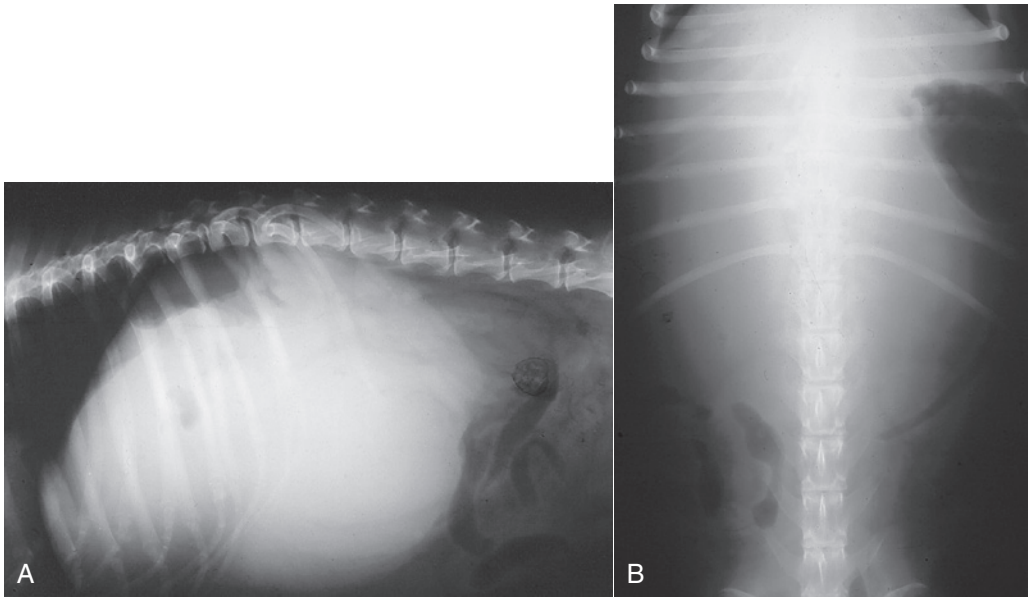


FIG 34.4
Lateral **(A)** and ventrodorsal **(B)** abdominal radiographs of a 9-year-old spayed female mixed-breed dog with a hepatocellular carcinoma enlarging the right lateral liver lobe. The dog was also severely hypoglycemic.

may result in caudal displacement of the liver, giving the erroneous impression of hepatomegaly using other radiographic criteria.

Because the liver may be contained entirely within the rib cage in normal cats and dogs, microhepatia is more difficult to recognize than hepatomegaly. Changes in the angle of the gastric fundus in the right lateral projection (see Fig. 34.2) could indicate a small hepatic shadow if the angle is more upright or perpendicular to the spine, especially if the stomach seems rather close to the diaphragm. The liver may also seem small in animals with traumatic diaphragmatic hernia and herniation of liver lobes into the thorax or in those with congenital peritoneopericardial hernia.

Focal hepatic enlargement is indicated by the displacement of organs adjacent to the affected lobe. The most common radiographically detectable focal hepatic enlargement is that of the right lateral lobe (Fig. 34.4). In this case, the body and pyloric regions of the stomach are shifted dorsally (lateral view) and to the patient's left (ventrodorsal view); the gastric fundus remains in normal position. Shifting of the stomach to the left is normal in cats and should not be mistaken for right hepatomegaly. If the left lateral lobe or lobes are enlarged, the gastric fundus moves to the left and caudally; the lesser curvature of the stomach may appear indented. Primary or metastatic neoplasia, hyperplastic or regenerative nodules, and cysts usually account for focal hepatic enlargement or for irregular liver margins without enlargement. If the gallbladder is massively enlarged because of EBDO, it may mimic a right cranial abdominal mass or an enlarged, rounded liver lobe. Changes in hepatic radiographic opacity are rare and are usually associated with hepatic or biliary tract infection caused by gas-forming bacteria (patchy and/or linear areas of decreased opacity) or mineralization (focal or diffuse spots of mineralization or mineralized bile ducts or biliary calculi; Fig. 34.5).

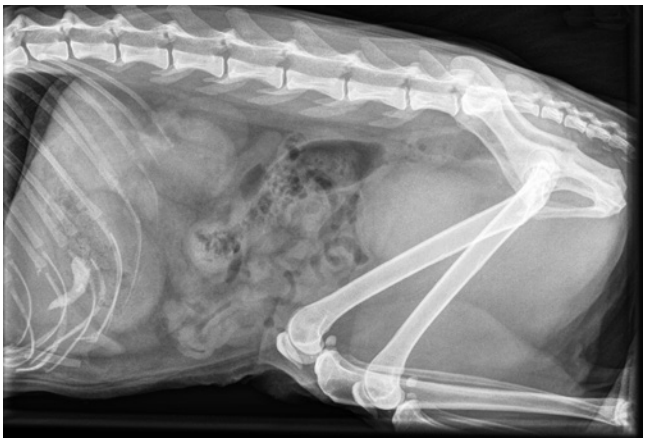


FIG 34.5
Lateral abdominal radiograph of a 12-year-old neutered male domestic short-haired cat with chronic cholangitis, cholecystitis, and pancreatitis. Note the radiodensity overlying the liver shadow, which was identified at surgery as a gallstone in the common bile duct. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

With the advent of US and computed tomography (CT), contrast radiographic procedures are seldom needed to confirm the presence of hepatic masses, cholelithiasis, EBDO, congenital PSS, and other structural diseases. The contrast study that can localize congenital PSS and is achievable in private practice is portal venography, although CT

angiography is the preferred method to diagnose PSS when available. Acceptable approaches for portal venography are splenoportography, operative mesenteric portography, and operative splenoportography. The two operative procedures require general anesthesia and a small abdominal incision; however, little sophisticated equipment is needed, and these procedures are associated with few complications.

A 22-gauge catheter is placed in the splenic vein or a mesenteric vein (Fig. 34.6), and the resting portal venous pressure is measured with a water manometer (normal = 6-13 cm H_2O). Portal pressure is measured as soon as possible in the procedure because prolonged anesthesia may complicate its interpretation. An injection of iodine-based contrast medium, 0.5 to 1 mL/kg, is then quickly made. Lateral and possibly ventrodorsal and oblique radiographs are made at the end of the injection. Contrast medium given to a normal cat or dog should flow into the portal vein, enter the liver, and branch multiple times, opacifying the extrahepatic and intrahepatic portal vasculature. Diversion of the contrast medium into the systemic circulation indicates PSS (Fig. 34.7). Measurement of portal pressure and a liver biopsy can be performed during the operative techniques; they are required to distinguish acquired PSS from congenital PSS, which is essential to rendering an accurate prognosis and developing the correct treatment plan. As a general rule, cases of congenital PSS are usually single, whereas acquired PSS are multiple, so the mesenteric portography may suggest a diagnosis. It may be necessary to repeat the contrast study after congenital PSS ligation if there is concern about the adequacy of the intrahepatic portal vasculature. In addition, it has been shown that the degree of intrahepatic portal vessel opacification on postligation portography is predictive for outcome (Lee et al., 2006).

Abdominal radiographs in patients with pancreatitis usually show mild or no changes, even in those with severe disease (Fig. 34.8). However, in patients with acute disease, abdominal radiography plays an important role in ruling out acute intestinal obstruction, which would result in obvious changes, primarily dilated, gas-filled, stacking loops of intestine and the presence of radiopaque foreign bodies. Typical radiographic changes in dogs and cats with acute pancreatitis include a focal decrease in contrast in the cranial abdomen associated with local peritonitis; a dilated, fixed (C-shaped),

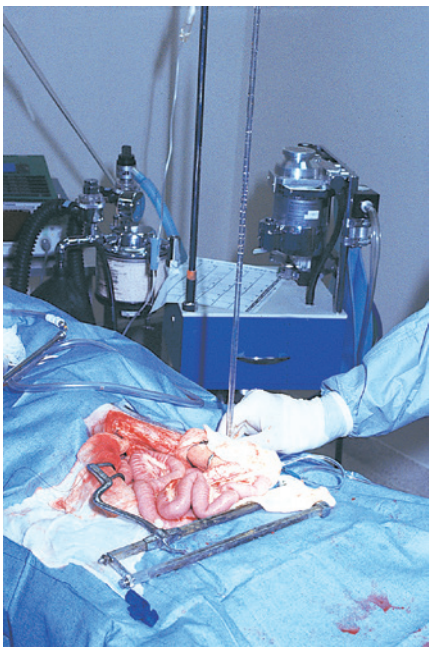


FIG 34.6
A 22-gauge intravenous catheter attached to an extension set, three-way stopcock, and water manometer has been placed in a mesenteric vein in preparation for intraoperative measurement of resting portal pressure. The catheter may also be secured in place and used for operative portal venography.

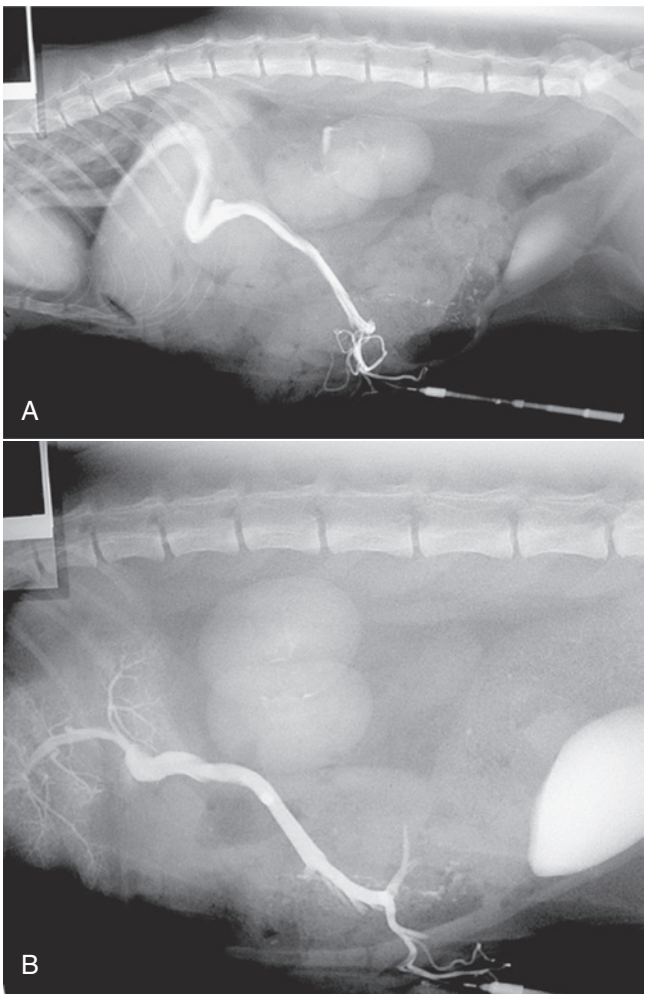


FIG 34.7
Operative mesenteric portal venography in a young domestic short-haired cat before **(A)** and after **(B)** surgical correction of a congenital portosystemic shunt. Note improvement in hepatic portal blood flow in **(B)** with arborization of the contrast material within the small portal vessels in the liver. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

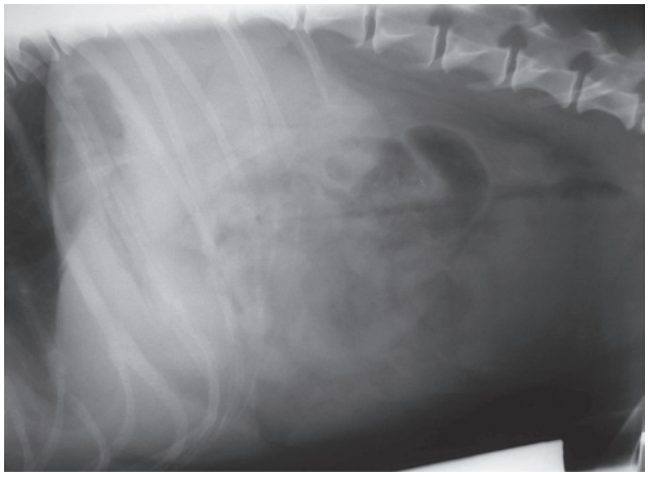


FIG 34.8
Lateral abdominal radiograph from a 7-year-old Jack Russell Terrier with acute pancreatitis. There are minimal changes apparent apart from a mild loss of abdominal contrast, in spite of the severity of the disease. This does, however, help rule out acute obstruction because the intestinal loops are not dilated and gas-filled. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

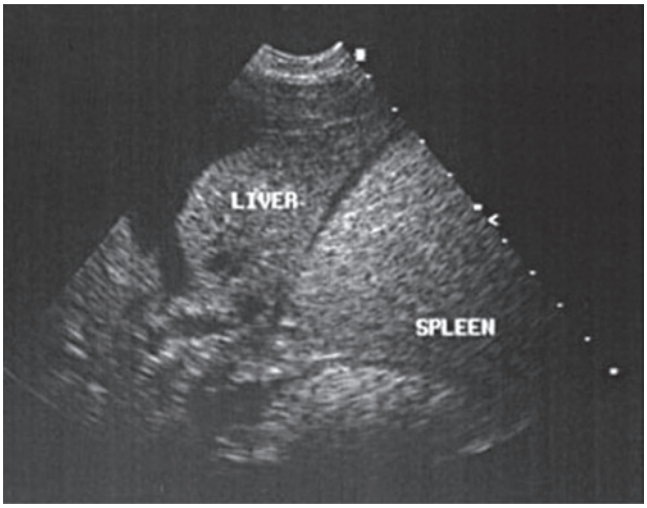


FIG 34.9
Abdominal ultrasound is enhanced by the presence of ascites. Shown is an ultrasound of the abdomen of a dog with chronic hepatitis and ascites. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

and laterally displaced proximal duodenum on ventrodorsal views; and caudal displacement of the transverse colon. Occasionally, a mass effect may be seen in the region of the pancreas, usually the result of fat necrosis. Pancreatic tumors by contrast are usually small, but it is impossible to differentiate fat necrosis from neoplasia using imaging alone. Abdominal radiographs appear normal in many dogs and cats with acute or chronic pancreatitis. Barium studies should be avoided, if possible, because they do not contribute to diagnosis.

ULTRASONOGRAPHY

Abdominal US is the preferred diagnostic modality for evaluating the hepatobiliary system in dogs and cats. However, it is important to realize that it has limited sensitivity and specificity for liver disease. Operating on the principle that a pulse of sound (echo) can be reflected when it passes through the interface between two different materials, US can detect differences between homogeneous liquids of low echogenicity, such as blood and bile, and more heterogeneous echogenic structures made up of several soft tissues. Whereas abdominal effusion obscures abdominal detail on survey radiography, it enhances the ability of US to detect abnormalities (Fig. 34.9). However, bone and gas-filled organs reflect the sound beam completely (acoustic shadowing), so that structures beneath cannot be imaged by US. The procedure does not require anesthesia but the patient must be still, and good contact between the transducer and abdominal skin must be ensured by clipping the haircoat and applying acoustic coupling gel. Animals are usually positioned in dorsal or lateral recumbency. The hepatic parenchyma, gallbladder, large hepatic and portal veins, and adjacent caudal vena cava are all visible in the liver of the normal cat and dog. Unlike plain radiography, which requires two views to complete the study, US makes many slices through several planes to create a three-dimensional reconstruction of the target structures.

Performing US and interpreting the recorded images are a blend of technical skill and experience. It is important to note that the sensitivity of US in hepatic disease is not 100%. In a recent study, the liver appeared ultrasonographically abnormal in only 48% of dogs with histologically confirmed chronic hepatitis and in only 68% of dogs with hepatic lymphoma. Therefore a normal ultrasonographic appearance certainly does not rule out hepatic disease or neoplasia (Warren-Smith et al., 2012). It is also important to remember that US does not diagnose what the lesions are (i.e., it cannot yield a histologic diagnosis). With a few exceptions, which predominantly involve lesions of the biliary tract and vessels, the ultrasonographic appearance of a variety of benign and malignant hepatic lesions can appear similar and histology of a liver biopsy is usually required for diagnosis. An animal should never be euthanized on the basis of an ultrasonographically identified tumor without histologic confirmation because benign nodular hyperplasia or focal inflammatory lesions can look the same. Table 34.5 outlines the typical appearances of different hepatic lesions on US.

Neoplasia may appear as hyperechoic or hypoechoic and focal, diffuse, or normal liver. Hepatic lymphoma often appears diffusely hypoechoic but can also appear hyperechoic or normal. Some tumors, such as metastatic hemangiosarcomas, have a classically nodular hypoechoic appearance (Fig. 34.10) and may appear as target lesions, which are relatively

TABLE 34.5

Ultrasonographic Findings in Dogs and Cats With Hepatobiliary Disease

FINDING	POSSIBLE INTERPRETATIONS
Parenchyma	
Anechogenicity	
Focal	Cyst(s)—may be singular or multiple with septae; thin-walled Abscess(es)—may be poorly demarcated and have a heterogeneous echo pattern Hematoma(s)—appearance depends on maturity Lymphoma—may look like cyst if solitary
Hypoechogenicity	
Focal	Focal or multifocal neoplasia Regenerative nodule formation Extramedullary hematopoiesis Normal liver surrounded by hyperechoic liver Hematoma(s)
Diffuse	Abscess(es) or granuloma(s) Neoplastic or inflammatory cell infiltrates (hepatitis) Passive congestion Hepatocellular necrosis Amyloid Extramedullary hematopoiesis
Hyperechogenicity	
Focal	Focal or multifocal neoplasia Nodular hyperplasia Mineralization (creates shadowing artifact) Fibrosis Gas (creates reverberation artifact) Hematoma or abscess
Diffuse	Fatty infiltration (attenuates the sound beam) Lymphoma Fibrosis Neoplastic or inflammatory cell infiltrates (hepatitis) Hepatocellular necrosis Steroid hepatopathy (dogs only)
Tubular Structures—Biliary Tract	
Dilated intrahepatic and extrahepatic bile ducts	Extrahepatic bile duct obstruction; persistent or recently relieved Some cases cholangitis syndrome (cats) Choledochal cyst (rare)
Distended gallbladder	Normal (prolonged fasting)
Distended gallbladder and cystic duct	Cystic duct obstruction
Distended gallbladder and common bile duct	Extrahepatic bile duct obstruction; persistent or recently relieved
Focal areas of gravity-dependent hyperechogenicity within biliary tract or gallbladder that cause acoustic shadowing	Cholelithiasis
Focal areas of hyperechogenicity within gallbladder that settle to dependent portion of gallbladder when animal's position changes	"Sludged" or inspissated bile from severe cholestasis, prolonged anorexia, and dehydration
Stellate or "kiwi fruit" appearance to gallbladder	Gallbladder mucocele
Intraluminal echoic masses in gallbladder	Neoplasia (polyp, malignant neoplasm) Adherent inspissated bile

TABLE 34.5

Ultrasonographic Findings in Dogs and Cats With Hepatobiliary Disease—cont'd

FINDING	POSSIBLE INTERPRETATIONS
Apparent thickened gallbladder wall	Cystic hyperplasia (focal) Cholecystitis, cholangitis Infectious canine hepatitis Hypoalbuminemia with edema formation Abdominal effusion Neoplasia
Tubular Structures—Blood Vessels	
Dilated hepatic veins and portal veins	Right-sided congestive heart failure Pericardial disease Intrathoracic caudal vena cava occlusion Hepatic vein occlusion (Budd-Chiari syndrome)
Prominent hepatic arteries	Reduced portal blood flow
Distended portal vein with reduced velocity and flow with or without hepatofugal flow	Portal hypertension of any cause (by Doppler)
Inapparent hepatic vessels	Cirrhosis Severe fatty infiltration
Inapparent portal veins	Congenital portosystemic shunt Portal vein thrombus Intrahepatic portal vein hypoplasia
Aberrant vessel that communicates with systemic circulation	Intrahepatic or extrahepatic congenital portosystemic shunt
Connection between a portal vein and an artery within one or more liver lobes	Arterioportal venous fistula
Many tortuous veins clustered around left kidney and along colon	Acquired portosystemic shunts associated with portal hypertension

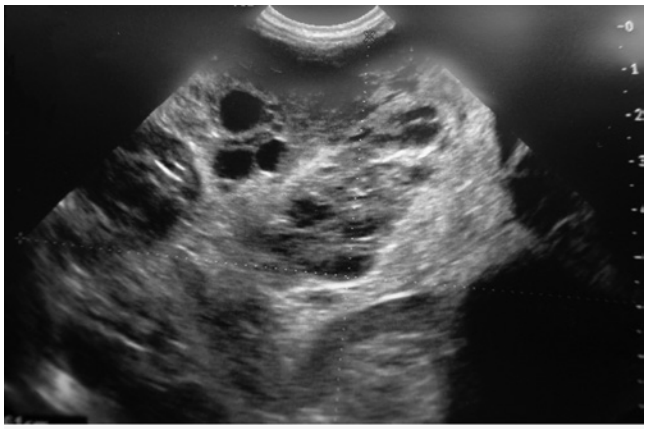


FIG 34.10
Ultrasonographic appearance of a hepatic hemangiosarcoma in a dog. Note the multiple hypoechoic nodules. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

specific for neoplasia, but even hemangiosarcomas may be missed on US in 15% of cases. Contrast-enhanced US has been used to improve visualization of small hepatic metastases in dogs. Marolf (2017) has reviewed this and other advanced imaging modalities in liver disease. Typically, hepatic lipidosis in cats causes an increase in echogenicity and so do steroid hepatopathy, diffuse hepatic steatosis, and diffuse fibrosis (e.g., cirrhosis) in dogs. However, a cirrhotic liver may also appear normal ultrasonographically.

Dilated anechoic (black) vascular channels and echoic bile ducts can be identified; biliary tract imaging is particularly useful in cats with suspected biliary tract disease (Fig. 34.11) or dogs and cats with suspected EBDO. The bile duct can be followed ultrasonographically along its course toward the small intestine, and lesions in the pancreas or duodenum obstructing it can be identified. A dilated gallbladder may indicate prolonged anorexia, unless dilated bile ducts, particularly the common bile duct, are also seen, which supports EBDO or chronic cholangitis/cholangiohepatitis in cats (see Fig. 34.11). The bile ducts and gallbladder can also appear normal in cats with acute or chronic cholangitis.

Intrahepatic or extrahepatic anomalous vessels may also be identified in animals with clinicopathologic evidence of

congenital or acquired PSS (Fig. 34.12). Congenital PSS are typically single vessels, whereas acquired PSS are usually multiple. Use of Doppler color flow imaging confirms the location of the suspicious vessel(s) and the direction of blood flow within it. Doppler imaging can also provide supportive evidence of intrahepatic portal hypertension by allowing the assessment of the speed and direction of portal flow, although the accuracy of transhepatic ultrasonographic measurement of portal pressure is low compared with direct measurement with a manometer in the portal vein. Portal blood flow toward the liver (hepatopetal) is normal; away from the liver (hepatofugal) is abnormal and indicates portal hypertension. It is also possible to investigate liver shunting with US using a microbubble technique to demonstrate the passage of bubbles in agitated saline injected in the spleen beyond the sinusoids of the liver in dogs with PSS (Gómez-Ochoa et al., 2011).

Whether the lesion is determined to be focal or diffuse, US can also be used as a guide to obtain diagnostic specimens for cytologic or histopathologic evaluation. However, with the exception of gallbladder aspiration for the diagnosis of suppurative cholangitis in cats and dogs, US-guided fine-needle and Tru-Cut biopsies have potentially serious limitations (see later section, "Liver Biopsy").

In humans, an adapted US machine (Fibroscan) is used to assess the degree of hepatic fibrosis in chronic liver disease by a technique called transient elastography. It works on the principle that the echo reflected from the plane of liver through which the US beam passes will vary, depending on the amount of fibrosis present. The manufacturer's machine settings are critical for accurate readings and are optimized for human patients. However, the results of a pilot study in dogs were promising (Rivero-Juárez et al., 2012), and this technology may become more widely available for veterinarians in the future.

US is a relatively specific method of diagnosing pancreatitis in dogs. Locating the pancreas can be a challenge and ultrasound is only sensitive in the hands of an experienced operator. Pancreatitis is ultrasonographically visible because of the associated edema, pancreatic swelling, and peripancreatic fat necrosis and peritonitis (Fig. 37.5). It therefore

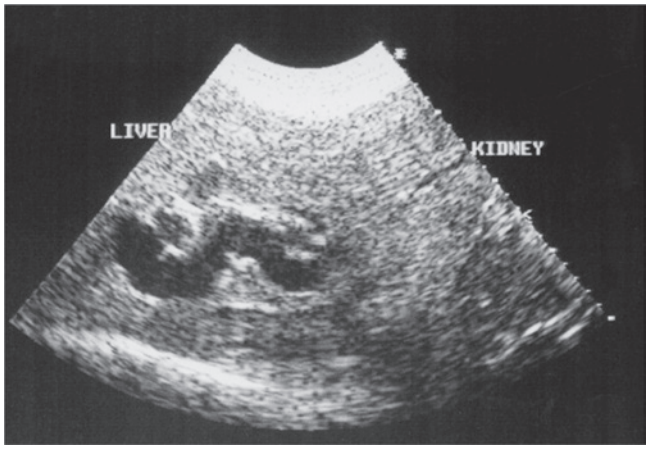


FIG 34.11
Ultrasonographic appearance of dilated biliary tract in a cat with chronic cholangitis. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

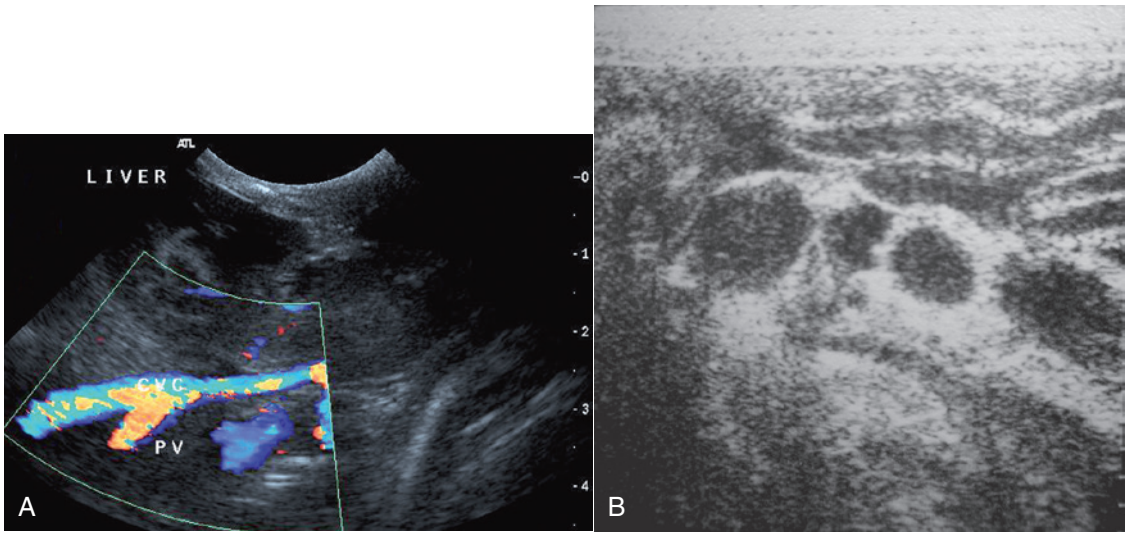


FIG 34.12
(A) Doppler ultrasonographic findings of a congenital extrahepatic portocaval shunt in a young English Springer Spaniel. **(B)** Ultrasonographic appearance of multiple extrahepatic acquired portosystemic shunts in a 6-year-old German Shepherd with noncirrhotic portal hypertension. *CVC,* Caudal vena cava; *PV,* portal vein. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

follows that acute cases of pancreatitis, which classically show these features, are more often visible ultrasonographically than low grade, chronic forms with little edema. US is also useful to assess for concurrent pancreatic masses, abscesses, or pseudocysts and to detect associated cholangitis and small intestinal wall thickening. An animal with acute pancreatitis usually shows a characteristically focal area of pain as the ultrasound probe is positioned over the pancreas.

COMPUTED TOMOGRAPHY

CT is increasingly available in veterinary medicine and can be used to image a variety of hepatic diseases and masses. It is most commonly indicated in imaging PSS and has now largely replaced contrast radiography in identifying PSS and giving detailed anatomic information (Nelson and Nelson, 2011). CT requires a general anesthetic but is less invasive than contrast radiography. US can be performed under sedation and is less expensive than CT. Therefore, if a shunt can be accurately identified with plain or bubble US, a CT is not necessarily indicated. However, with complex shunts of unclear anatomy on US, CT can provide invaluable information before surgery (Fig. 34.13).

Abdominal CT has so far proved largely disappointing for the diagnosis of pancreatitis in dogs and cats, although a recent study suggested it might be more reliable than ultrasound, particularly to allow visualization of the entire pancreas and for diagnosis of associated portal vein thrombosis.



FIG 34.13
CT angiogram with three-dimensional mapping of a 2-year-old neutered female Border Terrier with a congenital portosystemic shunt of unusual anatomy. The shunting vessel can be seen leaving the left gastric vein cranial to the kidney and then coursing cranially in a tortuous path over the liver, finally entering the caudal vena cava just caudal to the diaphragm. (Courtesy Dr. Paddy Mannion, Cambridge Radiology Referrals, Cambridge, England.)

With acute pancreatitis, dogs had an enlarged, homogenously to heterogeneously attenuating and contrast-enhancing pancreas with ill-defined borders, as has been reported in humans (Adrian et al., 2015).

MAGNETIC RESONANCE IMAGING

MRI is used frequently in human medicine for imaging of the biliary tract and pancreatic ducts. MR cholangiopancreatography allows accurate imaging of duct abnormalities without any need for contrast. There are no reports yet of its clinical use in dogs and cats, but a recent study in normal cats showed promise for future clinical use (Marolf et al., 2011; Marolf 2017).

SCINTIGRAPHY

Scintigraphy is used in hepatobiliary disease in cats and dogs most frequently to diagnose PSS. The isotope selected is technetium-99m (^{99m}Tc). The isotope has a short half-life (6 hours); thus although the animal must be relatively isolated for 24 to 48 hours, and urinary and fecal waste stored until radioactivity has fallen to background levels, there is minimal radiation hazard to the animal or involved personnel. For diagnosis of PSS in dogs, after placement of ^{99m}Tc-pertechnetate into the descending colon, the vascular path taken by the isotope after absorption is plotted. Time-activity curves determine whether the isotope arrived in the liver first, which is normal, or in the heart and lungs, which is compatible with any type of portal venous bypass of the liver. This approach has the advantage of specifically evaluating the portal blood supply rather than the hepatic mass, which may or may not be reduced in animals with congenital PSS or primary hepatobiliary disease and acquired PSS. The test results do not provide anatomic detail but only evidence of the presence or absence of congenital or acquired portosystemic shunting and is largely being replaced by CT angiography, which provides more precise anatomic information.

BIOPSY AND CYTOLOGY

LIVER CYTOLOGY

Fine-needle aspiration of the liver for cytologic analysis is rarely advisable because of low diagnostic yield and often misleading results. The exceptions to this are aspirating bile for culture and cytology, and for quick diagnosis of hepatic lipidosis in cats and aspiration for suspected neoplasia (Fig. 34.14). One study showed that cytology had a high positive predictive value for hepatic neoplasia (round cell tumors and carcinoma) but a low positive predictive value for inflammatory disease (Bahr et al., 2013). In addition, a negative result on cytology should not exclude neoplasia because the same study showed that only 50% of patients with a histologic diagnosis of neoplasia had a positive cytology. An overall correlation of only 30% in dogs and 51% in cats was found in another study comparing the cytologic diagnosis with the histopathologic diagnosis of a variety of liver diseases (Wang et al., 2004).



FIG 34.14
A 4-year-old spayed female domestic short-haired cat with suspected hepatic lipidosis positioned in right lateral recumbency for blind, fine-needle aspiration for cytology. With care taken to avoid the spleen, the needle is directed craniomedially into the liver.

LIVER BIOPSY: INDICATIONS

For most primary hepatobiliary diseases of cats and dogs, a hepatic biopsy is needed to establish a final diagnosis and prognosis, and to guide treatment. It is usually impossible to make a definitive diagnosis and reach a logical decision about management without a liver biopsy. Without a biopsy, therapy of liver disease in dogs and cats will be at best nonspecific, and at worst dangerous and counterproductive. Therefore some type of biopsy should be obtained wherever possible, and certainly steroid, copper-chelating, and antifibrotic therapies should not be used without biopsy confirmation of disease and stage. Biopsy is indicated to do the following: (1) explain abnormal results of hepatic status and/or function tests, especially if they persist for longer than 1 month; (2) explain hepatomegaly of unknown cause; (3) determine hepatic involvement in systemic illness (although biopsy is not always necessary for this); (4) stage neoplastic disease; (5) objectively assess response to therapy; or (6) evaluate progress of previously diagnosed, not specifically treatable disease. It is much easier to justify a liver biopsy clinically for the diagnosis of disease (indications 1-4) than for assessing response to therapy (objectives 5 and 6). A liver biopsy is an invasive procedure and should only be performed if it is in the best interests of the patient—that is, will affect treatment or prognosis. Sequential biopsies to assess response to treatment are of limited usefulness unless the treatment will be altered on the basis of the results. In addition, sampling artifact is often observed in biopsies of diffuse liver disease; small biopsies tend to yield differing results, even if taken at the same time, because of the small sample size and patchy nature of the pathology. This makes the results of sequential liver biopsies difficult to interpret. Are they different because the disease has progressed or simply because they sampled a different part of the liver? Several approaches for liver biopsy are available, and the choice is dictated by patient and operator considerations (Box 34.4). In addition, in most cases of hepatic disease, the accuracy of histologic diagnosis is better with larger (surgical or laparoscopic wedge) rather than smaller (needle) biopsies.

BOX 34.4

Patient and Operator Considerations for Hepatic Biopsy

Patient

1. Characteristics of the suspected hepatobiliary disorder—liver size (small, normal, enlarged); texture (fibrotic or friable); focal, multifocal, or diffuse distribution; presence of abdominal effusion
2. Clinical stability and suitability for anesthesia
3. Coagulation status and platelet count

Operator

1. Available equipment
2. Experience with chosen technique
3. Complication rate for chosen technique
4. Size of specimen needed
5. Access to reliable veterinary pathology laboratory
6. Cost of procedure and client finances
7. Predicted accuracy of results

LIVER BIOPSY: TECHNIQUES

All cats and dogs undergoing hepatic biopsy are fasted for at least 12 hours, regardless of the approach selected.

In an especially small and/or firm fibrotic liver, it is difficult to obtain a biopsy specimen by percutaneous needle methods; small, fragmented specimens that are challenging to interpret are often the result (Fig. 34.15). There is less than a 40% correlation between 18-gauge needle biopsy and wedge biopsy for certain hepatobiliary diseases (e.g., chronic hepatitis or cirrhosis, cholangitis, portovascular anomaly, fibrosis). If a needle technique is selected, the largest available instrument is used (preferably, 14 gauge; minimum, 16 gauge) and multiple samples are taken to ensure that there are enough samples for examination. Pathologists suggest that at least six portal triads should be examined to allow an accurate diagnosis, and in humans up to 12 to 15 triads are recommended. However, needle biopsy specimens often have fewer than this (see Fig. 34.15).

The animal's coagulation status is determined before a liver biopsy is performed, regardless of the approach. Hemorrhage is the major risk of liver biopsy in dogs and cats. However, it remains unclear and controversial which markers of coagulation status, if any, are predictive of perioperative bleeding. Ideally, a complete coagulation profile (one-stage prothrombin time [OSPT], APTT, fibrin degradation products, fibrinogen content, platelet count) is obtained; a platelet count and an activated clotting time in a glass tube, as a screening test of the intrinsic coagulation cascade, are also

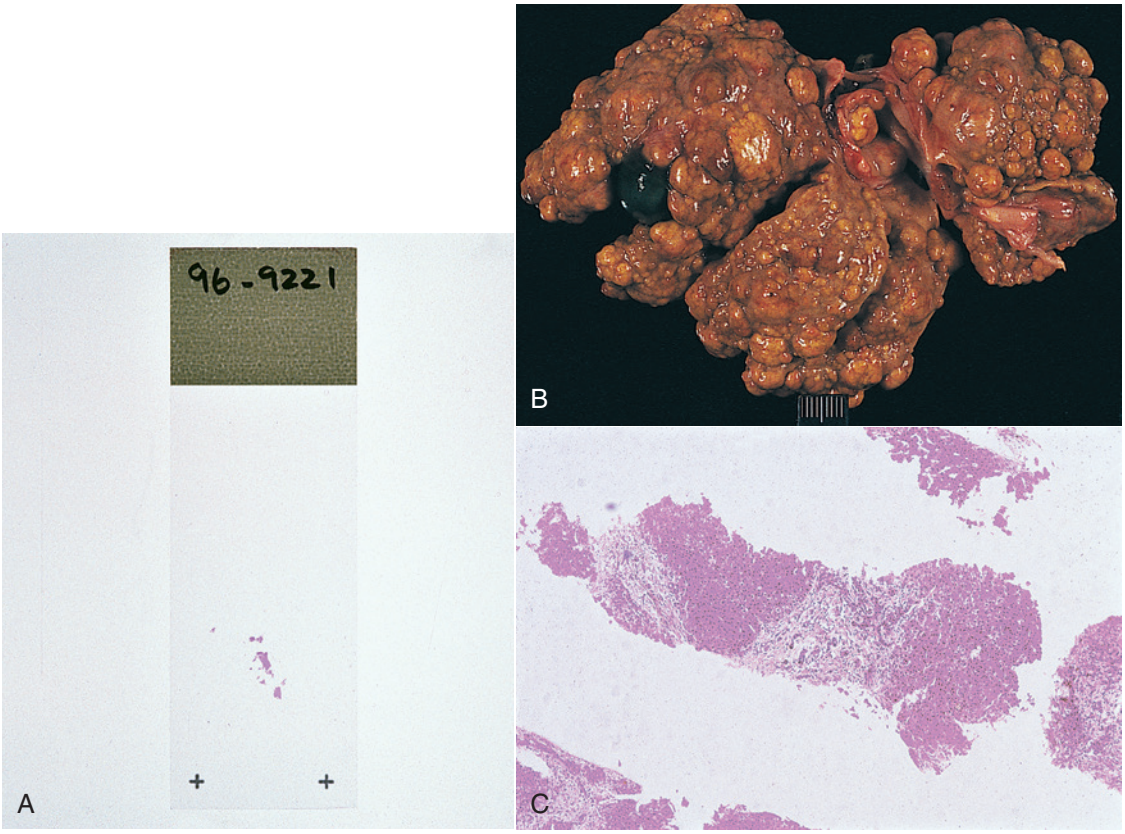


FIG 34.15
(A) Liver specimen obtained percutaneously (with ultrasound guidance) from a dog with hepatic fibrosis and nodular regeneration. **(B)** The specimen was difficult to obtain because the liver was firm and rubbery in texture. **(C)** The resultant sample was difficult to interpret histologically.

acceptable. One study showed that bleeding after US-guided biopsy is more likely if the platelet count is less than 80,000 cells/μL or if the OSPT (dogs) or APTT (cats) is prolonged (Bigge et al., 2001), but these results were not repeated in other studies. If possible, von Willebrand factor is measured in susceptible breeds in advance of biopsy because results of standard coagulation tests are usually normal in affected dogs. A buccal mucosal bleeding time test provides indirect assessment of platelet function (see Chapter 87). In dogs with von Willebrand disease, desmopressin acetate (DDAVP) is given (1-4 μg/kg SQ) before surgery to enhance the shift of von Willebrand factor activity from endothelial cells to the plasma.

Mild abnormalities in coagulation test results do not preclude liver biopsy. Results of routine coagulation tests may not correlate with liver bleeding times. Liver biopsy should be delayed if there is clinical evidence of bleeding or marked abnormalities in coagulation test results. Because animals with complete EBDO may be vitamin K–deficient (manifested by prolongation of OSPT and APTT), treatment with vitamin K_1 (0.5-1 mg/kg [maximum, 10 mg] subcutaneously every 12 hours for three treatments) is indicated for 1 or 2 days before surgery. This is particularly true in cats. Dogs with EBDO may in fact be hypercoagulable (see previous section), so vitamin K supplementation may not be indicated in them. Vitamin K supplementation can also improve coagulation times in animals with other liver disease, particularly cats. Repeating the OSPT and APTT within 24 hours after the administration of vitamin K_1 should demonstrate normal or near-normal values. If not, the dose can be adjusted and the procedure delayed. If bleeding is excessive during or after biopsy and cannot be controlled locally with direct pressure or application of a clot-promoting substance, fresh whole blood or plasma is given (see Chapter 80 for transfusion guidelines).

TECHNIQUES

The preferred techniques for liver biopsy are laparoscopy or laparotomy with wedge biopsy. These are preferred over transcutaneous Tru-Cut–type needle biopsies (US-guided or blind) because wedge biopsies give a more reliable diagnosis. The diagnostic accuracy of needle biopsies was compared with wedge biopsies of liver from the same patients, and there was agreement in the diagnoses only 48% of the time (Cole et al., 2002). This is likely because of the greatly increased risk of sampling artifact with needle biopsies (see earlier). US-guided transcutaneous Tru-Cut biopsies are, however, less invasive than laparotomy or laparoscopy, can

be taken under heavy sedation or general anesthesia, and are better than no biopsy at all. However, they are often too small and nonrepresentative (see Fig. 34.15), and it is not possible to obtain enough tissue for quantitative copper measurement by Tru-Cut needle biopsy. Multiple biopsies should be taken with as large a Tru-Cut needle as possible to maximize the chances of obtaining diagnostic samples. The animal should be monitored carefully for hemorrhage afterward (preferably hospitalized overnight), which although uncommon, can develop unnoticed in these animals and can be life-threatening.

Laparotomy is much more invasive but allows examination of other abdominal organs (e.g., pancreas, small intestine), observation of the liver, and careful biopsy. The risk of hemorrhage is, therefore smaller than with Tru-Cut biopsies because any bleeding can be seen and dealt with at the time of surgery. The biopsies obtained are generally bigger and more diagnostic except that focal lesions deep in the parenchyma may be missed if US has not been used as well. If one part of the liver looks normal and another part abnormal, biopsies should be obtained from both areas because the apparently normal part may be the diseased area. Laparotomy is clearly indicated if there is a mass that could be resected (Fig. 34.16). Laparoscopy is less invasive than laparotomy and has similar advantages. It is the preferred method of obtaining diagnostic liver biopsies if there is access to equipment and operator experience (Fig. 34.17), and has been shown to have a low complication rate, even in dogs with advanced liver disease and coagulopathies (McDevitt et al., 2016). Recovery is much quicker than with laparotomy, and animals can usually be sent home on the same day as the procedure. With laparotomy and laparoscopy, consideration should be given to obtaining a bile sample by aspiration and examining and taking biopsies from other organs such as the pancreas at the same time, as indicated in the

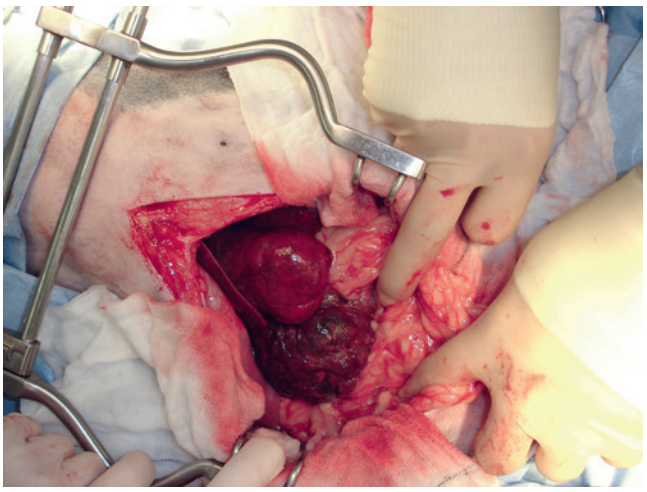


FIG 34.16
Laparotomy for resection of a hepatic mass in a dog. A diagnosis of hepatocellular carcinoma was made on histopathology. (Courtesy Dr. Laura Owen, Soft Tissue Surgery Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

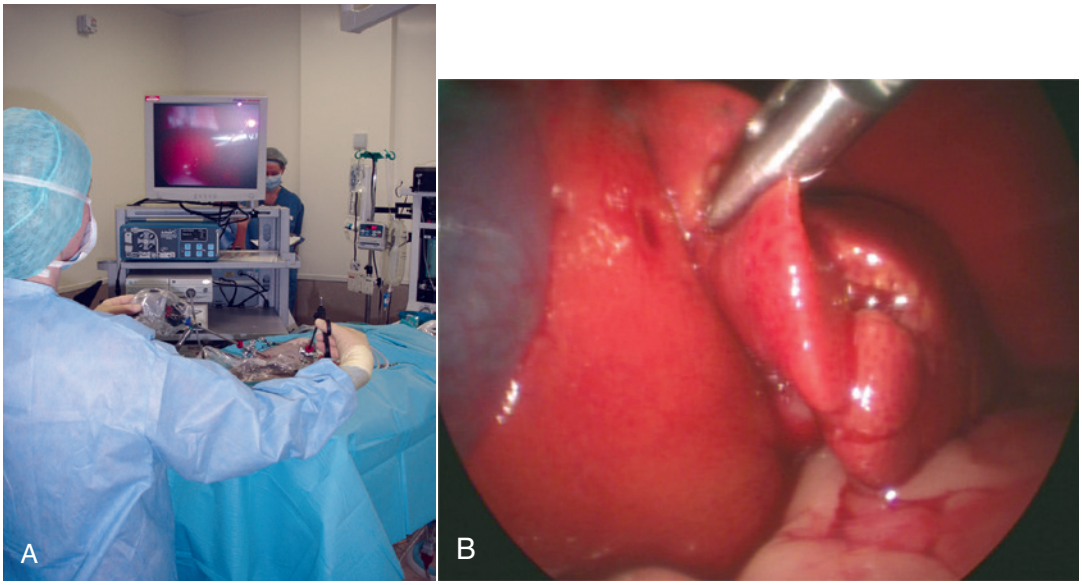


FIG 34.17
(A) Laparoscopic liver biopsy performed in a 7-year-old female cross-breed dog with a history of vomiting, anorexia, and increased liver enzyme levels. The final histologic diagnosis was idiopathic chronic hepatitis. **(B)** Biopsy being taken from a liver lobe. The gallbladder is visible on the left. A gallbladder aspirate was also taken using a transcutaneous needle under laparoscopic visualization. (Courtesy Dr. Laura Owen, Soft Tissue Surgery Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

animal's previous investigations. Serious consideration should also be given to placing a feeding tube at the same time to avoid a second anesthetic for feeding tube placement at a later date should this prove necessary.

Laparotomy and laparoscopy require a general anesthetic. A few dogs with end-stage chronic hepatitis and cats with acute hepatic lipidosis are very poor anesthetic risks and likely to die if anesthetized for any procedure. These cases should have fine-needle aspiration or Tru-Cut biopsies under careful sedation or supportive care until their clinical condition improves enough to allow the use of a safe general anesthetic.

US-guided Tru-Cut biopsies may be performed under sedation or general anesthesia. If a concurrent gallbladder aspirate is being obtained, a general anesthetic is preferred to allow breath-holding during the procedure. Biopsy can be performed blindly if the cat or dog has generalized hepatomegaly and the operator is confident of the path of the needle. The most common needle biopsy instruments are the Tru-Cut (Cardinal Health, Dublin, Ohio) and Jamshidi Menghini (Cardinal Health, Kormed, Seoul, Korea) needles. The Jamshidi Menghini biopsy needles can be operated with one hand, and aspiration is used to sever and contain the specimen within the barrel of a 6- or 12-mL syringe. The Tru-Cut needle requires two hands to operate and relies on the tissue falling into the specimen trough and then being severed by the sharp outer cannula (Fig. 34.18). One-handed, semiautomatic (e.g., Tenmo Evolution biopsy needle, Cardinal Health; Vet-core biopsy needle, Smiths Medical, Dublin, Ohio; Global Veterinary Products, Amarillo, Tex) and automatic (e.g., Pro-Mag Ultra Automatic biopsy instrument, Angiotech, Wheeling, Ill; Bard Biopty biopsy instrument and Bard Biopty-Cut biopsy needle, Bard Biopsy Systems, Tempe, Ariz) versions of this instrument are also available. These biopsy needles are intended for single use. The automatic biopsy instrument or semiautomatic biopsy needle device can be used to obtain liver biopsies in dogs, but only the semiautomatic biopsy needle device should be used in cats. One study identified a high risk of fatal complications (unexpected fatal shock reaction) when an automatic biopsy instrument was used to obtain liver biopsies in cats (Proot and Rothuizen, 2006).

Biopsy can be done of any palpably enlarged lobe as long as care is taken to angle the needle to avoid puncturing the gallbladder. Usually the animal is placed in right lateral recumbency for this purpose, and biopsy of the left lateral lobe is done. Elevating the head and thorax slightly may assist in presenting the liver to the operator. Two or three complete core specimens are obtained; if indicated, one core specimen is placed in a sterile container for culture and sensitivity testing. Each of the remaining core specimens is placed on a piece of stiff paper (e.g., filter paper) in correct orientation (Fig. 34.19) before immersion in fixative for histologic examination and/or special testing.

After biopsy, a small bandage is applied to keep the site clean during recovery, and the animal is placed in a position to allow its body weight to compress the region of the biopsy sites in the liver (e.g., left lateral recumbency). Consideration should be given to postoperative analgesia; puncture of the liver capsule can be painful. The animal should be monitored carefully for any evidence of hemorrhage for several hours after the procedure. As long as the biopsy procedure proceeded smoothly and without unpleasant surprises (animal awake and struggling), only basic monitoring of mucous

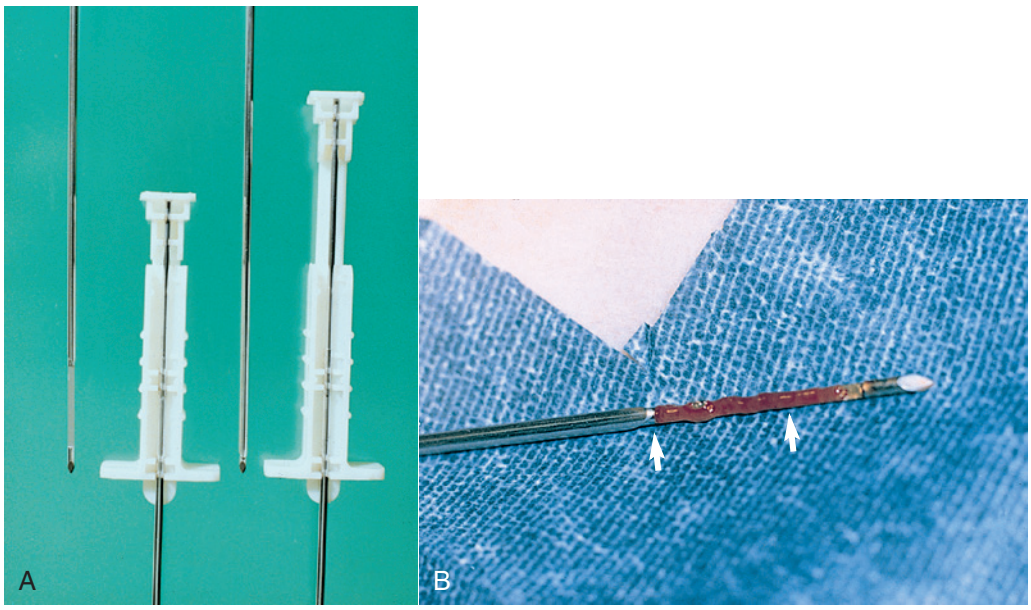


FIG 34.18
(A) Tru-Cut biopsy needle with the specimen trough exposed *(left)* and then covered by the sharp outer cannula *(right)*. **(B)** Liver tissue filling the specimen trough *(between arrows)*.



FIG 34.19
Needle biopsy specimen affixed to a stiff piece of paper to preserve orientation of the sample during formalin fixation for histopathologic examination.

membrane color, heart rate, and the skin puncture site is needed. Naturally, if excessive hemorrhage or damage to other organs occurs with this blind technique, detection and treatment may be delayed.

Aspiration of the gallbladder for cytologic analysis and culture can be accomplished with US guidance or by laparoscopy. Bile leakage may occur, even if a small-gauge needle is used, so attempts are made to evacuate the gallbladder completely; the needle should be placed in the gallbladder through the liver parenchyma to help prevent leakage. Some surgeons prefer to obtain bile during laparotomy when a purse-string suture can be applied to the aspiration site to prevent seepage. Large-volume abdominal effusion hinders direct inspection of the liver and associated structures and must be removed before laparoscopic biopsy is attempted. This is best achieved slowly with diuretics while the biopsy procedure is delayed. Rapid removal at the time of surgery can result in a marked decrease in blood albumin concentration unless accompanied by a plasma transfusion.

Liver tissue specimens taken by any technique are submerged in buffered 10% formalin at a ratio of at least 10 parts formalin to 1 part tissue. Samples for copper histochemical staining or tissue quantification are harvested and fixed or preserved according to the specifications of the pathology laboratory selected to do the assays. A portion of the specimen can be frozen or stored in RNA later (see https://www.thermofisher.com) or a similar preservative for molecular studies (e.g., polymerase chain reaction for organisms or tumor clonality). The liver sections should be sent to a veterinary pathologist with a specialty in liver disease. Appropriate stains should be used for copper, fibrous tissue, and other samples, and their use should be discussed with the attending pathologist. Stains recommended for every liver biopsy are hematoxylin and eosin; a fibrosis stain and a copper stain. Other histologic stains are then used according to need (Webster et al., 2019).

PANCREATIC BIOPSIES

Pancreatic biopsy is the only definitive way of making a diagnosis but is not recommended in most cases. For any biopsy to be justified clinically, the benefits should outweigh the risks. Ultimately, the results should alter outcome in the case, and this usually means they should alter treatment decisions. In small animals, there are situations where a biopsy might give prognostic rather than treatment information and also alter outcome (for example, the owner may decide on euthanasia as a result of finding a pancreatic tumor). If the biopsy doesn't do either of these things, then it is difficult to justify ethically. It is difficult to biopsy a pancreas noninvasively, and the procedure usually requires laparotomy or laparoscopy. Fine needle aspiration cytology of the pancreas has been described and shows some promise in helping differentiate pancreatitis from neoplasia in dogs (Bjorneby and Kari, 2002) although the author's experience suggests this is as challenging as prostatic cytology and requires a cytologist experienced at looking at pancreatic aspirates to differentiate hyperplasia from neoplasia.

The gold standard for diagnosis of pancreatitis is biopsy and histopathologic examination, but even histology of a pancreatic biopsy is not 100% sensitive because the lesions of pancreatitis are patchy particularly early in the disease process, so a small surgical biopsy may miss the disease. To diagnose the disease definitively needs multiple large sections taken throughout the organ (Newman et al., 2004), and this is clearly only possible postmortem.

There are no clearly defined veterinary guidelines about when to biopsy the pancreas. However, if we reflect the human situation quite closely, the single biggest reason to biopsy a pancreas is to rule in or out neoplasia. In this case, there is often a justification to undertake a laparotomy or laparoscopy and obtain a biopsy. Nodules in the pancreas are as likely to be inflammatory as neoplastic, particularly in Cocker Spaniels with IgG4+ chronic pancreatitis (see Chapter 37), so a biopsy is required to definitively diagnose neoplasia, and dogs and cats with pancreatic masses should NOT be euthanized on the table without histology.

The indications for biopsy in pancreatitis are less clear. Generally, the cause of pancreatitis in dogs and cats is unknown so the treatment is supportive and nonspecific, and a biopsy will not change that. There is one exception, which is the multisystemic immune-mediated disease in English Cocker spaniels, described in Chapter 37. But even in this disease, diagnosis can be made presumptively on the basis of immune-mediated disease in other organs, and a pancreatic biopsy is not necessary. Undertaking a general anesthetic and laparotomy or laparoscopy in a dog or cat with acute disease is dangerous; these dogs or cats have systemic inflammatory response and multiorgan dysfunction, and need stabilizing before surgery. Mortality in dogs and cats with pancreatitis is usually as a result of multiorgan failure, not the localized pancreatitis itself, and undertaking a GA and laparotomy in a dog that is already unstable is likely to make things worse. There are no studies in dogs assessing the risk of mortality with early surgery in acute

pancreatitis, but in humans there is clear evidence that early surgery in acute pancreatitis actually increases mortality compared with delaying surgery for 2 to 4 weeks after symptom onset, and thus this is avoided unless there is a high suspicion of malignant neoplasia (McKay et al., 2004; Wittau et al., 2010).

However, bearing all these factors in mind, it is still well worthwhile taking a careful pancreatic biopsy in any animal that is having an exploratory laparotomy or surgery for another reason, and pancreatitis is a possibility. In the past, these were discouraged because of a fear of postoperative pancreatitis. However, this appears to be a theoretical rather than real concern as long as the surgeon only takes a small biopsy and preserves pancreatic blood supply.

Pancreatic biopsy appears to be safe and does not carry a high risk of postoperative pancreatitis, provided that the pancreas is handled gently and the blood supply is not disrupted. A study of pancreatic biopsy in 27 normal dogs showed elevations in some pancreatic enzyme levels postbiopsy but not in cPLI, and there were no clinical signs of pancreatitis after surgery (Cordner et al., 2010).

Suggested Readings

Adrian AM, et al. Computed tomographic angiography under sedation in the diagnosis of suspected canine pancreatitis: a pilot study. *J Vet Intern Med*. 2015;29:97.

Aravinthan A, et al. The senescent hepatocyte gene signature in chronic liver disease. *Exp Gerontol*. 2014;60:37.

Bahr KL, et al. Accuracy of US-guided FNA of focal liver lesions in dogs: 140 cases (2005-2008). *J Am Anim Hosp Assoc*. 2013;49:190.

Balkman CE, et al. Evaluation of urine sulfated and nonsulfated bile acids as a diagnostic test for liver disease in dogs. *J Am Vet Med Assoc*. 2003;222:1368.

Bigge LA, et al. Correlation between coagulation profile findings and bleeding complications after ultrasound-guided biopsies: 434 cases (1993-1996). *J Am Anim Hosp Assoc*. 2001;37:228.

Bjorneby JM, Kari S. Cytology of the pancreas. *Vet Clin North Am Small Anim Pract*. 2002;32:1293–1312.

Cole T, et al. Diagnostic comparison of needle biopsy and wedge biopsy specimens of the liver in dogs and cats. *J Am Vet Med Assoc*. 2002;220:1483.

Collings AJ, et al. A prospective study of basal insulin concentrations in dogs with congenital portosystemic shunts. *J Small Anim Pract*. 2012;53:228.

Cordner AP, et al. Effect of pancreatic tissue sampling on serum pancreatic enzyme levels in clinically healthy dogs. *J Vet Diagn Invest*. 2010;22:702.

Forman MA, et al. Evaluation of serum feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med*. 2004;18:807.

Fry W, et al. Thromboelastography in dogs with chronic hepatopathies. *J Vet Intern Med*. 2017;31:419.

Gallagher AE, et al. Hyperphosphatasemia in Scottish terriers: 7 cases. *J Vet Intern Med*. 2006;20:418.

Gaskill CL, et al. Serum alkaline phosphatase isoenzyme profiles in phenobarbital-treated epileptic dogs. *Vet Clin Pathol*. 2004;33:215.

Gerritzen-Bruning MJ, et al. Diagnostic value of fasting plasma ammonia and bile acid concentrations in the identification of portosystemic shunting in dogs. *J Vet Intern Med*. 2006;20:13.

Gómez-Ochoa P, et al. Use of transsplenic injection of agitated saline and heparinized blood for the ultrasonographic diagnosis of macroscopic portosystemic shunts in dogs. *Vet Radiol Ultrasound*. 2011;52:103.

Goodband EL, et al. Validation of a commercial 1,2-O-Dilauryl-Rac-Glycero Glutaric Acid-(6′-methylresorufin) ester lipase assay for diagnosis of canine pancreatitis accepted for publication. *Vet Record Open*. 2018 26;5(1):e000270.

Graca R, et al. Validation and diagnostic efficacy of a lipase assay using the substrate 1,2-o-dilauryl-rac-glycero glutaric acid-(6' methyl resorufin)-ester for the diagnosis of acute pancreatitis in dogs. *Vet Clin Pathol*. 2005;4:39.

Hall EJ, et al. Laboratory evaluation of hepatic disease. In: Villiers E, Blackwood L, eds. *BSAVA manual of canine and feline clinical pathology*. 2nd ed. Gloucestershire, England: British Small Animal Veterinary Association; 2005.

Hess RS, et al. Clinicopathological, radiographic and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). *J Am Vet Med Assoc*. 1998;213:665.

Jensen AL, et al. Preliminary experience with the diagnostic value of the canine corticosteroid-induced alkaline phosphatase isoenzyme in hypercorticism and diabetes mellitus. *Zentralbl Veterinarmed*. 1992;39:342.

Kelley D, et al. Thromboelastographic evaluation of dogs with acute liver disease. *J Vet Intern Med*. 2015;29:1053.

Koblik PD, et al. Transcolonic sodium pertechnetate tc 99m scintigraphy for diagnosis of macrovascular portosystemic shunts in dogs, cats, and pot-bellied pigs: 176 cases (1988-1992). *J Am Vet Med Assoc*. 1995;207:729.

Kook PH, et al. Agreement of serum spec cPL with the 1,2-o-dilauryl-rac-glycero glutaric acid-(6′-methylresorufin) ester (DGGR) lipase assay and with pancreatic ultrasonography in dogs with suspected pancreatitis. *J Vet Intern Med*. 2014;28:863.

Kortum AJ, et al. Hepatocyte expression and prognostic importance of senescence marker p21 in liver histopathology samples from dogs with chronic hepatitis. *J Vet Intern Med*. 2018;32:1629.

Kuzi S, et al. Plasma antithrombin activity as a diagnostic and prognostic indicator in dogs: a retrospective study of 149 dogs. *J Vet Intern Med*. 2010;24:587.

Lawler DF, et al. Benign familial hyperphosphatasemia in Siberian Huskies. *Am J Vet Res*. 1996;57:612.

Lee KC, et al. Association of portovenographic findings with outcome in dogs receiving surgical treatment for single congenital portosystemic shunts: 45 cases (2000-2004). *J Am Vet Med Assoc*. 2006;229:1122.

Liptak JM. Hepatobiliary tumors. In: Withrow SJ, Vail DM, Page R, eds. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St Louis: Saunders Elsevier; 2013:405.

Mansfield CS, et al. Association between canine pancreatic-specific lipase and histologic exocrine pancreatic inflammation in dogs: assessing specificity. *J Vet Diagn Invest*. 2012;24:312.

Marolf AJ, et al. Hepatic and pancreaticobiliary MRI and MR cholangiopancreatography with and without secretin stimulation in normal cats. *Vet Radiol Ultrasound*. 2011;52:415.

Marolf AJ. Diagnostic imaging of the hepatobiliart system: an update. *Vet Clin North Am Small Anim Pract*. 2017;47:555.

Mayhew PD, et al. Evaluation of coagulation in dogs with partial or complete extrahepatic biliary obstruction by means of thromboelastography. *J Am Vet Med Assoc*. 2013;242:778.

McDevitt HL, et al. Short-term clinical outcome of laparoscopic liver biopsy in dogs: 106 cases (2003-2013). *J Am Vet Med Assoc*. 2016;248:83.

McKay CJ, et al. The continuing challenge of early mortality in acute pancreatitis. *Br J Surg*. 2004;91:1243.

McCord K, et al. A multi-institutional study evaluating the diagnostic utility of the spec cPL and SNAP cPL in clinical acute pancreatitis in 84 dogs. *J Vet Intern Med*. 2012;26:888.

Müller PB, et al. Effects of long-term phenobarbital treatment on the liver in dogs. *J Vet Intern Med*. 2000;14:165.

Nelson NC, Nelson LL. Anatomy of extrahepatic portosystemic shunts in dogs as determined by computed tomography angiography. *Vet Radiol Ultrasound*. 2011;52:498.

Newman S, et al. Localization of pancreatic inflammation and necrosis in dogs. *J Vet Intern Med*. 2004;18:488.

Oppliger S, et al. Agreement of the serum spec fPL™ and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester lipase assay for the determination of serum lipase in cats with suspicion of pancreatitis. *J Vet Intern Med*. 2013;27:1077.

Oppliger S, et al. Agreement of serum feline pancreas-specific lipase and colorimetric lipase assays with pancreatic ultrasonographic findings in cats with suspicion of pancreatitis: 161 cases (2008-2012). *J Am Vet Med Assoc*. 2014;244:1060.

Proot SJ, Rothuizen J. High complication rate of an automatic Tru-Cut biopsy gun device for liver biopsy in cats. *J Vet Intern Med*. 2006;20:1327.

Ramstedt KL, et al. Changes in gallbladder volume in healthy dogs after food was withheld for 12 hours followed by ingestion of a meal or a meal containing erythromycin. *Am J Vet Res*. 2008;69:647.

Rivero-Juárez A, et al. Liver stiffness using transient elastography is applicable to canines for hepatic disease models. *PLoS ONE*. 2012;7:e41557.

Seibert RL, et al. Evaluation of a semiquantitative SNAP test for measurement of bile acids in dogs. *Peer J*. 2014;2:e539.

Sevelius E, Andersson M. Serum protein electrophoresis as a prognostic marker of chronic liver disease in dogs. *Vet Rec*. 1995;137:663.

Spillmann T, et al. Canine pancreatic elastase in dogs with clinical exocrine pancreatic insufficiency, normal dogs and dogs with chronic enteropathies. *Eur J Comp Gastroenterol*. 2000;5:1.

Spillmann T, et al. An immunoassay for canine pancreatic elastase 1 as an indicator of exocrine pancreatic insufficiency in dogs. *J Vet Diagnost Invest*. 2001;13:468.

Steiner JM, et al. Serum canine lipase immunoreactivity in dogs with exocrine pancreatic insufficiency. *J Vet Intern Med*. 2001;15:274.

Toulza O, et al. Evaluation of plasma protein C activity for detection of hepatobiliary disease and portosystemic shunting in dogs. *J Am Vet Med Assoc*. 2006;229:1761.

Trainor D, et al. Urine sulfated and nonsulfated bile acids as a diagnostic test for liver disease in cats. *J Vet Intern Med*. 2003;17:145.

Walker MC, et al. Postprandial venous ammonia concentrations in the diagnosis of hepatobiliary disease in dogs. *J Vet Intern Med*. 2001;15:463.

Wang KY, et al. Accuracy of ultrasound-guided fine-needle aspiration of the liver and cytologic findings in dogs and cats: 97 cases (1990-2000). *J Am Vet Med Assoc*. 2004;224:75.

Warren-Smith CMR, et al. Lack of association between ultrasonographic appearance of parenchymal lesions of the canine liver and histological diagnosis. *J Small Anim Pract*. 2012;53:168.

Webster CRL, et al. ACVIM Consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med* 2019;Mar 7. doi: 10.1111/jvim.15467. [Epub ahead of print]

Wittau M, et al. Changing role of surgery in necrotizing pancreatitis: a single-center experience. *Hepatogastroenterology*. 2010;57:1300.

Zini E, et al. Paraneoplastic hypoglycemia due to an insulin-like growth factor type-II secreting hepatocellular carcinoma in a dog. *J Vet Intern Med*. 2007;21:193.

CHAPTER 35

Hepatobiliary Diseases in the Cat



GENERAL CONSIDERATIONS

The causes, clinical signs, and prognosis of hepatobiliary tract diseases in cats are very different from those of dogs. Primary and secondary causes of liver disease in cats are outlined in Table 35.1. Cats typically have hepatobiliary disease or acute hepatic lipidosis, but chronic parenchymal disease is uncommon in this species; in addition, feline liver disease rarely progresses to cirrhosis, as is sometimes the case in dogs. The clinical signs of hepatobiliary disease in cats are generally nonspecific and similar to the signs of inflammatory bowel disease (IBD) and pancreatitis; the three conditions may coexist, further confusing diagnosis. Hepatic lipidosis presents with more classic signs of liver disease, including jaundice and encephalopathy. The most important differences between feline and canine hepatobiliary diseases are outlined in Table 35.2.

The feline hepatopathies in this chapter are described approximately in order of their frequency in clinical practice in the United States. Historically, hepatic lipidosis has been most common in the United States and cholangitis most common in Europe, but lipidosis is becoming increasingly common in Europe, and cholangitis is now commonly recognized in the United States.

HEPATIC LIPIDOSIS

Etiology and Pathogenesis

Feline hepatic lipidosis may be primary or secondary to another disease, but in either case it is associated with a high mortality unless the cat is intensively fed.

PRIMARY HEPATIC LIPIDOSIS

Primary or idiopathic hepatic lipidosis usually affects obese cats and remains the most common hepatic disease of cats in North America; it is also now emerging as an increasingly common problem in Europe and Israel (Bayton et al., 2018; Kuzi et al., 2017). It is effectively an acute hepatopathy with a massive accumulation of fat in hepatocytes leading to acute loss of hepatocyte function, which is reversible if the fat can be mobilized (Fig. 35.1). The reason for the differences in prevalence in different countries is unknown but intriguing. Some researchers suggest environmental differences (e.g., differences in outdoor or indoor lifestyle or feeding habits), genetic differences among cats, or both.

The pathogenesis of primary hepatic lipidosis remains incompletely understood, but it seems to involve a combination of excessive peripheral lipid mobilization to the liver, deficiency of dietary proteins and other nutrients that would usually allow fat metabolism and transport out of the liver, and concurrent primary disturbances in appetite. Excessive mobilization of peripheral fat occurs particularly during periods of anorexia or stress in previously overweight cats. Concurrently, anorexia results in deficiencies of dietary proteins and other nutrients; cats are particularly susceptible to these problems because of their high dietary requirements (see Table 35.2). Some of these nutrients are important in fat metabolism and mobilization, particularly methionine, carnitine, and taurine, so deficiencies in these nutrients are implicated as contributing to the pathogenesis of the disease. Methionine is an important precursor in the synthesis of an important hepatic antioxidant, glutathione, and hepatic concentrations of glutathione may decrease markedly in cats with hepatic lipidosis. Relative arginine deficiency will contribute to the resultant hepatic encephalopathy (HE) caused by decreased urea cycle activity. Concurrent primary appetite disturbances result in persistent and marked anorexia, which is likely caused by disturbances in the complex neurohormonal control of appetite. Recent studies have suggested that peripheral insulin resistance does not play a relevant role in the disease, unlike in human nonalcoholic fatty liver disease.

SECONDARY HEPATIC LIPIDOSIS

Secondary hepatic lipidosis is also common in cats; its pathogenesis is similar to that of the primary disease but is complicated by the more marked neuroendocrine responses to stress. Secondary lipidosis can therefore be seen in cats that are less obese than those presenting with the primary

TABLE 35.1

Clinically Relevant Hepatobiliary Diseases in Cats

PRIMARY	SECONDARY
Common	
Idiopathic lipidosis	Secondary lipidosis
Neutrophilic cholangitis	Hyperthyroidism
Lymphocytic cholangitis	Pancreatitis Diabetes mellitus
Uncommon or Rare	
Congenital portosystemic shunt	Secondary neoplasia (less common than primary)
Extrahepatic bile duct obstruction	Biliary stasis associated with extrahepatic sepsis
Liver flukes (except common in hunting cats in endemic areas)	Hepatic abscess
Primary neoplasia	
Infections (see Box 35.5)	
Drug- or toxin-induced hepatopathy	
Biliary cysts	
Sclerosing cholangitis/biliary cirrhosis	
Congenital ductal plate abnormalities	
Primary copper-associated hepatopathy	
Hepatic amyloidosis	
Intrahepatic arteriovenous fistula	

disease and even in cats with a normal or thin body condition. Any anorexic cat with concurrent disease must therefore be regarded as being at high risk of hepatic lipidosis, and appropriate feeding support should be instituted as rapidly as possible. Secondary lipidosis may occur in association with any disease causing anorexia, but has been most commonly recognized in cats with pancreatitis, diabetes mellitus (DM), other hepatic disorders, IBD, and neoplasia.

Clinical Features

Most affected cats are middle-aged, but they can be of any age or sex. In a recent study from Israel, 99% of affected cats were neutered and 66% were female (Kuzi et al., 2017). There is no reported breed predilection. Cats with primary lipidosis are commonly obese, are housed indoors, and have experienced a stressful event (e.g., introduction of a new pet into the household, abrupt dietary change) or an illness that has caused them to become anorexic and lose weight rapidly. The initiating event is not always known. Secondary lipidosis may affect cats of normal or thin body condition as well as obese animals, and the clinical signs are complicated by those of the concurrent disease. For example, the clinical signs of acute diabetic ketoacidosis are similar to those of developing hepatic lipidosis.

Clinical signs are typical of an acute (reversible) loss of hepatocyte function and of hepatocyte swelling, with resultant intrahepatic cholestasis. Cats are usually jaundiced and have intermittent vomiting and dehydration. They may also have diarrhea or constipation. There is usually palpable hepatomegaly on physical examination. HE, most often manifested as depression and ptyalism, is related to severe hepatocellular dysfunction and relative arginine deficiency to which the anorexic cat is predisposed. Previously obese cats have extensive loss of muscle mass but maintain certain fat stores, such as those in the falciform ligament and inguinal region (Fig. 35.2).

Diagnosis

The only truly definitive and reliable method of diagnosing and identifying concurrent and causative conditions is histopathology of a wedge biopsy of liver obtained at laparotomy or laparoscopy or (less reliably) a Tru-Cut-type biopsy taken under ultrasonographic guidance. However, all of these procedures require a general anesthetic, and most cats with hepatic lipidosis are too ill on presentation to be safely anesthetized. Therefore using fine-needle aspiration (FNA) cytology of the liver performed blindly or under ultrasonographic guidance in an awake or sedated cat can yield a preliminary diagnosis; this will allow intensive management and tube feeding for a few days to stabilize the patient before anesthesia is considered for a more definitive diagnosis. Because coagulopathies are common in cats with lipidosis, a few days of therapy will help correct them before considering surgery. The clinician must be aware, however, that FNA cytology, although useful for emergency diagnosis and management, can be misleading in cats, and hepatic parenchymal disease can be misdiagnosed as lipidosis using this technique. In addition, concurrent diseases of the liver and other organs, including the pancreas and small intestine, will be overlooked without a laparoscopic or surgical biopsy. It is important to differentiate mild to moderate lipid accumulation in hepatocytes, which is common in sick and anorexic cats and causes no clinical problems, from clinically severe lipidosis on cytology (see Fig. 35.1).

FNA can be performed under ultrasonographic guidance while the cat is being evaluated or obtained blindly if there is palpable hepatomegaly. The procedure is performed in a similar way to aspiration of a mass. The enlarged liver is palpated, and the abdominal wall overlying it is clipped and prepped. A 22-gauge needle is passed through the skin into the liver from ventrally on the left side, which prevents inadvertent puncturing of the gallbladder, and gentle suction is applied to a 5-mL syringe two or three times, before withdrawing and gently expressing the needle contents onto a slide (see Fig. 34.14). Analgesia is recommended for either procedure because puncture of the liver capsule is painful. Opiate partial agonists, such as buprenorphine, are a good

TABLE 35.2

Important Differences Between Cats and Dogs With Hepatobiliary Disease

PARAMETER	CATS	DOGS	REASON FOR DIFFERENCE
Disease spectrum	Cats have a higher prevalence of hepatobiliary diseases than dogs. Chronic parenchymal disease, fibrosis, cirrhosis, and portal hypertension are much less common than in dogs. Concurrent biliary tract disease, pancreatitis, and inflammatory bowel disease are possible in either species but are more common in the cat. Ascending infections of the bile duct are also proposed to be more common in cats. Cats are particularly susceptible to clinically serious hepatic lipidosis (primary or secondary).	Chronic parenchymal disease is the most common, usually progressing to fibrosis and cirrhosis, with portal hypertension. Biliary tract disease (acute and chronic) does occur but is uncommon. Secondary hepatic lipidosis can develop in association with other diseases but is not usually a clinical problem.	Unknown. It has been proposed that the high prevalence of biliary tract disease is caused by differences in anatomy, but this has not been proved. In most cats, the bile duct joins the single major pancreatic duct before entering the small intestine at the major duodenal papilla, whereas in most dogs the bile duct enters the duodenum separately from two pancreatic ducts. Underlying cause of hepatic lipidosis in cats is not fully elucidated (see text) but likely caused by differences in metabolism.
Ability to metabolize drugs or toxins	Cats have a relative deficiency of glucuronyl transferase, reducing their ability to metabolize drugs and toxins and making them more susceptible to oxidant toxins. However, cats are pickier with their food and therefore less likely to scavenge toxins.	Because dogs are generally more likely to scavenge, they may have more access to hepatotoxins. Dogs generally have no deficiency of enzymes, but there are some breed variations (e.g., Doberman Pinschers that have an impaired ability to detoxify potentiated sulfonamides).	Cats are less likely than dogs to have toxic liver damage associated with environmental toxins. However, cats are generally less able to metabolize toxins than dogs and are therefore more susceptible than dogs to toxic liver damage caused by many potentially hepatotoxic drugs.
Isoenzymes of alkaline phosphatase (ALP) and steroid hepatopathies	Cats do not produce a steroid-induced isoenzyme of alkaline phosphatase (ALP) and the half-life of ALP is very short in cats (6 hours). Hyperadrenocorticism (HAC) is rare in cats.	Dogs have a steroid-induced isoenzyme of ALP and ALP that has a long half-life; the half-life of hepatobiliary ALP is 66 hours and the half-life of glucocorticoid-induced ALP is 74 hours. Hyperadrenocorticism is common in dogs.	Even mild increase in ALP levels in cats suggests a significant ongoing problem. ALP level does not increase with steroid therapy (or HAC before the development of diabetes mellitus) in cats. Steroid treatment and HAC are major differentials for high ALP levels in dogs.
Hepatic metabolism of glucose and protein	Adapted to high-protein diet—postprandial hepatic gluconeogenesis from protein and constantly high activity of protein catabolizing enzymes in the liver, which cannot be downregulated. High dietary requirement for arginine for the hepatic urea cycle. Taurine is an essential dietary requirement, and bile salts are all conjugated with taurine.	Adapted to use dietary starch; postprandial insulin release results in glucose storage. Dogs can downregulate hepatic protein, metabolizing enzymes as necessary when the diet is low in protein. Lower arginine requirement than cats. No obligate dietary taurine requirement provided diet contains enough sulfur amino acids.	Cats will rapidly develop protein-calorie malnutrition and start breaking down their own body protein if fed a protein-restricted diet in liver disease. Arginine deficiency can contribute to the development of hyperammonemia in cats with liver disease if the cat is fed a diet deficient in arginine (e.g., dairy protein). Taurine, arginine, and protein deficiency can contribute to the pathogenesis of hepatic lipidosis in cats.

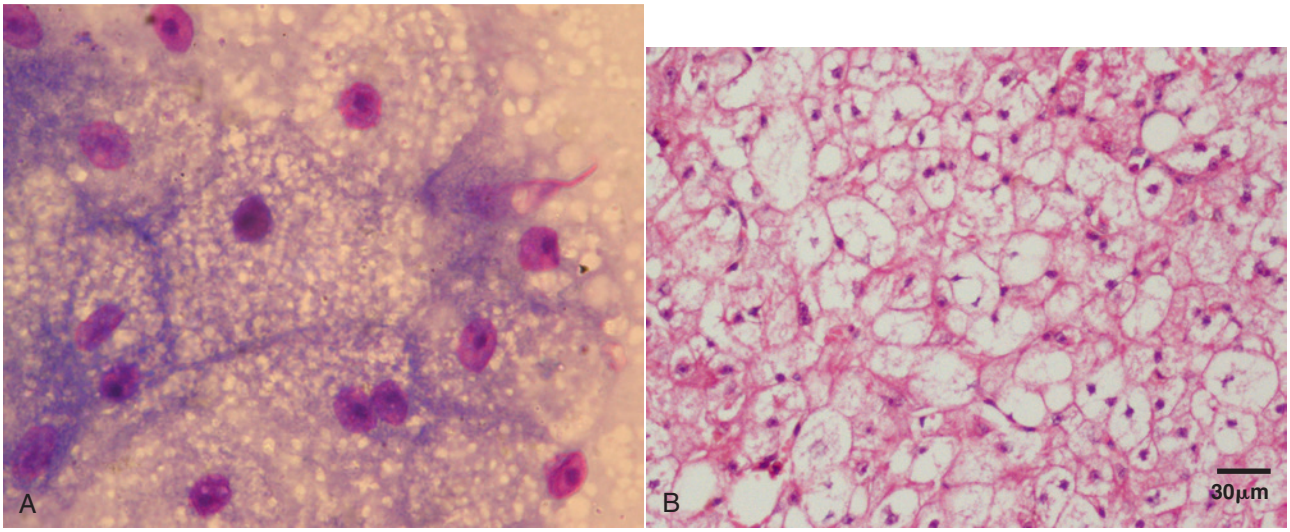


FIG 35.1
(A) Cytology of feline hepatocytes with hepatic lipidosis showing marked swelling of hepatocytes with lipid. **(B)** Histologic section of liver from a cat with hepatic lipidosis. Note marked swelling of hepatocytes with fat (H&E stain). Bar = 30 μm. (**A,** Courtesy Elizabeth Villiers from Hall EJ et al, editors: *BSAVA manual of canine and feline gastroenterology,* ed 2, Gloucestershire, England, 2005, British Small Animal Veterinary Association.)

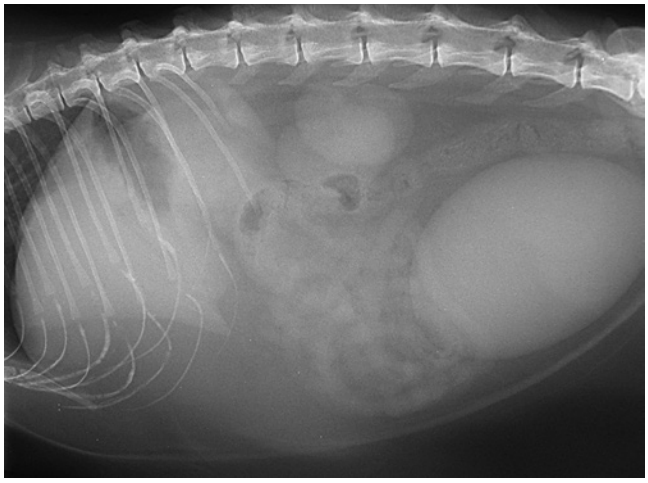


FIG 35.2
Lateral abdominal radiograph of a domestic short-haired cat with hepatic lipidosis secondary to prolonged fasting because of a diet change. Note maintenance of a large falciform fat pad below the liver in spite of weight loss and loss of subcutaneous fat dorsal to the spine. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

choice; buprenorphine appears to be more effective than butorphanol as an analgesic in cats.

Clinically relevant hepatic lipidosis is usually easily recognizable on routine Giemsa or Diff-Quik staining of cytology samples or routine hematoxylin and eosin (H&E)–stained histology samples (see Fig. 35.1). It is possible to use special staining procedures with Oil Red O stain applied to snap-frozen biopsy samples to confirm that hepatocellular vacuolation is indeed lipid, but these procedures are not practical in a private practice setting. In addition, glycogen accumulation is uncommon in feline (as opposed to canine) hepatocytes.

Clinicopathologic findings reflect cholestasis and marked hepatocellular dysfunction. Hyperbilirubinemia is present in more than 95% of cases, and levels of the hepatocellular enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are also markedly elevated in most cats. Alkaline phosphatase activity (ALP) is also markedly increased in more than 80% of cases; this is particularly relevant in cats, in which this enzyme has a short half-life and no steroid induction (see Table 35.2). In cats with classic primary (idiopathic) lipidosis, a particular hallmark of the disease is an inappropriately low γ-glutamyl transferase (GGT) level, which is only mildly increased in the face of marked increase in the concentration of the other cholestatic markers (i.e., bilirubin and ALP). This is in contrast to cats with primary biliary tract disease or extrahepatic bile duct obstruction (EBDO) in which both GGT and ALP levels are usually high. However, in cats with secondary lipidosis associated with an underlying primary hepatopathy or pancreatic disease, the GGT level may be high as well. Therefore finding a high GGT level does not rule out hepatic lipidosis but should stimulate the search for an underlying cause. Blood urea nitrogen (BUN) concentration is low in more than half of the cats with lipidosis, reflecting generalized hepatocyte dysfunction. Electrolyte abnormalities are relatively common and can contribute to mortality if not addressed. Up to one third of cats are hypokalemic, and hypophosphatemia has been reported in 17% of cases; hypomagnesemia has also been reported in cats with lipidosis. Hypokalemia was a poor prognostic indicator in one study (Center et al.,

1996) and a more recent study identified hypoproteinaemia, hypoalbuminaemia, increased serum creatine kinase activity, hypocholesterolaemia, and hepatic failure at presentation as significantly associated with mortality. In addition, worsening hypoalbuminaemia, hyperammonaemia, hyperbilirubinaemia, or electrolyte disorders during hospitalization were also associated with mortality (Kuzi et al., 2017). There is no value in measuring serum bile acid levels as an indication of hepatic function in these cats because they will be high as a result of the concurrent cholestasis. Fasting cholesterol and glucose concentrations may also be high, and sometimes hyperglycemia is so marked that it results in glucosuria. This is usually a metabolic stress response and typically resolves after appropriate therapy. However, some cats may become diabetic as a result of an underlying disease process, or DM may be the cause of their lipidosis; therefore blood and urine glucose and ketone levels should be monitored carefully. The appearance of ketonuria in addition to glycosuria in a hyperglycemic cat is highly suggestive of overt DM. Serum ketone concentrations do increase in cats with hepatic lipidosis, but urine ketones are reported to be normal (Gorman et al., 2016).

Hemostatic abnormalities are common in cats with lipidosis, occurring in 20% to 60% of cases. Anemia is present in about 25% of cats, and there are often Heinz bodies in their red blood cells. Neutrophilia is not characteristic but may occur as a result of comorbidities, such as pancreatitis.

Radiographs show diffuse hepatomegaly; abdominal effusion is uncommon (see Fig. 35.2). Ultrasonography helps differentiate parenchymal from biliary tract disease and also allows assessment of other abdominal organs to detect underlying disease, particularly of the pancreas and intestine. Characteristically, the lipidotic liver appears hyperechoic, although this is not a specific finding and can also be seen in cats with other generalized parenchymal diseases, such as lymphoma or hepatic amyloidosis, and also in clinically normal obese cats.

Additional diagnostic tests should be performed to determine the presence of comorbidities that could be causing protracted anorexia and secondary hepatic lipidosis. Tests should be selected according to clues in the history, physical examination, and clinicopathologic and ultrasonographic evaluations. For example, serum feline specific pancreatic lipase immunoreactivity should be evaluated in cats suspected of having pancreatitis (see Chapter 34).

Treatment and Prognosis

Treatment recommendations for cats with hepatic lipidosis are outlined in Box 35.1. The single most important factor in reducing mortality is early and intensive feeding of a high-protein diet. In all cases, this requires some form of tube feeding. If the cat is very ill at presentation, a nasoesophageal tube can be placed for the first few days while the cat is stabilized (Box 35.2; Fig. 35.3), and an esophagostomy or gastrostomy tube may then be placed for long-term feeding (Fig. 35.4; see Bexfield and Lee: *BSAVA Guide to Procedures in Small Animal Practice, edition 2* for more details). The advantages of esophagostomy or gastrostomy tubes over nasoesophageal tube are longer-term support, better tolerated by the animal, and it is possible to feed thicker food. They are also easier to manage and could be managed by the owner at home. However, it is necessary to use a general anesthetic for placement. For gastrostomy tubes, the tube must be in at least 5 to 7 days for surgical tubes and 14 to 21 days for endoscopically placed tubes to allow adhesions to form between the stomach and body wall.

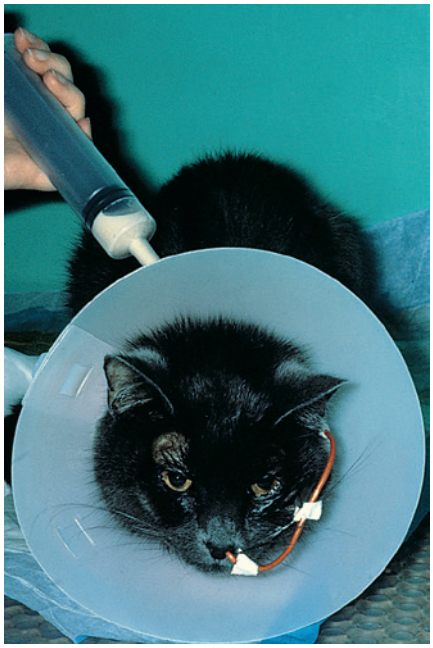


FIG 35.3
Nasoesophageal tube in place in a cat being fed a liquid enteral diet.

Most cats need 4 to 6 weeks of tube feeding, but many cats can be sent home with an esophagostomy or gastrostomy tube in place for home feeding once they have stabilized. A high-protein diet, such as those manufactured for feline intensive care patients, is ideal (e.g., Royal Canin Feline and canine convalescence support, Royal Canin USA, St Charles, Mo; Hill's a/d diet, Hill's Pet Nutrition, Topeka, Kan; or Fortol liquid feed, Arnolds, Amsterdam, New York). In some cats, however, a high-protein diet will worsen signs of encephalopathy during the first few days of therapy. Attempts should be made to control this by other methods, such as by feeding smaller amounts more frequently or infusion feeding slowly, rather than by reducing the protein content of the diet. Concurrent pancreatitis does not alter the dietary management; the current recommendations in cats with pancreatitis are to feed them as soon as possible and not to restrict fat (see Chapter 37).

Fluid and electrolyte abnormalities should also be addressed effectively in the first few days, and antiemetics should be used if necessary. Occasionally, cats with lipidosis may develop refeeding syndrome when oral nutrition is introduced, with a marked decrease in serum phosphate and potassium concentrations leading to hemolysis (Brenner et al., 2011). It is important to identify and treat this

BOX 35.1

Outline of Treatment of Hepatic Lipidosis in Cats

1. **Treat any identifiable underlying cause** but also start other treatments (steps 2 and 3) concurrently do not rely on—treating the cause alone to resolve the disease in secondary cases
2. **Institute fluid therapy as soon as possible**
   a. IV fluid support initially—maintenance rates plus replacement for any fluid lost, e.g., in vomiting. Normal saline with added potassium chloride as necessary is ideal. Avoid dextrose because it may worsen hyperglycemia.
   b. Measure and replace any electrolyte deficits, particularly potassium and phosphate. Carefully monitor blood glucose and electrolyte levels, particularly potassium and phosphate, which may become low during treatment. There is no evidence that adding insulin to the fluids is helpful; in fact, it increases the risk of serious hypokalemia and hypophosphatemia.
   c. After the first few days, fluid and electrolyte needs can be supplied via the feeding tube.
3. **Institute nutritional support as soon as rehydrated.**
   a. **How?** A nasoesophageal tube can be used for temporary support for the first few days before general anesthetic for more permanent tube placement. A gastrostomy or esophagostomy tube will usually be required long term because feeding will be necessary for 4 to 6 weeks in most cases.
   b. **What?** A diet as high in protein as possible should be given, preferably managing any resultant encephalopathy by other means, such as feeding small amounts often or if possible continuous infusion rather than bolus feeding. A diet such as Royal Canin Convalescence support canine and feline or Hill's a/d diet would be suitable. Some clinicians add extra nutrients such as taurine, arginine, B vitamins, or carnitine to the tube feed, but there is no firm evidence that any of these are necessary if a balanced feline diet is used. However, additional vitamins are necessary in some specific cats; cobalamin (vitamin B_{12}) may be deficient, particularly in cats with concurrent pancreatic and/or ileal disease (see Chapter 34) and should then be supplemented parenterally. Vitamin K–responsive coagulopathies are very common in cats with lipidosis, and some recommend supplementation in all cats at the start of treatment with 0.5 mg/kg IM q12h for three doses.
   c. **How much**? Start conservatively with the resting energy requirement (RER) because cats have had prolonged anorexia and complications of feeding are more common in the first few days. Start with 20% of RER on day 1 and build up gradually over a few days because of the risk of refeeding syndrome (see text). Start with small amounts frequently (or even slow-rate constant infusion) and gradually build up to higher volumes and lower frequency over the first week. The calorie intake can then be gradually increased to the metabolic energy requirement (MER).

$$\text{RER} = 50\ \text{Kcal} \times \text{BW Kg}$$

$$\text{MER} = 70 - 100\ \text{Kcal} \times \text{BW Kg}$$

(70 for neutered, indoor cats; 100 for lean active adult cats)

   d. Appetite stimulants are not recommended because they are of limited efficacy and potentially hepatotoxic.
4. **Antioxidant supplementation:** Particularly S-adenosylmethionine (20 mg/kg or 200 mg total, PO, once daily) on the basis of limited but supportive evidence in cats. Also vitamin E 100 iu/day (see text).
5. **Additional therapeutic support as necessary:** Antiemetics and promotility agents such as maropitant (1 mg/kg once a day SC or IV intravenously slowly over 1-2 minutes for up to 5 days) and ranitidine (2 mg/kg PO or IV twice a day) may be necessary if the cat is vomiting or has delayed gastric emptying with reflux of food up the feeding tube. There is currently no evidence supporting the use of ursodeoxycholic acid in cats with lipidosis.

BW, Body weight.

syndrome: phosphate can be supplemented by administering potassium phosphate (0.01-0.03 mM/kg/h intravenously until the serum phosphate concentration normalizes), and the food should be introduced more gradually.

Many cats require vitamin K therapy for the management of coagulopathies, 0.5 mg/kg of vitamin K_1 (phytomenadione) subcutaneously or intramuscularly q12h for 3 days; clinicians should not place any central catheters or invasive feeding tubes until hemostasis is normalized. There is the potential for serious and undetected bleeding around a central venous catheter in a cat with a coagulopathy. Antioxidant therapy is also indicated for cats with lipidosis because of the associated glutathione depletion in many cats. Vitamin E and S-adenosylmethionine supplementation should be considered: S-adenosylmethionine, 20 mg/kg orally (PO), once daily, given whole on an empty stomach, cats and dogs; or 100- to 400-mg total dose daily in cats. The ideal dose of vitamin E in a cat is unclear, but we use 100 IU daily.

Prognosis for recovery in cats with hepatic lipidosis is good as long as feeding is rapidly and effectively instituted. Studies have reported between 55% and 80% survival in intensively fed cats, whereas mortality is very high without supportive feeding. One large study (Center et al., 1996) suggested that older age was a poor prognostic indicator for

BOX 35.2

Placement of Nasoesophageal Feeding Tubes

This is used for short-term nutritional support (<1 wk) while stabilizing the cat before the placement of an esophagostomy or gastrostomy tube.

Placement

1. Premeasure tube to allow placement in caudal esophagus, not stomach; this minimizes gastric reflux. Premeasure to seventh intercostal (IC) space from nose or 75% of distance from nose to last rib if animal is so obese that ribs cannot be counted (orogastric—ninth IC space or 90% of distance from nose to last rib). Mark tube with pen or piece of tape.
2. Apply local anesthetic to nose. Mild sedation may occasionally also be necessary, preferably with buprenorphine or butorphanol.
3. Lubricate tube and advance into the ventral meatus; it is important not to advance into the middle or dorsal meatus or the tube will lodge at the ethmoturbinates. It may be helpful to raise the cat's head slightly to do this.
4. Hold the cat's head normally as you approach the pharynx to prevent tracheal intubation. Allow the cat to swallow, and advance the tube to a measured mark or tape.
5. To check that the tube is correctly positioned, instill water and air and auscultate over the left flank for bubbling in the stomach. If still uncertain, perform radiography. If the tube does not have a radiodense line, first inject some iodine-containing contrast material into the tube.
6. Pass the tube over the top of the cat's head, and suture or glue the tapes at the level of the nares and top of the head; be careful to avoid interfering with the cat's whiskers.
7. Put on an Elizabethan collar.
8. Flush regularly with warm water before and after feeds.

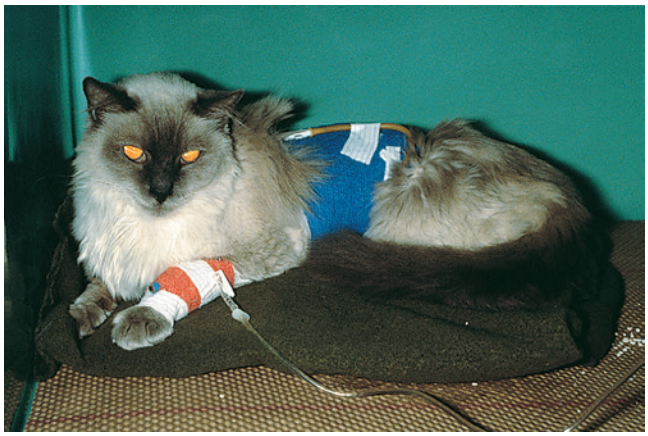


FIG 35.4
Cat with gastrostomy tube to permit long-term feeding.

survival and that cats with secondary hepatic lipidosis may do slightly worse than those with primary disease. However, the differences were not significant, which suggests that it is worth treating cats with secondary lipidosis as aggressively as those with primary disease.

BILIARY TRACT DISEASE

Biliary tract diseases are the second most common disorders of the feline liver in the United States and the most common feline liver disease in Europe (see Table 35.1). This contrasts with dogs, in which parenchymal diseases are most common. All disorders of the biliary tract in cats can present with similar clinical signs, including lethargy, anorexia, and jaundice. Clinical, clinicopathologic, and diagnostic imaging findings do not allow differentiation of the types of diseases; in most cases, cytology, bile culture, and histopathology of the liver are necessary for accurate diagnosis and most effective treatment as detailed in Table 35.3.

CHOLANGITIS

Cholangitis refers to inflammation of the biliary tract, which in some (but not all) cats may also extend to the surrounding hepatic parenchyma (cholangiohepatitis). It is more common in cats than in dogs, and it is typically divided into three categories, likely associated with different etiologies—neutrophilic cholangitis, lymphocytic cholangitis, and chronic cholangitis associated with liver fluke infestation. The nomenclature of feline biliary tract disease has been standardized by the World Small Animal Veterinary Association (WSAVA; Rothuizen et al., 2006; see Table 35.3). However, there is ongoing debate about the overlap between lymphocytic cholangitis and chronic neutrophilic cholangitis, and it has been suggested that these two categories should be combined into a broader non–suppurative cholangitis-cholangiohepatitis group (Warren et al., 2011). A wide variety of alternative names have been used in the literature in the past, sometimes blurring the categories and making comparisons between studies difficult. It is likely that there are several chronic forms of the disease with different etiologies and that increased understanding in the future will lead to improved nomenclature (see Table 35.3).

Cats with inflammatory biliary tract disease also often have concurrent pancreatitis and/or intestinal disease (often termed *triaditis*, Fragkou et al., 2016). It has been proposed that this is a reflection of the anatomy of their pancreatic and bile ducts, which usually join before entering the proximal duodenum through a common outflow tract. It has been suggested that this increases the likelihood of intestinal contents being refluxed up the pancreatic and bile ducts during vomiting. It is also possible that sphincter of Oddi spasm secondary to IBD, which has been reported in cats (Furneaux, 2010), blocks the pancreatic and bile ducts in some cats. However, it is likely that the reasons are multifactorial and that the disease associations also reflect common causative agents or events independent of anatomy in this species.

TABLE 35.3

Current World Small Animal Veterinary Association Classification of Feline Biliary Tract Disease

NAME OF DISEASE	NAMES PREVIOUSLY USED IN THE LITERATURE	CAUSE OF DISEASE	FINDINGS ON LIVER PATHOLOGY	RECOMMENDED DIAGNOSTIC PROCEDURES
Neutrophilic cholangitis, acute phase	Suppurative or exudative cholangitis-cholangiohepatitis.	Likely ascending bacterial infection from small intestine.	Neutrophils in lumen and/or epithelium of bile ducts. May also be edema and neutrophils in periportal area, parenchyma, and occasionally hepatic abscess.	Cytology and culture of bile aspirates are necessary for diagnosis. Ultrasound and histopathology can be suggestive but are not obligatory, and changes may be absent on either of these.
Chronic neutrophilic cholangitis (included in the neutrophilic cholangitis category by the WSAVA, but overlap with lymphocytic cholangitis category)	Some reported cases of "lymphocytic" or "chronic" cholangiohepatitis would now fall into this category.	Unknown. Some cases may be chronic persistent bacterial infections, and some cases may have the same etiology(ies) as lymphocytic cholangitis.	Mixed inflammatory infiltrate in portal areas, including neutrophils, lymphocytes, plasma cells, and sometimes some fibrosis and bile duct proliferation.	Liver histopathology necessary for diagnosis. Changes may be found on ultrasound and bile cytology but sensitivity limited; will not yield definitive diagnosis.
Lymphocytic cholangitis	Lymphocytic cholangiohepatitis, lymphocytic portal hepatitis, chronic cholangiohepatitis, nonsuppurative cholangitis, but note overlap of these definitions with the chronic phase of neutrophilic cholangitis.	Unknown; may be immune-mediated disease.	Infiltration of small lymphocytes into portal regions. Variable portal fibrosis and bile duct proliferation. Lymphocytes may also be present in biliary epithelium. Occasional plasma cells, eosinophils may be seen. Difficult to differentiate some cases from well-differentiated lymphoma.	Liver histopathology necessary for diagnosis. Changes may be found on ultrasound and bile cytology but sensitivity limited; will not yield definitive diagnosis.
Chronic cholangitis associated with liver fluke	—	Liver fluke	Dilated larger bile ducts with papillary projections and marked periductal and portal fibrosis. Slight to moderate inflammation of portal areas and ducts with neutrophils, macrophages, limited numbers of eosinophils. Flukes, eggs may be seen in ducts.	Ultrasonography of dilated bile ducts + history of possible exposure + demonstration of fluke eggs in feces or bile aspirates (see text). Histopathology supportive.

Adapted from Rothuizen J et al: *WSAVA standards for clinical and histological diagnosis of canine and feline liver diseases,* Oxford, England, 2006, Saunders Elsevier.

Neutrophilic Cholangitis

Neutrophilic cholangitis is also known as suppurative cholangitis, exudative cholangitis-cholangiohepatitis, and acute cholangitis-cholangiohepatitis.

Pathogenesis and Etiology

This process is believed to be caused by an ascending bacterial infection originating in the small intestine. The most common organism isolated is *Escherichia coli,* although *Streptococcus* spp., *Klebsiella* spp., *Pseudomonas* spp., *Enterococcus* spp., *Clostridium* spp., and even occasionally *Salmonella* spp. may be involved. Concurrent pancreatic and intestinal disease is common (see earlier). The result is a neutrophilic infiltrate in the lumen of the bile duct and often infiltration of the bile duct walls with neutrophils, and edema and neutrophils within the portal areas (Fig. 35.5). Occasionally, an associated hepatic abscess may develop. Cholecystitis (inflammation of the gallbladder) may occur concurrently, or the two conditions may occur separately. A more chronic stage of neutrophilic cholangitis is also recognized; in these cases there is a mixed inflammatory infiltrate in the portal areas consisting of neutrophils, lymphocytes, and plasma cells. Some of these cases are thought to represent more chronic, persistent infection of the biliary tract, although a recent study using fluorescence in situ hybridization failed to find more bacteria in these cases than in control cats (Warren et al., 2011). There is significant overlap between cats with chronic neutrophilic cholangitis and cats with lymphocytic cholangitis; the rest of this section describes only acute neutrophilic cholangitis.

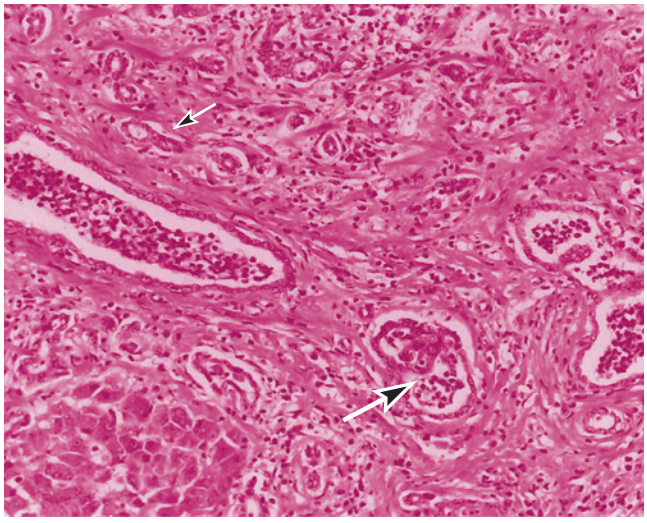


FIG 35.5
Photomicrograph of liver specimen from a cat with neutrophilic cholangitis. Note the neutrophilic and histiocytic inflammation in and around the bile ducts *(large arrow)*. Biliary ductular hyperplasia is also present *(small arrow)* (H&E stain Bar = 100·m). (Courtesy Pathology Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

Clinical Features

Cats of all ages and breeds can be affected, but acute cholangitis is most often seen in young to middle-aged cats. It usually presents acutely (less than 1 month's history), although it may be present longer. Cats typically have signs of biliary stasis and sepsis with lethargy, pyrexia, and jaundice.

Diagnosis

Clinicopathologic and imaging findings overlap with those in other diseases of the biliary tract, so a definitive diagnosis of neutrophilic cholangitis cannot be made simply from a characteristic history and clinicopathologic findings. However, cats with this acute disease tend to have higher segmented and band neutrophil counts, ALT activities, and total bilirubin concentrations than cats with lymphocytic cholangitis. Rather surprisingly, a recent study documented that some cats with acute neutrophilic cholangitis had normal white blood cell counts and liver enzyme levels, and there was significant overlap in clinicopathologic values among cats with acute neutrophilic cholangitis, chronic neutrophilic cholangitis, and lymphocytic cholangitis. Therefore clinicopathologic findings were neither sensitive nor specific for the disease (Callahan Clark et al., 2011). Also, hepatic ultrasonography is neither sensitive nor specific. Affected cats may have an enlarged hyperechoic liver on ultrasonography and may develop dilated biliary tracts more chronically, but cats with the acute disease usually have no dilation of the biliary tract on ultrasonography, and the hepatic parenchyma may appear normal (Callahan Clark et al., 2011; Marolf et al., 2012). Pancreatic abnormalities are also commonly seen on ultrasound in cats with neutrophilic cholangitis, supporting the presence of triaditis in some affected cats.

An accurate diagnosis of neutrophilic cholangitis caused by acute ascending infection requires cytology and culture of bile. Histopathology of the liver alone is not enough in this particular disease because in many cases the disease is confined to the biliary tract, and changes on liver pathology are mild and nonspecific. Samples of bile for bacterial culture can be taken carefully from the gallbladder during laparotomy or laparoscopy or under ultrasonographic guidance. There is a small but definite risk of bile leakage, particularly if the gallbladder wall is devitalized and/or there is increased intravesical pressure. In a study of six cats with neutrophilic cholecystitis, one cat developed gallbladder rupture and bile peritonitis after ultrasound-guided cholecystocentesis (Brain et al., 2006). However, in one study of transcutaneous gallbladder aspiration in 12 normal cats (Savary-Bataille et al., 2003) and in another study of 83 cats (Byfield et al., 2017), there were no cases of gallbladder rupture. If the clinician has a concern about the integrity of the gallbladder wall, it might be safer to obtain a sample at laparotomy or laparoscopy rather than under ultrasonographic guidance. In the latter case, a general anesthetic is strongly recommended to prevent patient movement while the needle is in the gallbladder, which greatly increases the risk of bile leakage. Some clinicians place the needle in the gallbladder through the hepatic parenchyma to further reduce the risk of leakage.

The cat should be monitored carefully for any leakage of bile after the procedure; any suspicion of leakage and bile peritonitis warrants surgery. Cytology of bile usually shows bacteria and neutrophils, and culture and sensitivity tests should be performed.

Treatment and Prognosis

Cats should be treated for 4 to 6 weeks with an appropriate antibiotic on the basis of the results of culture and sensitivity tests. Amoxicillin is a good initial choice at a dose of 15 to 20 mg/kg PO q8h. Ursodeoxycholic acid may be given as an additional choleretic and antiinflammatory agent at a dose of 15 mg/kg PO q24h, although there are no studies demonstrating its benefit in cats with neutrophilic cholangitis. Septic or extremely sick cats may require hospitalization for IV fluid and IV antibiotic administration during the initial stages of therapy. Careful attention should be paid to feeding anorexic cats to prevent the concurrent development of hepatic lipidosis, which was found in one third of the cats with cholangitis in a recent study (Callahan Clark et al., 2011); a high-protein diet designed for critical care use, as outlined in the lipidosis section, is more appropriate for these animals than a protein-restricted liver diet. The prognosis is generally good, and these cats usually recover completely provided they are treated early and appropriately. It is thought that some cases of the more chronic form of neutrophilic cholangitis may represent long-term persistence of a low-grade infection in untreated or only partially treated cats.

Lymphocytic Cholangitis

Lymphocytic cholangitis is also termed *lymphocytic cholangiohepatitis, lymphocytic portal hepatitis,* and *nonsuppurative cholangitis*. Some cases of chronic neutrophilic cholangitis as defined by the WSAVA may also overlap with lymphocytic cholangitis.

Pathogenesis and Etiology

Lymphocytic cholangitis is a slowly progressive chronic disease characterized by infiltration of the portal areas of the liver with small lymphocytes. Occasionally, plasma cells and eosinophils can be seen. The presence of neutrophils might change the name of the disease to chronic neutrophilic cholangitis, but some authors include a predominantly lymphocytic disease with a small number of neutrophils in the lymphocytic chronic cholangitis category. Histologic changes vary among cases, probably reflecting a variety of as yet unknown etiologies. In the largest study on the histology of the disease (Warren et al., 2011), many cats had biliary hyperplasia and peribiliary fibrosis, but a small number of cases showed ductopenia (loss of bile ducts). The lymphocyte infiltrate was predominantly of T cells, but portal B-cell aggregates seemed to be a particular feature of the disease. Bile duct targeting by inflammatory cells was common. In severe cases the main differential diagnosis on histology is lymphoma, and in some cases, differentiating the two diseases can be difficult. The cause is unknown, and the variety of clinical and histologic presentations suggests more than one cause. Some researchers have suggested an immune-mediated etiology, but the disease does not resolve with immunosuppressive medication. Other studies have suggested possible infectious etiologies, such as *Helicobacter* or *Bartonella* spp. (Boomkens et al., 2004; Greiter-Wilke et al., 2006; Kordick et al., 1999), although recent work has not supported infectious causes (Warren et al., 2011). However, the use of immunosuppressive medication in all these cases is subject to question.

Clinical Features

Cats with lymphocytic cholangitis were previously reported to be typically young to middle-aged, and Persians appeared to be overrepresented, but recent studies report it in older cats with no obvious breed predisposition (Callahan Clark et al., 2011; Warren et al., 2011). Affected cats tend to have a long history (months to years) of waxing and waning low-grade illness. Many become jaundiced, and they often lose weight and have intermittent anorexia and lethargy, but they are less likely to be pyrexic than cats with neutrophilic cholangitis. About one third of cats may also present with a high-protein ascites, reportedly most commonly in the United Kingdom. This makes differentiation from feline infectious peritonitis (FIP) important. Ultimately, the differentiation in these cats can be made only on histopathology.

Diagnosis

Diagnosis in these cases relies ultimately on hepatic histopathology, although ultrasonographic and clinicopathologic findings can support a presumptive clinical diagnosis. Increases in liver enzyme levels are mild to moderate and tend to be less marked than in cats with neutrophilic cholangitis. Peripheral blood neutrophilia is less common than in cats with the acute disease but may be present. A particular feature of most cats with lymphocytic cholangitis is an increase in γ-globulin concentration, which again may cause confusion with FIP. However, some cats have normal white blood cell counts and liver enzyme levels, so these findings are neither sensitive nor specific (Callahan Clark et al., 2011). Radiographic signs are also nonspecific; there may be hepatomegaly (which is often caused by enlargement of the larger bile ducts) and in some cases abdominal effusion but radiographs are often normal (Fig. 35.6). Ultrasonography is more helpful and reveals dilation of the biliary tract in some patients (see Fig. 34.11). The common bile duct typically appears dilated, and there may be dilation of the gallbladder and sludge in it. The main differential diagnosis for these cats is EBDO; the ultrasonographer should attempt to rule this out by carefully imaging the surrounding pancreas, small intestine, and mesentery, although it can be difficult to rule out EBDO completely particularly if it is caused by an echolucent lesion or sphincter of Oddi spasm.

It is very important to evaluate a hemostasis profile before performing a liver biopsy in view of how commonly coagulation times are prolonged in cats with liver disease. Vitamin K should be given before the biopsy (0.5 mg/kg of vitamin

K_1 SC or IM, q12h for 3 days) if there is any concern about hemostasis; fresh-frozen plasma should be available to manage potential postbiopsy bleeding. The author routinely administers vitamin K for 2 to 3 days before liver biopsy in all cats. It is recommended that biopsies be taken from multiple lobes because histologic findings can vary considerably among liver lobes (Callahan Clark et al., 2011; Warren et al., 2011). Bile aspiration is not necessary unless the disease is more acute and there is a possibility of neutrophilic cholangitis. Histology is important to rule out FIP (see Chapter 96) and lymphoma (see Chapter 79). Hepatic lymphoma shows a predilection for portal areas in cats, so it is an important differential diagnosis in these cats. Large cell lymphomas are relatively easy to diagnose, but small cell lymphomas appear similar cytologically and histologically to lymphocytic cholangitis. Features suggesting lymphoma include a dense lymphocytic infiltrate extending beyond the limiting plate, an absence of peribiliary fibrosis, and evidence of lymphoma in other tissues, such as the intestine and abdominal lymph nodes. The polymerase chain reaction (PCR) for antigen receptor rearrangement (PARR) assay (see Chapter 79) may be helpful in distinguishing lymphoma from inflammatory disorders. The typical hepatic lesion in cats with FIP is a multifocal pyogranulomatous reaction with evidence of vasculitis or perivasculitis, which is distinct from the periportal lymphocytic infiltrate seen in cats with lymphocytic cholangitis (Fig. 35.7). Serology or PCR assay for *Bartonella* spp. might be considered, although the importance of this organism in the naturally occurring disease is unclear.

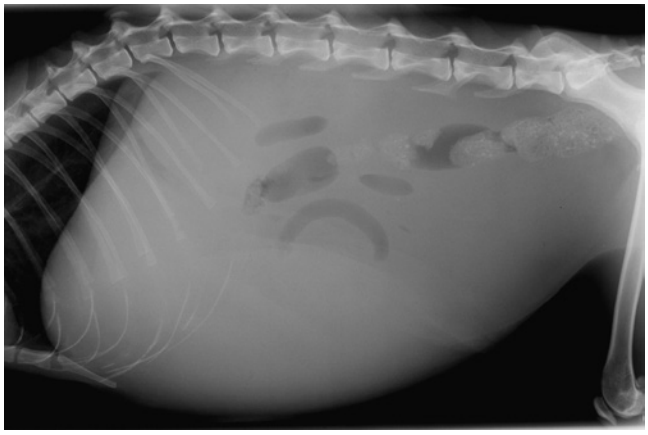


FIG 35.6
Lateral abdominal radiograph from a cat with lymphocytic cholangitis and associated ascites. The major differential diagnosis in this case would be feline infectious peritonitis. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

Treatment and Prognosis

Researchers disagree on the recommended therapy for this disease, which likely reflects uncertainty about its etiology. Several authors recommend immunosuppressive doses of corticosteroids. However, although these tend to ameliorate the acute flare-ups of the disease, they do not lead to resolution of signs, and the condition invariably recurs. Antibiotic therapy is wise, at least early in treatment, until an infectious etiology has been ruled out. There is a logical reason to use ursodeoxycholic acid (15 mg/kg PO q24h) in these cats for its choleretic and antiinflammatory effects, as well as its effect on modulating the bile acid pool and reducing toxic bile acids. Use of antioxidants such as S-adenosylmethionine (20 mg/kg or 200-400 mg total, once daily on an empty

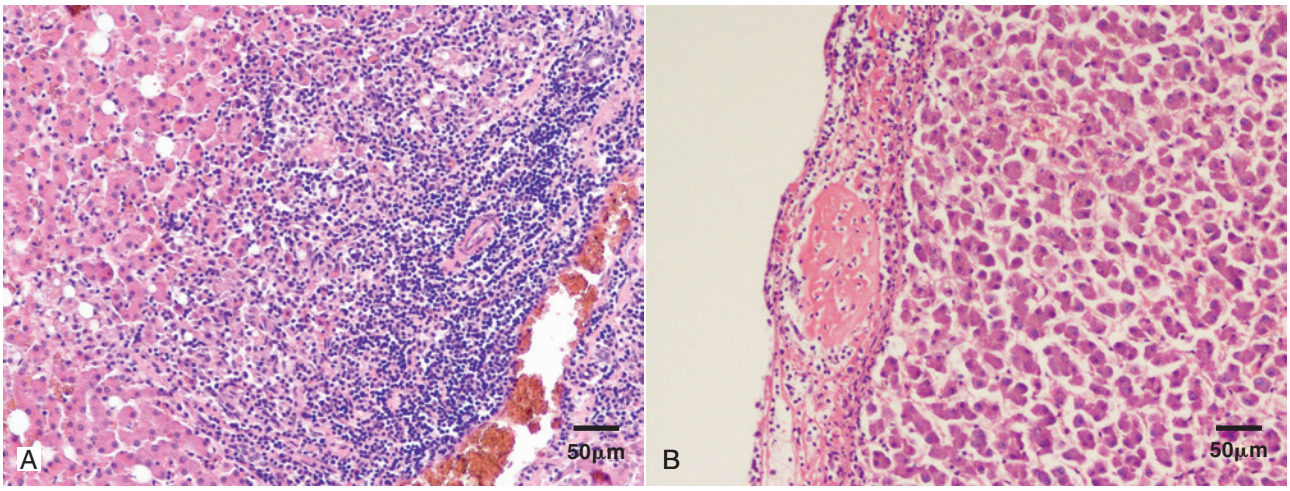


FIG 35.7
(A) Photomicrograph of liver specimen from a cat with severe lymphocytic cholangitis. There is an intense mononuclear cell infiltration surrounding the portal tract. **(B)** Photomicrograph of liver specimen from a cat with feline infectious peritonitis. Note the pyogranulomatous perivascular inflammation along the liver capsule (left-hand edge) (**A** and **B,** H&E stain). Bar = 50 µm. (Courtesy Pathology Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

stomach) and vitamin E (≈100 IU daily) is also logical because bile is a potent oxidizing toxin in the liver. A recent retrospective study of 26 cats with lymphocytic cholangitis, with a preponderance of older male cats and Norwegian Forest cats, suggested that cats had a longer survival time when given prednisolone alone than when given ursodeoxycholic acid alone (Otte et al., 2013). Further prospective studies are necessary to evaluate these therapies individually and together in a wider range of ages and breeds before the results can be generalized to all cats with lymphocytic cholangitis. Again, it is important to ensure that affected cats eat to prevent the development of concurrent hepatic lipidosis; as discussed earlier, a highly digestible, high-quality diet without protein restriction is indicated. A diet formulated for feline intestinal disease (e.g., Eukanuba feline intestinal, Procter & Gamble, Cincinnati, Ohio; Royal Canin feline selected protein; or Hill's i/d) might be the most appropriate because of the relatively high prevalence of concurrent IBD. Tube feeding should be considered if necessary (see earlier, "Hepatic Lipidosis"). Cats with more acute signs, particularly associated with concurrent intestinal and/or pancreatic disease, may require hospitalization and IV fluid therapy.

The prognosis for cure appears to be poor because the disease appears to wax and wane chronically in spite of treatment. However, few cats with lymphocytic cholangitis die as a result of their disease and those that do die have a high prevalence of concurrent pancreatic and intestinal disease, which may explain their poor outcome (Callahan Clark et al., 2011). This is likely because, as opposed to dogs, the disease does not generally progress to end-stage cirrhosis.

Sclerosing Cholangitis

Sclerosing cholangitis, or biliary cirrhosis, involves an end-stage fibrotic liver and is uncommon in cats except in association with liver fluke. Cats appear to be very resistant to hepatic fibrosis. The condition is characterized histologically by diffuse proliferative fibrosis of the bile duct walls spreading to involve the hepatic lobules and disrupting their architecture and circulation. It is thought in most cases to represent an end stage of chronic biliary tract disease, usually complete obstruction or chronic severe liver fluke infestation (see the next section). It is unusual for neutrophilic or lymphocytic cholangitis to progress to sclerosing cholangitis in cats. Some cases of ductal plate abnormality may be misdiagnosed as sclerosing cholangitis in cats (see later section). Affected cats present with typical clinical signs of chronic biliary tract disease (see previous "Cholangitis" and later "Extrahepatic Biliary Tract Obstruction"). Affected cats may also develop chronic portal hypertension, with the resultant development of ascites, gastrointestinal ulceration, and/or an acquired portosystemic shunt (PSS) and HE (see Chapter 33). Acquired PSSs are much less common in cats than in dogs. Sclerosing cholangitis is diagnosed on hepatic biopsy; again, it is very important to evaluate hemostasis profiles before biopsy and to administer vitamin K_1 (0.5 mg/kg SC or IM q12h for up to 3 days) as necessary because vitamin K deficiency is common in cats with chronic biliary tract obstruction. It should be noted that cats with sclerosing cholangitis may have hepatomegaly on radiography, which is unexpected; cirrhosis usually results in a small liver in dogs. Presumably, this reflects the biliary tract dilation and florid peribiliary fibrosis in these cases. Treatment is supportive, with treatment of only the clinical signs associated with portal hypertension, as outlined in Chapter 36.

Liver Fluke Infestation

Etiology and Pathogenesis

Liver fluke infestation is regularly observed in cats from areas endemic for the family Opisthorchiidae *(Platynosomum* spp., and occasionally *Amphimerus pseudofelineus* and *Metametorchis intermedius).* It is estimated that, in Florida and Hawaii, the prevalence of *Platynosomum fastosum* (the most common feline liver fluke) is as high as 70%; the clinical feline disease is referred to as lizard poisoning. The flukes require two intermediate hosts: water snails and lizards, amphibians, geckos, or fish, depending on the species. The cat is the final host and is infested by ingesting the metacercariae in the second intermediate host. The immature flukes migrate from the intestine to the liver via the bile ducts and become adult and patent by 8 to 10 weeks. Eggs can then be found in the feces (inconsistent) or bile aspirates (more reliable). The severity of associated disease seems to depend on the parasite load and on individual responses. Many cases are mild. In some cases the pancreas may also be affected. The clinical signs are caused by peribiliary inflammation and fibrosis in the liver, culminating, in severe cases, in an obstructive jaundice. In experimental infestations, hepatic lesions are visible histologically starting approximately 3 weeks postinfestation. There is an initial distention of proximal bile ducts and a neutrophilic and eosinophilic inflammatory response, which progresses chronically to adenomatous duct hyperplasia and surrounding florid fibrosis. Eosinophils may be absent in the later stages of disease, and flukes and eggs may not be seen on histology.

Clinical Signs

Commonly, cats with low-grade infestations remain asymptomatic. However, heavy infestations can be associated with severe and often fatal disease (Haney et al., 2006; Xavier et al., 2007). In these cases clinical signs are typically those of posthepatic jaundice combined with those of inflammatory liver disease (e.g., jaundice, anorexia, depression, weight loss, lethargy). Diarrhea and vomiting have been features of clinical cases but do not occur in experimental cases; affected cats may also have hepatomegaly and ascites.

Diagnosis

Diagnosis is made after a history of exposure (cats often have a history of hunting lizards), combined with finding the flukes or eggs in feces or bile. Supportive findings are high liver enzyme levels typical of cholestasis; ALT, AST, and bilirubin concentrations are particularly high, but the ALP level is surprisingly often only mildly increased. Eosinophilia is inconsistent. Ultrasonography reveals changes typical of

biliary tract disease, such as dilation of the bile ducts. In one case fluke infestation also caused acquired polycystic disease of the biliary system (Xavier et al., 2007).

Ova may be found in the feces using the formalin-ether sedimentation method (Box 35.3). However, shedding of eggs is sporadic; also, eggs will not be present if the fluke infestation has resulted in a complete biliary obstruction. The most reliable way of demonstrating flukes and eggs is with bile aspirates.

Treatment

The ideal and most effective treatment regimen for feline liver flukes remains controversial. Currently, the most commonly recommended treatment is praziquantel (20 mg/kg SC q24h for 3 days). The prognosis for recovery in severely affected cats is poor.

CHOLECYSTITIS

Cholecystitis refers to inflammation of the gallbladder. Neutrophilic cholecystitis is frequently seen in cats but rarely in dogs. It may occur alone or in combination with neutrophilic cholangitis. Ultrasonographically, the gallbladder wall often appears thickened and sometimes irregular; there may be sludging of the bile and/or choleliths. Clinical signs, diagnosis, and treatment are similar to those of neutrophilic cholangitis (see earlier). Chronic thickening of the gall bladder wall may be an indications for surgical cholecystectomy since bacterial infections recur in these patients. Lymphocytic cholecystitis is also occasionally recognized and is treated like lymphocytic cholangitis (see earlier).

EXTRAHEPATIC BILE DUCT OBSTRUCTION

Pathogenesis and Etiology

EBDO is a syndrome associated with several different underlying causes. These may be categorized as extraluminal compressive or intraluminal obstructive lesions, but diseases often cause EBDO through a combination of these mechanisms; for example, cholangitis may result in a combination of extraluminal compression by associated edema and inflammation and intraluminal obstruction by inspissated bile. Therefore it is more practically helpful to divide the causes into common and less common causes (Box 35.4). Several studies have shown inflammation of the small intestine, pancreas, biliary tract, or a combination of these (known as triaditis) to be the most common cause of EBDO in cats; neoplasias of the biliary tract or pancreas are the next most common cause. Dysfunction of the sphincter of Oddi because of adjacent duodenal inflammation or neoplasia has also been recently reported in cats and may be more common than appreciated because of difficulties in diagnosis (Furneaux, 2010). Choleliths are uncommon in cats. Those reported in the literature are usually cholesterol or calcium salts, or a mixture of these, and are associated with cholangitis. They are variably radiodense depending on the amount of calcium in the stone, but they are easily visualized using ultrasonography (Fig. 35.8). Two of the three cases of bilirubin choleliths reported in the literature were from Somali cats with pyruvate kinase deficiency, and it was assumed that they were secondary to chronic hemolysis (Harvey et al., 2007). Therefore finding bilirubin choleliths in a cat should stimulate a search for underlying hemolytic disease.

BOX 35.3

Formalin-Ether Sedimentation Technique for Detecting *Platynosomum concinnum* Ova in Feces

1. Mix 1 g of feces in 25 mL saline; filter through a fine mesh screen.
2. Centrifuge solution for 5 min at 1500 rpm; discard the supernate.
3. Resuspend the pellet with 7 mL of 10% neutral buffered formalin; let stand for 10 min.
4. Add 3 mL of cold ether on top of solution and shake vigorously for 1 min. Centrifuge for 3 min at 1500 rpm.
5. Discard the supernate, resuspend the pellet in several drops of saline, and prepare slide of solution to examine microscopically.

From Bielsa LM et al: Liver flukes *(Platynosomum concinnum)* in cats, *J Am Anim Hosp Assoc* 21:269, 1985.

BOX 35.4

Causes of Extrahepatic Bile Duct Obstruction in Cats

Common Causes

One or a combination of inflammation of pancreas, duodenum, or biliary tree (most common)
Neoplasia, particularly of the biliary tree or pancreas (second most common)

Less Common Causes

Stricture of bile duct after inflammation, surgery, or trauma
Sphincter of Oddi dysfunction
Diaphragmatic with involvement of the gallbladder or common bile duct and subsequent compression
Cholelithiasis
- Usually cholesterol and/or calcium salts concurrent with cholangitis
- Occasionally bilirubin, associated with pyruvate kinase deficiency–induced hemolysis in Somali cats

Cysts (congenital or acquired) compressing biliary tree
Liver flukes
Foreign body

Note: Sepsis distant to the liver can produce an associated biliary stasis, which may appear clinicopathologically to be very similar to extrahepatic bile duct obstruction (EBDO). Also, biliary tract rupture (usually traumatic) produces clinicopathologic findings similar to those of EBDO but the cat is usually much sicker.

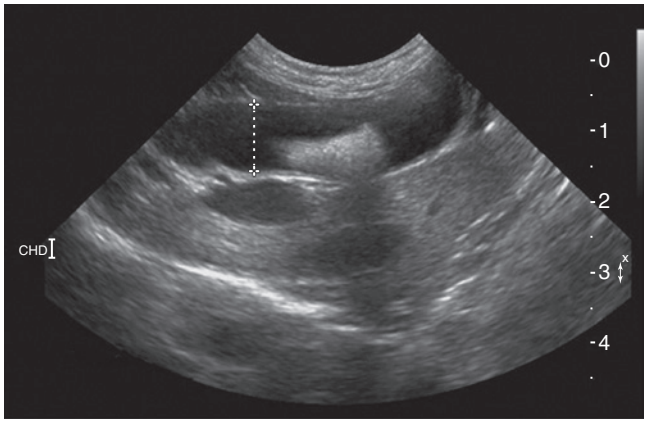


FIG 35.8
Ultrasound image of the common bile duct in a cat with choleliths causing extrahepatic biliary obstruction. Note that the bile duct is markedly dilated and contains a radiodense cholelith with distal acoustic shadowing. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

Clinical Features

In cats with EBDO, clinical signs, clinicopathologic findings, and survey radiographic findings are indistinguishable from those associated with other severe cholestatic hepatopathies; jaundice, anorexia, depression, vomiting, and hepatomegaly are the main presenting features. Cats with biliary obstruction can also be painful, and the clinician should be aware of subtle signs because cats tend to hide their pain. If biliary obstruction is complete, feces will be pale or acholic. There may be a cranial abdominal mass on palpation because of a very distended gallbladder or underlying neoplasia, but often abdominal palpation is normal (other than the hepatomegaly). Cats with EBDO are at particular risk of malabsorption of fat-soluble vitamins, including vitamin K, because of the lack of intestinal bile salts reducing fat digestion. This is compounded in many cases by the concurrent intestinal and/or pancreatic disease, which further reduces fat absorption. As discussed previously, it is very important in these cases to assess coagulation times before performing biopsies or surgery and to supplement vitamin K parenterally as necessary. However, to the author's knowledge, no correlation between the results of hemostasis profiles and development of postbiopsy bleeding has been established.

Diagnosis

Ultrasonography is the most useful diagnostic tool to differentiate EBDO from other biliary tract diseases in cats; sometimes, the cause of EBDO is determined. Clinicopathologic findings are nonspecific; the high concentrations and activities of hepatocellular and biliary enzymes, bilirubin, and cholesterol resulting from cholestasis are indistinguishable from those in cats with other cholestatic hepatopathies. Ultrasonography will usually reveal dilation of the gallbladder and extrahepatic and intrahepatic biliary trees (see Fig. 35.8), although gallbladder dilation is not a consistent or essential finding. A search should then be conducted for a possible cause of obstruction by carefully examining the small intestine, liver, and pancreas for evidence of inflammation or neoplasia. Biliary tract rupture can present in a similar way and should be ruled out by identifying and analyzing any free abdominal fluid; cats with biliary rupture have a high concentration of bilirubin in the fluid. FNA of bile from the gallbladder under ultrasonographic guidance should be avoided or approached with great care if EBDO is suspected or confirmed because of the high risk of leakage caused by the increased pressure. In these cats it is preferable to aspirate bile during surgery. It may be necessary to undertake an exploratory laparotomy to assess bile duct patency and the cause of the obstruction. Hemostatic function should be assessed first, and vitamin K therapy given (0.5 mg/kg of vitamin K_1 SC or IM q12h for 3 days). The liver, pancreas, and small intestine should be carefully inspected and biopsied as necessary.

Treatment

Treatment depends on the underlying cause of the EBDO and whether the obstruction is complete or partial. The prognosis for partial obstructions is surprisingly good when using medical management, and surgery may not be necessary in all cases. Studies of EBDO in acute-on-chronic pancreatitis in humans suggest that medical management rather than surgery or stenting is the treatment of choice in most cases and that there are usually no long-term sequelae (Abdallah et al., 2007). Similar studies have not been reported in cats.

If the feces are not acholic and there is some evidence of bile flow into the duodenum and no pain, cats can be managed medically with a choleretic (ursodeoxycholic acid, 15 mg/kg PO q24h) and an antioxidant (e.g., S-adenosylmethionine, 20 mg/kg, or 200-400 mg daily on an empty stomach) to protect the hepatocytes against bile-induced oxidant damage. The underlying disorder should also be treated as outlined in the preceding section. However, if the cat does not improve after several days or signs of complete obstruction develop, such as acholic feces, surgical intervention is indicated. Major biliary tract surgery in the cat carries a high morbidity and mortality, and should be undertaken only when necessary to relieve complete obstruction. More minor procedures such as sphincterotomy, cholecystectomy, and stent placement are better tolerated.

DUCTAL PLATE ABNORMALITIES

The ductal plate is the distinct layer of cells surrounding the developing portal triad in the fetus. Abnormalities in the development of this cause a variety of congenital disorders particularly affecting intrahepatic bile ducts including biliary cysts (see later) and congenital hepatic fibrosis. Although uncommon, these are reported in cats. Cats with inherited polycystic kidney disease often also have cysts within the liver. In some cases, these are associated with the classic

mutation for polycystic kidney disease, and in others, they are not (Guerra et al., 2015). Congenital hepatic fibrosis has also been reported in cats, and Persian cats appear to be over-represented (Bosje et al., 1988; Zandvliet et al., 2005). Affected cats usually present with signs of portal hypertension including ascites, lethargy and vomiting, and HE. Alternatively, lesions may be discovered incidentally on ultrasound. Portal hypertension is unusual in cats and should raise the suspicion of ductal plate abnormality particularly in areas where liver fluke is not endemic. Inexperienced pathologists may erroneously diagnose some cases of ductal plate abnormality as biliary cirrhosis. Cytokeratin staining of liver sections helps highlight the classic marked proliferation of small bile ducts seen in the bridging fibrosis in congenital hepatic fibrosis.

Affected cats are treated symptomatically for portal hypertension (see Chapter 36 for more details). Prognosis can be good with life-long treatment.

BILIARY CYSTS

Most cystic lesions in the feline liver are of bile duct origin and may be congenital or acquired. Congenital cysts are usually multiple and often present as part of a congenital ductal plate abnormality as described earlier, polycystic disease of several organs, including the kidneys. The cystic contents are clear. Persian cats and Persian crosses are at increased risk. Cysts may be an incidental finding on imaging, particularly if they are small, but large cysts can cause clinical signs as a result of destruction of hepatic tissue and also compression of surrounding bile ducts resulting in signs of biliary tract obstruction (see earlier). Treatment is not indicated if they are small and nonprogressive, but if they are large and causing problems, they may be treated surgically by removal or omentalization (Friend et al., 2001).

Acquired hepatic cysts may be single or multiple and may be small or very large. The contents may be clear, bloody, or bilious. They may occur secondary to trauma, inflammation, or neoplasia (including biliary cystadenomas; Fig. 35.9) or in rare cases caused by liver flukes. Therapy depends on the cause, but surgical management may be necessary if they are large. Cysts may also occur in the form of large, irregular sacculations of the extrahepatic bile duct (choledochal cysts).

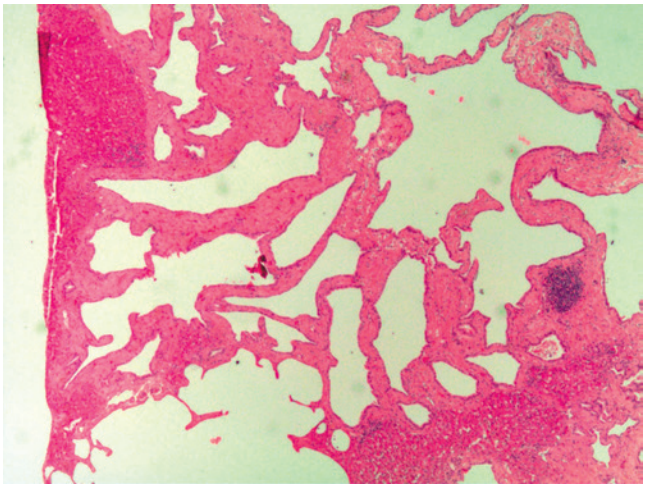


FIG 35.9
Photomicrograph of liver specimen from a cat with hepatic cystadenoma. Note the multiple cystic spaces lined with biliary epithelium (H&E stain). (Courtesy Pathology Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

HEPATIC AMYLOIDOSIS

Etiology

Hepatic amyloidosis is an uncommon but apparently emerging cause of liver disease in cats. Historically, amyloidosis was usually recognized as a familial disease in Abyssinian cats, which predominantly affects the kidneys although liver involvement is not uncommon. However, amyloidosis in Siamese cats is predominantly hepatic. Hepatic amyloidosis has also been reported in domestic shorthairs, oriental shorthairs, and a Devon Rex cat (Beatty et al., 2002). The amyloid in familial and sporadic cases is amyloid A (inflammatory), and in sporadic cases there is usually an underlying chronic inflammatory process in another organ (e.g., chronic gingivitis), which is thought to be the driving force for the formation of the inflammatory amyloid.

Clinical Signs

Affected cats usually present with signs of anemia and hypotension related to rupture of the hepatic capsule and hemoabdomen. These cats are predisposed to hepatic rupture because the liver is enlarged and rigid, and therefore easily damaged with normal trauma, such as jumping. Affected cats usually exhibit lethargy, anorexia, pale mucous membranes, bounding pulse, and heart murmur secondary to the anemia but rarely any specific signs of liver disease. There may be hepatomegaly on abdominal palpation.

Diagnosis

Diagnosis relies on histopathology of a liver biopsy; although clinicopathologic and ultrasonographic findings are supportive, it is important to rule out the major differential diagnoses of FIP, hepatic lipidosis, and hepatic lymphoma. The transient anemia resolves as blood is reabsorbed from the abdomen (autotransfusion). There are mild to marked increases in ALT activity and globulin concentration, but there are rarely increases in ALP and GGT levels, which helps differentiate amyloidosis from biliary tract disease and lipidosis. On ultrasonography, amyloidosis can resemble lymphoma and lipidosis, with hepatomegaly and a generalized increase in hepatic parenchymal echogenicity or a mixed hypoechoic and hyperechoic appearance (Beatty et al., 2002), but no dilation of the biliary tract. FNA cytology is not helpful because amyloid does not appear on the aspirate. Therefore hepatic biopsy, after careful evaluation of hemostasis profiles, is the recommended method of diagnosis.

Treatment and Prognosis

Treatment is supportive because there is no specific antiamyloid medication. Colchicine is of uncertain efficacy and is not indicated for cats because of its potential toxicity. Instead, the focus should be on reducing or eliminating the underlying inflammatory disorder driving the amyloid deposition and supportive care with antioxidants and vitamin K supplementation as necessary (0.5 mg/kg SC or IM every 7-20 days). Blood transfusions may be necessary in cats with acute hemoabdomen. The long-term prognosis is poor, and most cats die as a result of intraabdominal bleeding.

FELINE COPPER STORAGE DISEASE

Primary and secondary accumulation of copper is much less common in feline liver disease than in dogs (see Chapter 36), however, it has been reported (Whittemore et al., 2012; Hurwitz et al., 2014). It is therefore important to consider staining feline liver biopsies for copper.

Primary copper storage disease has been reported in cats with typical centrilobular distribution of copper on histology and a high dry weight concentration of copper on analysis of liver (Hurwitz et al., 2014). Affected cats can be any sex or breed but tended to be young (median 2 years). Clinical, clinicopathologic, and imaging findings overlap other feline hepatobiliary disorders, particularly cholangitis. All cats had elevated ALT and, in some affected cats, the elevation was marked. Diagnosis was on the basis of histopathology and on measurement of copper > 700 μg/g of liver sample dry weight. Cats were treated with a low copper diet (Prescription Diet L/D Feline Hepatic Health, Hills Pet Nutrition Inc, Topeka, Kansas or Veterinary Diet Feline Hepatic, Royal Canin, St Charles, MO.) and chelation with penicilliamine 10 to 15 mg/kg per os every 12 hours. Close monitoring is necessary because one cat developed hemolytic anaemia during treatment, which resolved with cessation of penicillamine. Alternatively, elemental zinc (2-4 mg per os every 24 hours) could be used instead of chelation, although the relative efficacy is unclear. It is important not to use zinc concurrently with penicillamine as zinc will compete with the copper for chelation. Administration of antioxidants is also wise (vitamin E and SAMe).

NEOPLASIA

Etiology

Primary liver tumors are uncommon in cats but appear to be more common than in dogs. Hepatic tumors are much less common in both species than in humans, possibly because two of the predisposing factors for development of liver tumors (hepatitis virus infection and α-protease inhibitor deficiency) have not been recognized in small animals. Cirrhosis also predisposes to liver tumors in humans but is rare in cats. Liver tumors represent 1% to 3% of all neoplasms in cats (Liptak, 2007) but up to 7% of the nonhematopoietic tumors. No predisposing factors have been identified except possibly primary copper storage disease (Hurwitz et al., 2014). In cats, in contrast to dogs, benign tumors are more common than malignant tumors; they are frequently an incidental finding during workup for other diseases.

An unusual benign tumor occasionally found in cats is the myelolipoma, which has a suggested association with chronic hypoxia and hepatic involvement in diaphragmatic hernias. Biliary carcinomas are the most common malignant tumors in cats, which may mirror the high prevalence of biliary tract disease in this species. Trematodes are also a predisposing cause in humans and possibly in some cats, but bile duct carcinomas also occur in cats outside the range of liver fluke infestations, so there are other factors involved. Also in contrast to dogs, primary hepatobiliary tumors are more common than metastatic neoplasia in cats. Secondary tumors include particularly hematopoietic tumors, such as lymphoma and, less commonly, leukemias, histiocytic tumors, and mast cell tumors, as well as metastases from other organs (e.g., pancreas, mammary glands, gastrointestinal tract). Hemangiosarcomas in the liver may be primary or secondary, and sometimes the origin is difficult to ascertain if multiple organs are involved, although primary hepatic hemangiosarcomas appear to be more common in cats than in dogs.

The common feline primary liver tumors recognized and their behavior are outlined in Table 35.4.

Clinical Features

Primary malignant tumors of the liver are usually seen in older cats (mean age, 10-12 years), and there is no obvious gender predisposition reported. The presenting clinical signs and clinicopathologic findings are indistinguishable from those in cats with other types of primary liver diseases. There may be lethargy, vomiting, weight loss, ascites, or jaundice. Some affected cats may have palpable hepatomegaly, ascites, or liver masses on abdominal palpation. However, at least 50% of cats with liver tumors are asymptomatic.

Diagnosis

Diagnosis relies on a combination of diagnostic imaging, cytology, and histology. A suspicion may be gained from the clinical findings, but given that more than half of affected cats have no clinical signs, the liver mass may be a serendipitous finding while the cat is being evaluated for another reason. On clinical pathology, high liver enzyme activity and bile acid concentration and mild anemia and neutrophilia are common but nonspecific findings. Jaundice is uncommon but can occur. Liver function is usually normal because the tumor must involve more than 70% of the liver mass before resulting in a reduction in liver function. The exception to this is a diffuse hematologic malignancy (e.g., lymphoma), which can result in a significant disturbance of hepatocyte function (including coagulopathies). The functional defects often resolve when the tumor is cytoreduced by chemotherapy.

TABLE 35.4

Primary Liver Tumors in Cats

TYPE OF TUMOR	BEHAVIOR
Bile Duct Tumor	
Biliary carcinoma (including cystadenocarcinoma) Biliary adenoma Gallbladder tumors	Most common primary liver tumor in cats (>50%) Biliary carcinoma most common malignant feline liver tumor Aggressive behavior—diffuse intraperitoneal metastases in 67%-80% of cases
Hepatocellular Tumor	
Hepatocellular carcinoma (HCC) Hepatocellular adenoma (hepatoblastoma; very rare)	Recognized but less common than biliary tumors Adenoma more common than carcinoma
Neuroendocrine Tumor	
Hepatic carcinoid	Very rare but very aggressive
Primary Hepatic Sarcoma	
Hemangiosarcoma, leiomyosarcoma, others	Uncommon Most locally aggressive, high metastatic rate Hemangiosarcoma most common primary hepatic sarcoma in cats

Note: Benign tumors are more common than malignant tumors in this species.

Radiographs may show hepatomegaly; the liver may have an irregular border or focal enlargement of one lobe. There may be also involvement of other organs (e.g., lymphadenopathy in cats with lymphoma), and thoracic radiographs may reveal evidence of metastases. However, radiographs may also be normal. Some malignant hepatic tumors commonly seed the peritoneum and metastasize to local lymph nodes or lungs. As in other diseases of the liver, ultrasonography is more helpful in identifying a hepatic mass and evaluating for metastases; it also allows for FNA of the mass(es). Hepatic tumors can also be cystic, particularly cystadenocarcinomas (see Fig. 35.9). Cats, unlike dogs, rarely have benign nodular hyperplasia in the liver, so this is not a likely differential diagnosis for a hepatic mass. Diffuse hepatic tumors (e.g., lymphoma) may show a diffuse change in echogenicity, or the liver may appear normal on ultrasonography. Important differential diagnoses for diffuse hepatic tumors are FIP, lipidosis, and amyloidosis. A thorough abdominal ultrasonographic examination should be undertaken to search for evidence of metastases. It should be kept in mind that, because benign tumors are more common than malignant tumors in cats, no animal should be euthanized on the basis of finding a hepatic mass with no evidence of metastases on ultrasonography.

A definitive diagnosis is usually obtained using cytology or histopathology; as mentioned earlier, cats with hepatic lymphoma may have ultrasonographically normal-appearing livers, so FNA should always be performed in these patients. In some cases FNA may be diagnostic, but in others they may be difficult to interpret, particularly in cats with benign hepatocellular tumors, in which the cells are indistinguishable from normal hepatocytes. Ultrasonography-guided Tru-Cut–type biopsies are usually diagnostic; alternatively, biopsies can be obtained during laparoscopy or laparotomy. In the case of an apparently single lesion, the clinician may elect to proceed straight to surgical removal and an excisional biopsy. Hemostasis profiles should be evaluated before performing a biopsy. It is unusual for the one-stage prothrombin time and activated partial thromboplastin time to be prolonged in cats with primary liver tumors, but they can be markedly prolonged in cats with diffuse hepatic infiltration with lymphoma or other diffuse secondary tumors (e.g., mast cell tumors). Biopsies should not be considered in these cases until clotting factors have been replenished with a fresh-frozen plasma transfusion.

Treatment

Treatment of primary hepatic tumors relies on surgical removal if they are resectable. This is advisable even in cats with benign tumors, including biliary adenomas. Treatment of diffuse, nodular, or metastatic tumors may be difficult. Primary hepatic tumors generally have a poor response to chemotherapy. It has been suggested that this is because hepatocytes, normal and transformed, have high expression of the multidrug resistance membrane-associated P-glycoprotein and that hepatocytes are naturally high in detoxifying enzymes. Radiotherapy is not wise because normal liver tissue is very radiosensitive. For additional information, please see Chapter 79 (the section on lymphoma) and Chapter 81 (the section on mast cell tumors).

Prognosis

The prognosis of benign tumors is good after resection but poor for cats with any type of malignant liver tumor. However, most cats with lymphoma of the liver respond to chemotherapy (see Chapter 78).

CONGENITAL PORTOSYSTEMIC SHUNTS

Etiology and Pathogenesis

PSSs are abnormal vascular communications between the portal and systemic circulations. They may be congenital or acquired secondary to portal hypertension. The latter are usually multiple vessels and are very rare in cats because they usually occur secondary to congenital hepatic fibrosis (see earlier) and cirrhosis, both uncommon in cats. Acquired PSS secondary to a congenital hepatic arteriovenous (AV) fistula

has been reported in a young cat but is very rare (McConnell et al., 2006).

Most cases of PSS in cats are therefore congenital, but even these are recognized less commonly than in dogs. Congenital PSSs are usually single or, at most, double vessels and may be intrahepatic or extrahepatic (Lipscomb et al., 2007). Extrahepatic PSSs represent abnormal communications between the portal vein or one of its contributors (e.g., left gastric, splenic, cranial, or caudal mesenteric or gastroduodenal vein) and the caudal vena cava or azygos vein. Intrahepatic PSSs may be left-sided, in which case they are believed to represent a persistence of the fetal ductus venosus after birth (patent ductus venosus [PDV]; White et al., 2001), or they may be right-sided or centrally located in the liver, in which case they are believed to be anomalous vessels.

The pathophysiology of congenital PSS largely relates to the shunting of unfiltered blood directly into the systemic circulation, resulting in hyperammonemia and HE. The pathophysiology of HE is outlined in Chapter 33. The shunting vessel acts as a low-resistance pathway for some of the portal blood, bypassing the higher resistance intrahepatic portal vasculature. Portal pressure is therefore lower than normal in cats with congenital PSS, which is an important distinguishing feature from (rare) cases of acquired shunting, in which there is portal hypertension and therefore increased portal pressure. Concurrent hepatic microvascular dysplasia or portal vein hypoplasia, which can confuse this differentiation, occurs in some dogs (see Chapter 36) but has only been reported in one cat (Sugimoto et al., 2018). Shunting may also allow bacteremia and potentially infections of hematogenous origin that may present as so-called pyrexia of unknown origin, although this is rare. Additional effects of portal blood bypassing the liver are hepatic atrophy and a reduction in the metabolic activity of the liver, which contributes to inefficient use of dietary components, poor growth, and loss of lean body mass.

Liver atrophy (microhepatia) and changes in hepatic organelle function are partly caused by changes in hepatic perfusion. The portal blood usually provides about 50% of the liver's oxygen requirement, but this is obviously reduced in cats with PSS. Cats with PSS typically have arteriolar hyperplasia in an attempt to compensate for the reduced portal flow, but they often still have some degree of hepatic underperfusion. In addition, PSS results in reduced delivery of hepatotrophic factors, such as insulin, to the liver, which further contributes to hepatic atrophy.

Clinical Features

Persian and Himalayan cats were reported to be at increased risk for congenital PSS in a small case series, and another series noted that purebred cats in general were overrepresented; however, cats of any breed, including mixed-breed cats, can be affected. Both sexes appear to be equally at risk. There is no reported association between breed and shunt types (unlike in dogs), although in one study 6 of 13 cats with an intrahepatic PSS were Siamese (Lipscomb et al., 2007). Most cases present before 2 years of age; many are younger than 1 year, but old cats with congenital PSSs are frequently recognized.

The typical clinical signs in cats with congenital PSS are gastrointestinal, urinary, or neurologic (HE), although the latter tend to predominate in cats and, anecdotally, are often more severe than in dogs. Cats typically present with a history of waxing and waning neurologic signs consistent with HE rather than a sudden acute HE crisis. The typical signs of HE are outlined in Box 33.3. Hypersalivation is a common sign of HE in cats but is rare in dogs. There is sometimes an association between signs of HE and feeding, which may relate to glutamine metabolism by enterocytes releasing ammonia; however, not all cats display these signs. Cats in acute crisis may present comatose or with seizures; cats appear to be more susceptible to seizures than dogs, preoperatively and postoperatively. The reason for this is unknown, although it has been suggested that sudden changes in the concentrations of ammonia and other metabolites in the blood after surgery or sudden changes in medical management may destabilize neurotransmitters in cats more than dogs. Drug intolerance is common, particularly prolonged recovery from routine anesthesia for spaying or neutering. Animals with PSS may also show intermittent vomiting and/or diarrhea. Urinary tract signs are caused by cystitis associated with urate calculi and polyuria or polydipsia, but they are less common in cats than in dogs. It is important to note that as opposed to dogs, many cats with urate stones in the bladder do not have a PSS. In one study from a large U.S. stone center, only 7 of 159 cats with urate stones had a diagnosis of a congenital PSS (Dear et al., 2011). Cats with congenital PSS also often show signs of poor growth compared with their litter mates (Fig. 35.10). There has been a reported high prevalence of copper-colored irises



FIG 35.10
A 6-month-old kitten with a congenital portosystemic shunt, demonstrating very small size for its age and also copper-colored irises, which are often noted in kittens with portosystemic shunts.

in cats with PSS (see Fig. 35.10), but this is not a consistent feature.

Because of the low portal pressure, ascites is not a feature in cats, which helps in distinguishing congenital PSS from the rare feline cases of acquired PSS, in which ascites is expected because of portal hypertension.

Diagnosis

A suspicion for congenital PSS can be gained from the history of recurrent neurologic signs combined with high fasting and/or postprandial bile acid or ammonia concentration in a young cat. Traditional ammonia tolerance tests are not recommended because they can precipitate severe HE. Postprandial ammonia or bile acid determinations are safer alternatives. Serum bile acid levels should be measured before and 2 hours after feeding (see Box 34.3). If the ammonia level is measured instead, the postprandial sample should be taken 6 hours after feeding (Walker et al., 2001). Other typical (but not pathognomonic) clinicopathologic findings in some cats include a low serum urea concentration, mildly increased liver enzyme levels, and microcytosis. Notable differences from dogs are that decreases in total protein or albumin levels, hypoglycemia, and anemia are much less common in cats. Urine specific gravity is low in many dogs but occurs in fewer than 20% of affected cats. If fasting bile acid concentrations are very high, it is not necessary to obtain a postprandial sample, but the diagnostic sensitivity of doing both is higher than only measuring fasting concentrations. If biliary stasis (which also causes high bile acid concentrations) is ruled out and the cat does not have hepatic lipidosis (which causes hepatocellular failure and HE, with increases in bile acid and ammonia concentration in many cases), it is likely that the cat has a congenital PSS because other causes of HE and high bile acid concentrations are uncommon in cats. A recent case report noted significant increases in postprandial ammonia and bile acid concentrations in a cat with congenital hypothyroidism, which resolved with treatment of the hypothyroidism. The reason for this was unknown, but this is an important, albeit rare, differential diagnosis for PSS in a young cat (Quante et al., 2010). Hypocobalaminemia can also cause signs of HE with elevated ammonia but normal bile acids. This is more common in dogs but has been reported in a cat (Simpson et al., 2012). Abdominal radiographs show a small liver in 50% of cases (Lamb et al., 1996) but, for definitive diagnosis, the shunting vessel must be visualized.

Visualization of the shunting vessel is achieved by ultrasonography, portal venography, or computed tomography (CT) angiography (see Chapter 34). A liver biopsy should be taken at the time of surgery or portovenography, after evaluation of hemostasis profiles, to rule out other or concurrent conditions. This shows histologic features similar to those in dogs, typical of portal venous hypoperfusion, with loss of smaller portal veins, increased numbers of arterioles, hepatocellular atrophy with lipogranulomas, and sometimes periportal sinusoidal dilation but minimal inflammation.

Treatment

Treatment involves complete or partial ligation of the shunting vessel using one of several methods, including silk or cellophane, or ameroid constrictors; however, a detailed explanation is beyond the scope of this text. The procedure is best reserved for referral centers, particularly in cats, which are more prone to complications than dogs. The postoperative mortality in cats appears to be higher than in dogs, which is often caused by intractable, severe neurologic signs. Pretreatment with phenobarbital has been attempted, but too few cases have been reported to assess its value. Propofol infusions are often used for HE-associated seizures in dogs, but care must be taken in cats because of their susceptibility to Heinz body hemolytic anemia when they are given propofol infusions.

Cats should be managed medically before surgery and for a period of about 2 months after surgery while the portal vasculature and liver mass recover. This involves careful dietary management (see later) with additional antibiotics (usually amoxicillin, 15-20 mg/kg PO q8h) and sometimes also a soluble fiber source such as lactulose (2.5-5 mL PO q8h, to effect). Some anecdotal data suggest that changes in medical management should be made more gradually in cats than in dogs to prevent the risk of seizures (e.g., change the diet first, add antibiotics after 1 week or more, and then add the soluble fiber source later). Details of the medical management of HE are given in Chapter 36. Cats do not tolerate marked dietary protein restriction because of their high obligate protein requirement, and in fact dietary protein restriction is no longer indicated in affected animals. Little and often feeding of a highly digestible diet is recommended. A diet manufactured for cats with gastrointestinal disease (e.g., Hill's i/d or Royal Canin intestinal) is appropriate and, unlike in dogs, homemade diets based on dairy protein should be avoided in cats because dairy protein is relatively deficient in arginine, which is essential for the urea cycle. Such a deficiency will further predispose to hyperammonemia. Medical management alone is effective in some dogs long term (see Chapter 36) and anecdotally, some cats do well with medical treatment of congenital PSS, although this is less common than in dogs probably because of their high obligate protein metabolism; this would make them more susceptible to hyperammonemia, regardless of the diet fed.

Prognosis

The prognosis appears to be good if the PSS can be ligated. Medical management is worth attempting if the client declines surgery although insufficient cases have been reported to assess the long-term prognosis with either medical or surgical management in cats. However, clients should be warned that the short-term mortality rate after surgery is relatively high.

HEPATOBILIARY INFECTIONS

Several infectious organisms can infect the liver as a primary target or as part of a more generalized infection (Box 35.5).

BOX 35.5

Infectious Diseases With Hepatic Involvement in Cats

Disseminated mycobacterial infections
Histoplasmosis
Infection with *Cytauxzoon felis*
Infection with *Streptococcus* groups B and G in neonates
Leptospirosis (extremely rare)
Liver fluke (see text for details)
Feline infectious peritonitis
Toxoplasmosis
Bartonellosis
Salmonellosis
Tularemia *(Francisella tularensis)*
Tyzzer disease

Note: Neutrophilic cholangitis is often caused by ascending bacterial infection from the gut. *Bartonella* spp. may be involved in the etiology of some cases of lymphocytic cholangitis.

In addition, neutrophilic cholangitis likely has a primary infectious cause in most cats (see earlier).

Hepatic involvement is common in the dry and effusive forms of FIP (see Chapter 96). Because cats with effusive FIP can present with the same signs as cats with lymphocytic cholangitis, it is an important differential diagnosis for this disease. A liver biopsy may be necessary to distinguish them; one study suggested that Tru-Cut-type biopsy or FNA cytology of the liver is more sensitive than biopsy or aspiration of the kidney for diagnosis of FIP in cats (Giordano et al., 2005).

Disseminated toxoplasmosis is uncommon in cats, but when it occurs, the liver is usually involved with intracellular growth of *Toxoplasma gondii* during the active clinical disease, resulting in cell death. Effects of delayed hypersensitivity reactions and immune complex vasculitis also contribute to clinical illness. Trophozoite infection of the lungs, liver, and central nervous system (including the eyes) is usually responsible for clinical signs. As expected, high serum ALT levels and hyperbilirubinemia commensurate with the degree of hepatocellular necrosis are the typical serum biochemical findings in cats with liver involvement. Cholangiohepatitis resulting from infection of the biliary epithelium has been noted occasionally in experimental and spontaneously occurring cases of toxoplasmosis in cats. The distribution of affected tissues in disseminated histoplasmosis often includes the lung, eye, bone marrow, spleen, lymph node, skin, bone, and liver. Infection with *Bartonella* spp. can cause cholangitis in cats.

TOXIC HEPATOPATHY

Pathogenesis and Etiology

By definition, toxic hepatopathy refers to a hepatic injury directly attributable to exposure to environmental toxins or certain therapeutic agents. Any therapeutic agent might be hepatotoxic as a result of an idiosyncratic reaction, but only a limited number of toxicities due to the use of drugs have been reported in cats (Box 35.6) in addition to reported environmental hepatotoxins. Cats are particularly sensitive to phenol toxicity because of their limited hepatic glucuronide transferase activity. A variety of essential oils used topically have been reported to be hepatotoxic for cats. Essential oils are absorbed rapidly, both orally and dermally, and are metabolized by the liver to glucuronide and glycine conjugates; it is believed that cats are more sensitive than dogs to their hepatotoxic effects (Means, 2002).

Complete information that could support meaningful conclusions about the frequency, character, and substances that consistently cause hepatotoxicity in cats is not available. Clinicians therefore must rely on anecdotal reports, clinical observations, and data accumulated by central agencies such as the ASPCA Animal Poison Control Center (888-426-4435; $65 per case via credit card; https://www.aspca.org/pet-care/animal-poison-control) and the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine, in Washington, DC (suspected adverse drug experiences can be reported to 1-888-FDA-VETS), and in the UK

BOX 35.6

Causes of Clinically Relevant Hepatic Toxicity in Cats: Therapeutic Agents or Environmental Toxins

Therapeutic Agents

Acetaminophen, >50-100 mg/kg, but any dose potentially toxic
Amiodarone
Aspirin, >33 mg/kg/day
Diazepam
Essential oils
Griseofulvin
Ketoconazole
Megestrol acetate
Methimazole
MTP inhibitors (off-label use; see text)
Nitrofurantoin
Phenazopyridine
Stanozolol
Tetracycline

Environmental Toxins

Aflatoxin
Amanita phalloides (mushroom)
Dry-cleaning fluid (trichloroethane)
Inorganic arsenicals (lead arsenate, sodium arsenate, sodium arsenite)
Phenols
Pine oil + isopropanol
Thallium
Toluene
White phosphorus
Zinc phosphide

the Veterinary Poisons Information Service (https://vpisglobal.com/our-research/). In general, drug- or toxin-induced hepatic injury in cats is extremely uncommon, and most reactions are acute, occurring within 5 days of exposure. The character and severity of the toxic reaction depend on the characteristics of the substance, dose, and duration of exposure.

Three therapeutic agents have been reported to be hepatotoxic in some cats—tetracycline, diazepam, and stanozolol. Veterinarians have used these agents for years without known deleterious effects. For each drug, clinical and clinicopathologic signs of hepatotoxicosis developed within 2 weeks of daily oral administration at recommended dosages. The adverse hepatic reaction to tetracycline was serious but nonlethal, and the cat recovered completely after drug discontinuation and 6 weeks of supportive care (Kaufman et al., 1993). Histologic findings in the liver included centrilobular fibrosis, mild cholangiohepatitis, and mild lipid deposition in hepatocytes. In the cats that experienced diazepam-associated hepatic failure, the outcome was death in 16 of 17 despite intensive treatment. The oral dosages of diazepam that cats received, primarily for inappropriate urination, ranged from 1 mg every 24 hours to 2.5 mg every 12 hours. The histologic lesions in the liver were similar to those observed in the cat with tetracycline-associated hepatic injury but more severe: massive, predominantly centrilobular necrosis; suppurative cholangitis; and mild lipid vacuolation in some cats. Because of the severity of the lesions reported in cats apparently susceptible to diazepam-associated hepatic necrosis, serum liver enzyme levels should be evaluated during the window of days 3 to 5 of administration in cats given diazepam by mouth. Until there is more information to improve the understanding of this lethal and unpredictable hepatic reaction, use of other agents for control of behavior and elimination problems in cats is recommended. Cats that experienced an adverse reaction to stanozolol were healthy or had chronic renal failure (14 of 18 cats) or gingivitis or stomatitis (2 of 3 cats; Harkin et al., 2000). Serum ALT levels were markedly increased in most cats given 1 mg PO every 24 hours for several months or 4 mg PO every 24 hours (and 25 mg IM once) for 3 weeks; all but one survived after the drug was discontinued, and intensive supportive care was instituted. The histologic lesions were moderate to marked diffuse centrilobular lipidosis and evidence of intrahepatic cholestasis—accumulation of bile and lipofuscin in hepatocytes and Kupffer cells.

The discriminatory eating habits of cats may account for the relatively uncommon occurrence of hepatotoxicity from ingested environmental toxins such as pesticides, household products, and other chemicals. It is certainly possible that many adverse hepatic reactions to drugs or toxic chemicals go unnoticed in cats because the first clinical signs of illness are vomiting and diarrhea, after which the medication is stopped. If the signs resolve, there usually is no further evaluation, and the medication is not readministered to prove that the substance caused the reaction.

Diagnosis

Clinical evidence that suggests drug- or toxin-induced hepatic damage includes the following: supportive history (e.g., known exposure); normal liver size to mild generalized tender hepatomegaly; laboratory test results consistent with acute liver injury (e.g., high serum ALT and/or AST levels, hyperbilirubinemia); and, if the exposure was nonlethal, recovery with discontinuation of the agent and specific or supportive care. There are no pathognomonic histologic changes in the liver, although necrosis with minimal inflammation and lipid accumulation are considered typical findings. In many cases, all clinical and clinicopathologic markers of a toxic liver insult are present, but the inciting chemical cannot be identified. In the case of hepatotoxicity from therapeutic agents, idiosyncratic reactions can occur that are not dose-related, although drug overdose is usually the reason for liver injury.

Treatment

In cats with suspected acute hepatotoxicity, the basic principles for treatment of toxicoses are applied:

- Preventing further exposure and absorption
- Managing life-threatening cardiopulmonary and renal complications
- Hastening elimination of the substance
- Implementing specific therapy if possible
- Providing supportive care

Because few hepatotoxins have specific antidotes, the success of recovery often relies on time and aggressive supportive care. More guidance on supportive treatment of acute toxic hepatopathy is provided in Box 36.4.

Acetaminophen is one of the few toxins with a specific antidote. Acetaminophen is particularly toxic to cats, in which the usual hepatic detoxification pathways of sulfation and glucuronidation are particularly limited. Acetaminophen is oxidized to a toxic metabolite that causes methemoglobinuria within hours of ingestion and Heinz body anemia, hemolysis, and liver failure within 2 to 7 days of ingestion. *N*-acetylcysteine is a specific antidote that binds the toxic metabolite and increases the glucuronidation process. It should be administered at a dose of 140 mg/kg IV or PO as a loading dose and then continued at 70 mg/kg q6h for a total of seven treatments, or for up to 5 days. There is also evidence that additional S-adenosylmethionine (20 mg/kg, or 200-400 mg total daily) is beneficial in cats with acetaminophen toxicity because it replenishes glutathione, which inactivates the toxic metabolite (Webb et al., 2003). In addition, a recent study suggested that silymarin was beneficial for treating experimental acetaminophen toxicity in cats. A single dose of 30 mg/kg PO given to cats at the same time as acetaminophen or 4 hours later was as effective at preventing elevation in liver enzymes, bilirubin, and methemoglobin levels as a single dose of *N*-acetylcysteine (Avizeh et al., 2010). It is unclear how to extrapolate these findings to the clinical setting, but the use of *N*-acetylcysteine,

silymarin, and S-adenosylmethionine would be a logical step.

HEPATOBILIARY MANIFESTATIONS OF SYSTEMIC DISEASE

Several feline systemic illnesses have hepatic manifestations that may be identified by physical, clinicopathologic, and/or radiographic examination, but the major clinical signs can be attributed to another disease (see Table 35.1). In such cases the hepatic lesion should recede with satisfactory treatment of the primary illness.

Metastatic neoplasia could be the underlying reason for abdominal enlargement resulting from hepatomegaly or, rarely, malignant abdominal effusion, although primary neoplasia is more common than metastatic neoplasia in the feline liver. Some of the signs of hyperthyroidism, especially occasional vomiting, diarrhea, and weight loss, can resemble those of primary hepatobiliary disease. Thyrotoxic cats commonly have high liver enzyme levels; more than 75% of affected cats have high serum AP levels (2-12 times higher), although in cats it is not known whether this is of liver or bone origin or, as is true for hyperthyroid human patients, both. More than 50% of hyperthyroid cats have high serum ALT or AST levels (2-10 times higher). More than 90% of affected cats have high serum levels of at least one of the AP, ALT, or AST enzymes. Approximately 3% are hyperbilirubinemic. Histopathologic changes are minimal, and there appears to be little functional disturbance. It is thought that malnutrition, hepatocellular hypoxia, and the direct effects of thyroid hormone on liver cells are responsible for these liver-related abnormalities. Hepatomegaly associated with mild to moderate lipid deposition is a common physical examination finding in cats with DM; a small number of cats may also be icteric. Mild to moderate increases in liver-specific enzyme levels are typical. More severe clinicopathologic abnormalities might be expected in cats with more severe hepatic lipidosis. Hyperadrenocorticism is rare in cats and, unlike in dogs, obvious liver involvement is unusual. The liver is usually normal in size on radiographs, and it is unusual to find high serum AP and ALT levels in hyperadrenocorticoid cats. Unlike dogs, cats do not have a steroid-induced isoenzyme of ALP, and an increased ALT level, when recognized, is probably related to intercurrent DM.

Suggested Readings

Abdallah AAL, et al. Biliary tract obstruction in chronic pancreatitis. *HPB (Oxford)*. 2007;9:421.

Aronson LR, et al. Acetaminophen toxicosis in 17 cats. *J Vet Emerg Crit Care*. 1996;6:65.

Avizeh R, et al. Evaluation of prophylactic and therapeutic effects of silymarin and N-acetylcysteine in acetaminophen-induced hepatotoxicity in cats. *J Vet Pharmacol Ther*. 2010;33:95.

Bayton WA, et al. Histopathological frequency of feline hepatobiliary disease in the UK. *J Small Anim Pract*. 2018;doi:10.1111/jsap.12810.

Beatty JA, et al. Spontaneous hepatic rupture in six cats with systemic amyloidosis. *J Small Anim Pract*. 2002;43:355.

Boomkens SY, et al. Detection of *Helicobacter pylori* in bile of cats. *FEMS Immunol Med Microbiol*. 2004;42:307.

Bosje JT, et al. Polycystic kidney and liver disease in cats. *Vet Q*. 1998;20:136.

Brain PH, et al. Feline cholecystitis and acute neutrophilic cholangitis: clinical findings, bacterial isolates and response to treatment in six cases. *J Feline Med Surg*. 2006;8:91.

Brenner K, et al. Refeeding syndrome in a cat with hepatic lipidosis. *J Feline Med Surg*. 2011;13:614.

Brown B, et al. Metabolic and hormonal alterations in cats with hepatic lipidosis. *J Vet Intern Med*. 2000;14:20.

Buote NJ, et al. Cholecystoenterostomy for treatment of extrahepatic biliary tract obstruction in cats: 22 cases (1994-2003). *J Am Vet Med Assoc*. 2006;228:1376.

Byfield VL, et al. Percutaneous cholecystocentesis in cats with suspected hepatobiliary disease. *J Feline Med Surg*. 2017;19:1254.

Callahan Clark JE, et al. Feline cholangitis: a necropsy study of 44 cats (1986-2008). *J Feline Med Surg*. 2011;13:570.

Center SA, et al. A retrospective study of 77 cats with severe hepatic lipidosis: 1975-1990. *J Vet Intern Med*. 1996;7:349.

Center SA, et al. Fulminant hepatic failure associated with oral administration of diazepam in 11 cats. *J Am Vet Med Assoc*. 1996;209:618.

Dear JD, et al. Feline urate urolithiasis: a retrospective study of 159 cases. *J Feline Med Surg*. 2011;13:725.

Fragkou FC, et al. Prevalence and clinicopathological features of triaditis in a prospective case series of symptomatic and asymptomatic cats. *J Vet Intern Med*. 2016;30:1031.

Friend EJ, et al. Omentalisation of congenital liver cysts in a cat. *Vet Rec*. 2001;149:275.

Furneaux RW. A series of six cases of sphincter of oddi pathology in the cat (2008-2009). *J Feline Med Surg*. 2010;10:794.

Giordano A, et al. Sensitivity of Tru-cut and fine-needle aspiration biopsies of liver and kidney for diagnosis of feline infectious peritonitis. *Vet Clin Pathol*. 2005;34:368.

Gorman L, et al. Serum beta hydroxybutyrate concentrations in cats with chronic kidney disease, hyperthyroidism, or hepatic lipidosis. *J Vet Intern Med*. 2016;30:611.

Greiter-Wilke A, et al. Association of *Helicobacter* with cholangiohepatitis in cats. *J Vet Intern Med*. 2006;20:822.

Guerra JM, et al. Congenital hepatic fibrosis and polycystic kidney disease not linked to C >A mutation in exon 29 of PKD1 in a Persian cat. *FMS Open Rep*. 2015;1(2):2055116915619191. doi:10.1177/2055116915619191. eCollection 2015 Jul-Dec. Published online 2015 Dec 6.

Haney DR, et al. Severe cholestatic liver disease secondary to liver fluke *(Platynosomum concinnum)* infection in three cats. *J Am Anim Hosp Assoc*. 2006;42:234.

Harkin KR, et al. Hepatotoxicity of stanozolol in cats. *J Am Vet Med Assoc*. 2000;217:681.

Harvey M, et al. Treatment and long-term follow-up of extrahepatic biliary obstruction with bilirubin cholelithiasis in a Somali cat with pyruvate kinase deficiency. *J Feline Med Surg*. 2007;4:424.

Hurwitz BM, et al. Presumed primary and secondary hepatic copper accumulation in cats. *J Am Vet Med Assoc*. 2014;244:68.

Kaufman AC, et al. Increased alanine transaminase activity associated with tetracycline administration in a cat. *J Am Vet Med Assoc*. 1993;202:628.

Kordick DL, et al. Clinical and pathologic evaluation of chronic *Bartonella henselae* or *Bartonella clarridgeiae* infection in cats. *J Clin Microbiol*. 1999;37:1536.

Kuzi S, et al. Prognostic markers in feline hepatic lipidosis: a retrospective study of 71 cats. *Vet Rec*. 2017;181:512.

Lamb CR, et al. Ultrasonographic diagnosis of congenital portosystemic shunt in 14 cats. *J Small Anim Pract*. 1996;37:205.

Lipscomb VJ, et al. Complications and long-term outcomes of the ligation of congenital portosystemic shunts in 49 cats. *Vet Rec*. 2007;160:465.

Liptak JM. Hepatobiliary tumors. In: Withrow SJ, Vail DM, eds. *Withrow and MacEwen's small animal clinical oncology*. 4th ed. St Louis: Saunders; 2007.

Marolf AJ, et al. Ultrasonographic findings of feline cholangitis. *J Am Anim Hosp Assoc*. 2012;48:36.

Mayhew PD, et al. Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract*. 2002;43:247.

McConnell JF, et al. Ultrasonographic diagnosis of unusual portal vascular abnormalities in two cats. *J Small Anim Pract*. 2006;47:338.

Means C. Selected herbal hazards. *Vet Clin Small Anim*. 2002;32:367.

Otte CM, et al. Retrospective comparison of prednisolone and ursodeoxycholic acid for the treatment of feline lymphocytic cholangitis. *Vet J*. 2013;195:205.

Quante S, et al. Congenital hypothyroidism in a kitten resulting in decreased IGF-I concentration and abnormal liver function tests. *J Feline Med Surg*. 2010;12:487.

Rothuizen J, et al. *WSAVA standards for clinical and histological diagnosis of canine and feline liver diseases*. Oxford, England: Saunders Elsevier; 2006.

Savary-Bataille KC, et al. Percutaneous ultrasound-guided cholecystocentesis in healthy cats. *J Vet Intern Med*. 2003;17:298.

Simpson K, et al. Suspected acquired hypocobalaminaemic encephalopathy in a cat: resolution of encephalopathic signs and MRI lesions subsequent to cobalamin supplementation. *J Felin Med Surg*. 2012;14:350.

Sugimoto S, et al. Multiple acquired portosystemic shunts secondary to primary hypoplasia of the portal vein in a cat. *J Vet Med Sci*. 2018;doi:10.1292/jvms.17-0648.

Walker MC, et al. Postprandial venous ammonia concentrations in the diagnosis of hepatobiliary disease in dogs. *J Vet Intern Med*. 2001;15:463.

Warren A, et al. Histopathologic features, immunophenotyping, clonality and eubacterial fluorescence in situ hybridization in cats with lymphocytic cholangitis/cholangiohepatitis. *Vet Pathol*. 2011;48:627.

Webb CB, et al. S-adenosylmethionine (SAMe) in a feline acetaminophen model of oxidative injury. *J Feline Med Surg*. 2003;5:69.

Weiss DJ, et al. Relationship between feline inflammatory liver disease and inflammatory bowel disease, pancreatitis, and nephritis in cats. *J Am Vet Med Assoc*. 1996;209:1114.

White RN, et al. Anatomy of the patent ductus venosus in the cat. *J Feline Med Surg*. 2001;3:229.

Whittemore JC, et al. Hepatic copper and iron accumulation and histologic findings in 104 feline liver biopsies. *J Vet Diagn Invest*. 2012;24:656.

Xavier FG, et al. Cystic liver disease related to high Platynosomum fastosum infection in a domestic cat. *J Feline Med Surg*. 2007;9:51.

Zandvliet MM, et al. Acquired portosystemic shunting in 2 cats secondary to congenital hepatic fibrosis. *J Vet Intern Med*. 2005;19:765.

CHAPTER 36

Hepatobiliary Diseases in the Dog



GENERAL CONSIDERATIONS

There are marked differences between dogs and cats in the causes, types, and presentations of liver disease (see Table 35.2). In dogs, chronic liver disease is more common than acute disease and, notably, chronic parenchymal disease (chronic hepatitis) is much more common in dogs than in cats; it almost invariably leads to progressive fibrosis and cirrhosis. This contrasts with cats, in which primary biliary tract disease is more common but fibrosis and cirrhosis are extremely uncommon. The clinical signs of liver disease in dogs therefore tend to be even more nonspecific than in cats. Jaundice is less commonly associated with parenchymal disease and, because of the enormous reserve capacity of the liver, signs may not be evident until 75% of the liver mass is lost. The cause of chronic hepatitis in dogs is usually unknown, with a few notable exceptions, and treatment focuses on attempting to slow progression of the disease and treating the clinical signs. Dogs with chronic hepatitis often develop portal hypertension, and treatment of the associated complications is central to treatment of disease in dogs, whereas portal hypertension is very uncommon in cats. Both congenital and acquired portosystemic shunts (PSSs) are more commonly recognized in dogs than in cats; in addition, vacuolar and secondary hepatopathies are very common in dogs and can be confused with primary liver disease on presentation. The most common primary and secondary liver diseases in dogs are outlined in Table 36.1.

CHRONIC HEPATITIS

Chronic hepatitis is predominantly a histologic definition. It is essential to take a liver biopsy before making a diagnosis of chronic hepatitis in dogs, because reactive (secondary) hepatopathy is much more common than primary liver disease in this species (see later). Chronic hepatitis is defined by the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group as being characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and fibrosis (Van den Ingh et al., 2006; Fig. 36.1). The histologic definition says nothing about temporal chronicity, but this is impossible to judge because many dogs with chronic hepatitis have few or no clinical signs before biopsy, and elevated liver enzymes are often not detected unless a blood sample is taken for another reason such as preanesthetic check.

Chronic hepatitis is common in dogs and shows some noticeable breed predilections, suggesting a genetic basis to the disease. Box 36.1 lists dog breeds reported to have a high prevalence of chronic hepatitis, and Box 36.2 lists possible causes for genetic increases in susceptibility, all of which have been demonstrated in humans with chronic hepatitis and some of which have been recognized in other diseases in dogs. The only one that has been confirmed as a cause of chronic hepatitis in dogs is the mutation of a gene involved in metal storage in dogs with copper storage disease (see later). The others have been suspected but not proven, although increases in major histocompatibility complex (MHC) class II antigen haplotypes in some breeds suggest genetic susceptibility to autoimmune disease (see later).

Young to middle-aged dogs are most commonly affected, and the sex ratio varies among breeds. Dalmatians, Doberman Pinschers, and English Springer Spaniels with chronic hepatitis are typically younger than Labrador Retrievers, English Cocker Spaniels, and Cairn Terriers. It should also be noted that there are some notable geographic differences in breed-related liver diseases, which likely reflect differences in breeding in different countries; diseases common in the United States may be unusual in the United Kingdom, and vice versa. It is also important to remember that chronic hepatitis can affect mixed-breed and purebred dogs, and that recognition of one cause in a breed does not necessarily mean that chronic hepatitis in all dogs of that breed has the same cause. For example, in many Doberman Pinschers and West Highland White Terriers, chronic hepatitis is caused by copper accumulation, but in others it is not. In many cases of canine chronic hepatitis, the cause is unknown. This contrasts with the situation in humans, in whom most cases of chronic hepatitis are viral and some have defined and often effective treatments that can reverse the disease process. In dogs, chronic viral causes have not been convincingly demonstrated, but the histology in some cases is suggestive of this

TABLE 36.1

Liver Diseases in Dogs

PRIMARY	SECONDARY
Chronic hepatitis	Steroid-induced hepatopathy
Copper storage disease	Hepatic steatosis (lipidosis) (secondary to diabetes mellitus or hypothyroidism)
Congenital portosystemic shunt	Congestion: heart failure or heartworm disease
Drug- or toxin-induced hepatopathy	Idiopathic vacuolar hepatopathy in Scottish Terriers and others Reactive hepatitis (e.g., secondary to pancreatitis, inflammatory bowel disease) Metastatic neoplasia
Uncommon or Rare	
Biliary tract disease, all types	Hepatocutaneous syndrome
Hepatic infections (see text)	
Portal vein hypoplasia, microvascular dysplasia	
Ductal plate abnormality	
Hepatic arteriovenous fistula	
Acute fulminant hepatitis (all causes)	
Hepatic abscess	
Primary neoplasia	

BOX 36.1

Dog Breds Wih Reported Increased Risk of Chronic Hepatitis*

American and English Cocker Spaniels (worldwide, males > females)
Bedlington Terrier (worldwide, copper storage disease)
Cairn Terrier (United Kingdom)†
Dalmatian (United States, copper storage disease; United Kingdom, pathophysiology not reported†)
Doberman Pinschers (worldwide, some with copper storage disease and some without; Scandinavian reports suggest immune-mediated component, see text; females > males)
English Springer Spaniels† (United Kingdom, Norway; females > males)
Great Dane (United Kingdom)†
Labrador Retrievers (worldwide; copper storage disease in United States and Holland; not copper-associated in United Kingdom; females > males)
Samoyed (United Kingdom)†
West Highland White Terriers (worldwide; some copper-associated and some not)
Standard Poodle (Anecdotal USA not copper associated).

*No reported sex ratio unless stated.
†Data for recently reported UK breeds from Bexfield NH, et al: Breed, age, and gender distribution of dogs with chronic hepatitis in the United Kingdom, *Vet J* 193:124, 2012.
Note previously reported hepatitis in Skye Terriers is now believed to be a congenital ductal plate abnormality (see later in chapter).

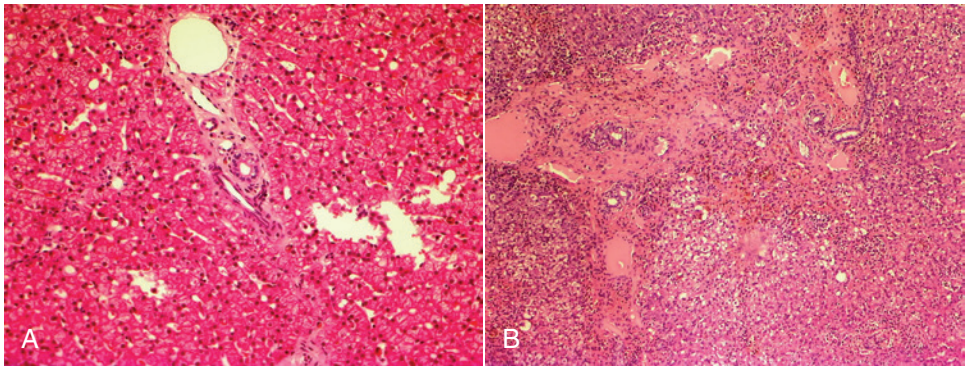


FIG 36.1
(A) Histopathology of normal liver from a middle-aged Yorkshire Terrier. Note the normal portal triad with hepatic portal vein, artery, and bile duct and hepatocytes arranged in neat cords with sinusoids in between (white holes in *bottom right* are a sectioning artifact) (H&E, ×200). **(B)** Histopathology of liver in a 3-year-old female English Springer Spaniel with severe chronic hepatitis. There is marked distortion of the normal lobular structure (compare to **A**), with inflammation, fibrosis, and hepatocyte vacuolation and necrosis. There is also some ductular hyperplasia and disruption of the limiting plate (H&E, ×100). (Courtesy Pathology Department, Veterinary Medicine, University of Cambridge, Cambridge, England.)

BOX 36.2

Possible Causes of Breed-Related Liver Disease

- Increased susceptibility to infectious causes of chronic hepatitis and/or chronicity of infection
- Mutation in gene involved in metal storage or excretion
- Mutation in gene involved in other metabolic processes (e.g., protease inhibitor production)
- Increased susceptibility to toxic hepatitis (e.g., impaired detoxification of drugs)
- Susceptibility to immune-mediated disease

and the search for infectious agents continues. Most cases therefore remain a nonspecific diagnosis of chronic hepatitis, and the treatment remains nonspecific and symptomatic. However, in a few notable exceptions, such as copper storage disease, some cases of granulomatous hepatitis, and toxic hepatitis, the cause may be known and treated specifically. These are outlined in separate sections of this chapter.

IDIOPATHIC CHRONIC HEPATITIS

Potential Etiology

The potential causes of canine chronic hepatitis are reviewed in Webster et al., 2019. Idiopathic chronic hepatitis likely represents an unidentified viral, bacterial, or other infection, an unidentified previous toxic event, or, in some cases, immune-mediated disease. However, because criteria for diagnosis of immune-mediated chronic hepatitis have not yet been agreed in dogs, immunosuppressive drugs should be used only cautiously when other potential causes have been ruled out as much as possible and the histology is suggestive of an immune-mediated disease. It is also very important to rule out primary or secondary copper buildup in all dogs with chronic hepatitis by staining liver biopsies for copper (see later). More details of when to suspect immune-mediated hepatitis are described in later sections ("Granulomatous Hepatitis" and "Infectious Causes of Canine Chronic Hepatitis").

Primary chronic hepatitis caused by infectious agents is uncommon in dogs, although there may be a yet-unidentified infectious cause in some dogs with what appears to be idiopathic chronic hepatitis. Clinicians should keep this possibility in mind before prescribing immunosuppressive medication. Granulomatous hepatitis is an uncommon histologic diagnosis in which there is a prominent histiocytic component to the inflammatory infiltrate. This is usually associated with either a foreign body-type reaction to increased copper in the liver or a chronic infectious cause, which should trigger a search for these potential etiologies.

To date, there has been no convincing demonstration of a viral cause of canine chronic hepatitis, although it has been suspected in several cases. The most common viral cause of chronic hepatitis in people is hepatitis B virus, a hepadnavirus. Similar hepadnaviruses associated with hepatitis have been identified in woodchucks, ground squirrels, tree squirrels, and ducks, but attempts to identify hepadnaviruses by polymerase chain reaction (PCR) assay in the liver of dogs with chronic hepatitis or hepatocellular carcinoma have failed. Hepatitis C virus, a *Hepacivirus,* is another increasingly common cause of chronic hepatitis in humans. The recent discovery of a hepatitis C–like virus in dogs created excitement with the possibility that this might also be associated with canine chronic liver disease (Kapoor et al., 2011). However, the virus was isolated from the respiratory tract, and subsequent studies have failed to associate the virus with chronic hepatitis in dogs (Bexfield et al., 2013). Two other viruses have been suggested as a possible cause of canine chronic hepatitis: canine adenovirus type 1 (CAV-1) and canine acidophil cell hepatitis virus. CAV-1 causes acute fulminant hepatitis in immunologically naive dogs but can also cause chronic hepatitis experimentally in partially immune dogs. However, its importance in naturally occurring chronic hepatitis is unclear, and studies are conflicting. An alternative viral cause of canine acute, persistent, and chronic hepatitis was proposed in Glasgow by Jarrett and O'Neil in 1985 and termed *canine acidophil cell hepatitis virus* pending isolation and identification. The virus appeared to be transmissible by subcutaneous (SC) injection of liver homogenate and serum, and was apparently capable of producing a chronic hepatitis marked by fibrosis and hepatocyte necrosis but sparse inflammatory changes (Jarrett and O'Neil, 1985; Jarrett et al., 1987). It was proposed at the time that this was the most important cause of hepatitis in Glasgow. However, there have been no further published studies by these or other workers regarding the identity or significance of this virus, so its identity and role remain unknown.

Bacterial infections have been sporadically reported as a cause of canine chronic hepatitis, but their importance is unclear. Bile-tolerant *Helicobacter* spp. can cause hepatitis centered on the bile ducts in rodents; there was one report of necrotizing hepatitis associated with *Helicobacter canis* infection in a pup (Fox et al., 1996). However, no further work has been reported in dogs, and a clear association between *Helicobacter* infection and liver disease has yet to be demonstrated.

Leptospiral infections may be a clinically relevant and underestimated cause of chronic hepatitis in dogs. Most dogs in the United States are vaccinated regularly against *Leptospira interrogans* serovars *canicola* and *icterohaemorrhagiae* (bivalent vaccine), and the new quadrivalent vaccine also protects against *L. interrogans* serogroup Australis serovar Bratislava and *L.kirschneri* serogroup Grippotyphosa serovar Bananal/Lianguang, so it is assumed that leptospiral infection is now a rare disease. However, recent studies have shown an emergence of diseases associated with both vaccinal and other serovars; in addition, there is little immunologic cross-reaction with the vaccine serovars. Typically, acute *leptospiral* infections cause both liver and kidney disease. However, more chronic infections can cause chronic hepatitis alone. Infection with predominantly vaccinal serovars was recently reported in a case series of 10 dogs

with chronic granulomatous hepatitis without renal involvement from the UK (McKallum et al., 2019). Nine dogs were vaccinated. Infection with atypical leptospires, particularly *Leptospira grippotyphosa,* can cause a chronic hepatitis with ascites, particularly in young dogs, but azotemia is uncommon in these dogs. Histologically, the livers of dogs with confirmed leptospire infection have portal and intralobular inflammation (i.e., mainly lymphocytic-plasmacytic, with variable amounts of neutrophils and macrophages). Some dogs have very prominent histiocytic (i.e., macrophage-rich) inflammation. There may also be periportal and portoportal fibrosis that could disrupt the hepatic architecture. The organisms are sparse and difficult to find with conventional staining techniques, so it is possible that some cases of leptospiral hepatitis are misdiagnosed as immune-mediated disease on the basis of their histologic appearance. There is also often a poor serologic response in affected dogs, further complicating diagnosis. In one study, only three out of nine dogs tested were positive on serology, and only one was positive on blood PCR, but none were positive on urine PCR (McKallum et al., 2019). The cases were diagnosed with fluorescent in-situ hybridization and PCR speciation from histology blocks.

Adamus et al. (1997) noted the similarity in age bias (6–9 months) and histologic appearance between leptospiral hepatitis and lobular dissecting hepatitis, and it has been suggested that undiagnosed infections may be a cause of lobular dissecting hepatitis in some young dogs (see later). There have also been sporadic reports of *Bartonella henselae* and *Bartonella clarridgeiae* in dogs with chronic liver disease, but again their significance as a cause of the disease is unclear. Peliosis hepatitis, rather than chronic hepatitis, is the more typical histologic appearance associated with *Bartonella* spp. infection in humans and was reported in one dog (Kitchell et al., 2000). Serology, culture, or PCR assay for *Bartonella* spp. is available (see Chapter 94).

One study (Boomkens et al., 2005) evaluated 98 liver samples from dogs with chronic hepatitis using nested PCR for Hepadnaviridae, *Helicobacter, Leptospira,* and *Borrelia* spp.; hepatitis A, C, and E viruses; canine adenovirus; and canine parvovirus, and failed to find evidence of infection in any of the dogs. Another more recent study also failed to find CAV-1, canine parvovirus, canine herpesvirus, and pathogenic *Leptospira* spp. in English Springer Spaniels with chronic hepatitis in England (Bexfield et al., 2011). More work is needed before potentially infectious causes of chronic hepatitis in dogs can be completely ruled out. However, the clinician would be wise to consider further testing in any dog with a marked pyogranulomatous component to their chronic hepatitis on serology. Submission of the histology block for eubacterial fluorescent in-situ hybridization would be wise in these cases.

Lobular Dissecting Hepatitis

Lobular dissecting hepatitis is an idiopathic inflammatory disorder recognized predominantly in young dogs; it has a typical histologic appearance of fibrotic dissection of lobular parenchyma into individual and small groups of hepatocytes. It has been reported in several breeds, including families of Standard Poodles and Finnish Spitzes. It has been proposed that lobular dissecting hepatitis does not represent a distinctive disease but is a response of the juvenile liver to various insults. Infectious etiologies have been suggested, although not proven, and the age of onset and histologic appearance bear a striking resemblance to atypical leptospiral infection in dogs. Treatment recommendations are similar to those for canine chronic hepatitis (see later).

Immune-Mediated Chronic Hepatitis

Some cases of canine chronic hepatitis are likely to be immune-mediated, although it is difficult for the clinician and pathologist to confidently make this diagnosis. Diagnostic criteria used in humans, including measurement of circulating autoantibodies and ruling out viral causes, have not been validated in dogs. Any dog with a prominent lymphoplasmacytic infiltrate on histology may have immune-mediated disease, but other causes of this inflammation, including infectious and reactive disease, should be ruled out before considering immunosuppressive therapy because of other potential causes of lymphoplasmacytic inflammation, including secondary (reactive) liver disease (see later) and chronic infections (see earlier). The presence of a mild inflammatory infiltrate should prompt consideration of reactive hepatopathy, particularly if there is no associated hepatocellular apoptosis or necrosis. The presence of concurrent pyogranulomatous inflammation should prompt a search for copper or an infectious cause (see earlier).

Immune-mediated chronic hepatitis is suspected in some Doberman Pinschers and also some English Springer Spaniels on the basis of associations with certain MHC class 2 antigen haplotypes. There are a few papers investigating the use of immunosuppressive medications in affected dogs, which are detailed in the treatment section later that also support an immune-mediated pathogenesis in some dogs.

Toxic Causes of Chronic Hepatitis

Toxins and drug reactions generally cause acute necrotizing hepatitis rather than chronic disease. Phenobarbital or primidone can cause acute or chronic hepatotoxicity (see later). Lomustine (CCNU) can also cause delayed, cumulative, dose-related chronic hepatotoxicity that is irreversible and can be fatal. Concurrent treatment with SAM-e appeared to be partly protective against hepatotoxicity from CCNU in a recent study in dogs (Skorupski et al., 2011). Another occasional reported cause of chronic liver damage is phenylbutazone. Carprofen can also be associated with acute and chronic liver disease in dogs. Most other reported hepatotoxic drugs and toxins cause an acute hepatitis (see later, "Acute Hepatitis"; Box 36.5). Certain mycotoxins, including aflatoxins, can cause acute or chronic liver disease in dogs, depending on the dose ingested and period of exposure. Dogs scavenge and eat contaminated food more often than humans do, so it is possible that some cases of canine chronic hepatitis are caused by acute or chronic ingestion

of unidentified toxins. In addition, although poorly documented, it is very possible that herbal and nutraceutical supplements could cause chronic liver disease in some dogs. Daily ingestion of cheap, poorly quality-controlled joint supplements based on shellfish has been associated with chronic liver disease in humans, likely due to a contaminating toxin. Reports of joint supplement hepatotoxicity in dogs have only been seen with a large overdose, but chronic low-dose toxicity remains possible. Because a wide variety of drugs and herbals have been reported as causing hepatic adverse reactions in humans and dogs, a drug reaction should be considered in any dog with chronic hepatitis that is also on long-term therapy of any type, and a careful history of supplement use should be obtained, although care should be taken not to overdiagnose drug reactions. Chronic hepatitis should be considered as possibly being drug-related only when there is a clear temporal relationship with drug intake and likely alternative causes have been excluded.

Shared Pathogenesis of All Forms of Chronic Hepatitis

The pathogenesis of chronic hepatitis relates to the loss of hepatic mass resulting in loss of function and, late in the disease process, development of portal hypertension. In many cases hepatocyte swelling, fibrosis, and portal hypertension also contribute to cholestasis and jaundice. Ongoing inflammation may also result in bouts of pyrexia and hepatic pain with associated gastrointestinal (GI) and other signs, and many dogs with chronic hepatitis develop negative nitrogen balance and protein-calorie malnutrition. Loss of hepatic function accounts for coagulopathies and adverse drug reactions in affected dogs.

Portal hypertension is an important consequence of chronic hepatitis and fibrosis, and its effects contribute to the clinical signs and death of many affected animals. It causes a typical triad of clinical signs of ascites, GI ulceration, and hepatic encephalopathy (HE). In a healthy dog the pressure in the portal vein is lower than the pressure in the caudal vena cava. However, in association with obstruction and disruption of the sinusoids by fibrosis and hepatocyte swelling, portal pressure rises until it exceeds that in the caudal vena cava (portal hypertension). This results in splanchnic congestion, with splenic congestion, gut wall edema, and eventually ascites. The mechanisms of ascites formation in dogs with liver disease are complex but involve activation of the renin-angiotensin-aldosterone system (RAAS), with sodium retention in the kidneys and increased circulating fluid volume (see Chapter 33).

If the rise in portal pressure is sustained, multiple acquired PSSs will develop by the opening up of previously nonfunctional vessels; this allows for some of the portal blood to bypass the liver and enter the portal vein directly (Fig. 36.2). These acquired PSSs differ from congenital PSSs in that they are multiple and exist in the presence of increased portal pressure, whereas in patients with congenital PSSs, the portal pressure is low. Acquired PSSs lead to HE by a mechanism similar to that for congenital PSS (see Chapter 33). However, the HE must be medically treated because the ligation of acquired PSSs is contraindicated (see section on treatment of PSS later). This is because acquired PSSs are important escape valves to allow dissipation of some of the portal hypertension; therefore any attempt to ligate them will result in fatal splanchnic congestion. Acquired PSSs in humans are also recognized to reduce the risk of serious GI ulceration associated with portal hypertension. Because of this, they are sometimes created surgically in humans with cirrhosis to reduce the risk of serious bleeds. The same is likely to be true in dogs; GI ulceration is one of the most common causes of death in dogs with chronic hepatitis, and acquired PSSs will help reduce this risk.

Clinical Features of All Forms of Chronic Hepatitis

Dogs of any age or breed can be affected with chronic hepatitis, but there is an increased suspicion in middle-aged dogs of the breeds listed in Box 36.1. Some of these breeds may also be affected by copper storage disease, granulomatous hepatitis, or immune-mediated hepatitis (see earlier and later sections). The functional and structural reserve capacity of the liver implies that dogs with chronic hepatitis usually have no clinical signs until late in the disease process, when more than 75% of liver function has been lost. By this stage, there is already extensive destruction of liver mass, and treatment will be less effective than it would have been earlier in the disease (Fig. 36.3). It is therefore beneficial to diagnose the disease earlier, and dogs with persistently high liver

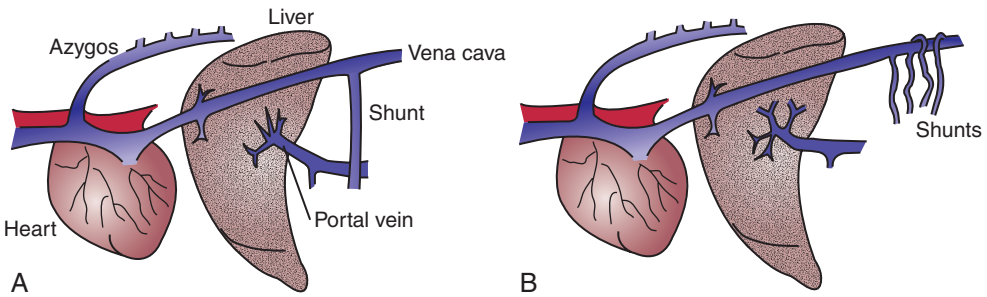


FIG 36.2
Diagrammatic representation of congenital and acquired portosystemic shunts. **(A)** Congenital portocaval shunt. **(B)** Multiple acquired shunts. These develop only if the pressure in the portal vein is higher than the pressure in the vena cava.

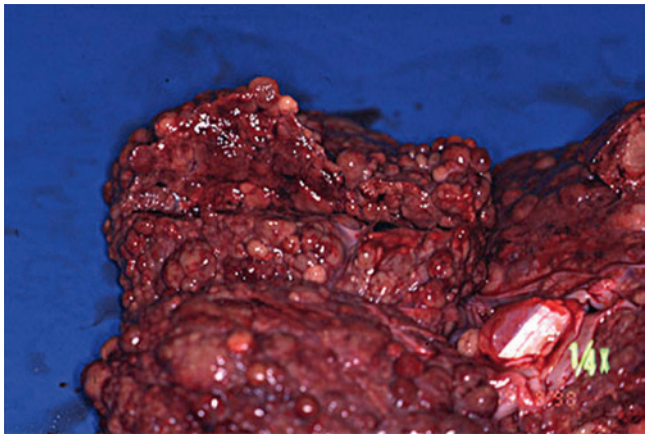


FIG 36.3
Liver from a 6-year-old Bearded Collie that had shown clinical signs for only 1 month before dying from end-stage liver disease. The diagnosis was chronic hepatitis with macronodular cirrhosis and very little normal liver tissue remaining.

enzyme activities (particularly hepatocellular enzymes such as alanine aminotransferase [ALT]) should not be ignored. If liver enzyme activities are high for several months and other causes have been ruled out (see later, "Secondary Hepatopathies"), a liver biopsy should be obtained. This is even more important in breeds at high risk and in those predisposed to treatable diseases, such as copper storage disease.

Once dogs have lost a significant amount of liver mass, they will display clinical signs, but these are typically low-grade, waxing and waning, and nonspecific, making differential diagnosis from other diseases a challenge. Vomiting and diarrhea, anorexia, and polyuria-polydipsia (PU-PD) are common. Jaundice and ascites occur in some dogs at presentation and develop later in others but not in all cases. Ascites at presentation has been identified as a poor prognostic indicator in humans and in two studies in dogs (Poldervaart et al., 2009; Raffan et al., 2009) because it may represent more advanced disease with secondary portal hypertension. Poldervaart et al. (2009); Gómez Selgas et al. (2014) also identified jaundice as a negative prognostic factor in dogs with idiopathic chronic hepatitis. HE is uncommon and usually seen only in dogs with end-stage disease. The presence of HE strongly suggests the development of an acquired PSS. Dogs with chronic hepatitis usually have some degree of protein-calorie malnutrition as a result of chronic hepatic functional impairment and concurrent GI signs (see Chapter 33). They are often overtly thin. They may be depressed but are also often surprisingly alert considering the severity of their disease.

Diagnosis

Ultimately, a definitive diagnosis requires a liver biopsy, but disease is suspected from the clinical signs and clinicopathologic features. Clinical signs, clinicopathologic findings, and imaging may be supportive of chronic hepatitis but are not specific. A serum biochemical profile may show a combination of high activities of hepatocellular enzymes (ALT and aspartate aminotransferase [AST]) and cholestatic enzymes (alkaline phosphatase [ALP] and γ-glutamyltransferase [GGT]) and evidence of decreased parenchymal liver function (low urea, low albumin, and sometimes high bilirubin and bile acid concentrations). Persistent increases in ALT levels are the most consistent finding in dogs with chronic hepatitis but can also be found in other primary and secondary hepatopathies. A high ALP activity is much less specific in dogs, particularly because there is a steroid-induced isoenzyme. Hepatocellular enzymes can become normal in end-stage disease because of a lack of liver mass, but by that stage function test results (e.g., ammonia and bile acid concentrations) will be abnormal, and the dog may even be jaundiced.

Radiographic findings are nonspecific. Dogs with chronic hepatitis often have a small liver (contrasting with cats, in which hepatomegaly is more common), but the liver may also appear small in normal dogs, and the assessment of liver size is further confused by the variations in the gastric axis in deep-chested dogs. If ascites is present, radiographs are not helpful because the fluid obscures all abdominal detail. Ultrasonography is much more useful for assessing hepatic architecture (see Chapter 34). Dogs with chronic hepatitis often have a small, diffusely hyperechoic liver on ultrasonography, although the liver may look ultrasonographically normal in some cases. In other cases it may appear nodular because of macronodular cirrhosis and/or concurrent benign nodular hyperplasia (see later). It is impossible to definitively differentiate benign from malignant nodules on ultrasonographic appearance alone; cytology or biopsy is essential to obtain a definitive diagnosis.

End-stage chronic hepatitis with cirrhosis may appear very similar to noncirrhotic portal hypertension or congenital ductal plate abnormality from a diagnostic standpoint, yet the treatment of the latter is very different, and the long-term prognosis is much more favorable than with cirrhosis. Therefore a liver biopsy is necessary for a definitive diagnosis and appropriate treatment. Hemorrhage is the most significant risk of liver biopsy, and therefore it is the consensus amongst veterinary hepatologists to obtain a hemostasis profile (one-stage prothrombin time, activated partial thromboplastin time, and platelet count) before obtaining a biopsy and to address any coagulopathies or thrombocytopenia before the procedure. However, publications fail to show a clear association between any one measure of hemostasis and the risk of bleeding complications postbiopsy. Fine-needle aspiration (FNA) cytology is of limited value in the diagnosis of chronic hepatitis; the most representative biopsies are wedge biopsies obtained during laparotomy or laparoscopy. Ultrasonographically guided Tru-Cut–type needle biopsies can be of some benefit but are often misleading (see Chapter 34 for more details on biopsy techniques).

Treatment

The goals of treatment of dogs with chronic hepatitis include treating any identified underlying cause, slowing progression of the disease if possible, treating clinical signs such as ascites and HE, and supporting liver function and the animal's nutritional and metabolic needs.

Treatment of Underlying Cause

If an infectious cause is identified, this should be treated appropriately. Any significant copper buildup should be chelated (see later) and managed with a low copper diet. Any suspected hepatotoxic drug or nutraceutical should be removed and replaced as necessary with a safe alternative. This can be particularly difficult in the case of a dog with chronic hepatitis and concurrent life-limiting degenerative joint disease where the continued use of nonsteroidal anti-inflammatory drugs (NSAIDs) is contraindicated.

Diet

Dietary management is always an important part of treatment for patients with liver disease because the liver is the first stop for nutrients on their way from the gut to the systemic circulation, and it is intimately involved in the metabolism of nutrients. This metabolism is compromised in patients with liver disease; in addition, dogs with chronic hepatitis typically have protein-calorie malnutrition, so excessive restriction of nutrients can be harmful.

The nutritional requirements for dogs with liver disease are outlined in Table 36.2. The most important consideration is dietary protein concentration. It is now recognized in humans and dogs with liver disease that, to avoid a negative nitrogen balance, dietary protein should not be restricted. However, it is important to feed a high-quality, highly digestible protein to reduce hepatic work and decrease the amount of undigested protein that reaches the colon, where it is converted to ammonia. Most ammonia reaching the systemic circulation in the portal blood of animals with congenital and acquired PSSs originates not from dietary protein but from enterocyte catabolism of glutamine as their main source of energy. This cannot be avoided without starving the enterocytes, so other means of controlling HE are recommended in addition to dietary restriction (see later). Most prescription diets available for dogs with liver disease (Hill's l/d diet, Hill's Pet Nutrition, Topeka, KS; Royal Canin Hepatic Formula, Royal Canin USA, St Charles, MO) are ideally formulated, except that they have lower protein than is ideal for a dog with chronic hepatitis. Therefore these diets should be fed as a baseline in small amounts and often with the addition of high-quality protein to the food. Dairy and vegetable protein produce the best results in humans and dogs with liver disease; cottage cheese is a good choice to add to the diet. The amount to add to the food is difficult to estimate. It is advisable to start with 1 or 2 tablespoons of cottage cheese per meal, monitor clinical signs and blood protein levels, and for gastrointestinal disease such as Hill's ID diet or Royal Canin gastrointestinal or a clinical diet formulated adjust accordingly. Alternatively, a clinical diet formulated for liver disease with a less restricted protein content can be used, such as Purina HP.

Drugs

Drug support in dogs with idiopathic chronic hepatitis is nonspecific, and attempts to slow the progression of disease and control clinical signs. Specific drug treatments are reserved for patients with an identified underlying cause. Without a biopsy, nonspecific treatment should consist of choleretics, antioxidants, and diet. The use of glucocorticoids and copper chelators must be reserved for biopsy-confirmed cases only.

Choleretics

Ursodiol is widely and commonly used in dogs with chronic hepatitis. It is a synthetic hydrophilic bile acid that is choleretic and modulates the bile acid pool in biliary stasis, making the bile less toxic to hepatocytes. It also has antiinflammatory and antioxidant properties, and studies suggest that it is synergistic with SAM-e and vitamin E. The only absolute contraindication is complete biliary obstruction, which is very rare in dogs and would usually result in obvious acholic feces. It can be used in any dog with chronic hepatitis, particularly in those associated with biliary stasis, and can safely be used without a biopsy. However, as with other drugs used for the treatment of canine liver disease, there is limited, although encouraging, evidence about its efficacy. It may be more helpful in some diseases than others, but this has not yet been determined for dogs. The recommended dose is 10 to 15 mg/kg orally (PO) q12h (or divided into two doses given q12h).

Antioxidants

A variety of antioxidants are used in dogs with chronic hepatitis. The best documented are vitamin E and SAM-e. Vitamin E appears to be beneficial at a dosage of 400 IU/day PO for a 30-kg dog, given as a water-soluble preparation once a day. Dosages for smaller dogs are scaled appropriately. SAM-e is a glutathione precursor and is of particular benefit for dogs with toxic hepatopathy (see earlier) and those with biliary stasis because bile is a potent oxidant. It is synergistic with vitamin E and ursodiol, and an argument could be made for it being beneficial in any dog with chronic hepatitis. The recommended dose is 20 mg/kg PO q24h. There are some studies documenting its use in dogs, but more research is needed to define in which diseases it is most useful. SAM-e is a very unstable molecule because it is a methyl donor and must therefore be carefully packaged and given on an empty stomach. The pharmacokinetics and GI availability in dogs have been published for the pure preparation (Denosyl, Nutramax Laboratories, Edgewood, MD; Center et al., 2005). However, SAM-e is increasingly being marketed as a polypharmacy nutraceutical in preparations with other nutraceuticals and vitamins combined. Pharmacokinetic and absorption data should be sought from the manufacturers of these products to ensure that the SAM-e is absorbed in effective amounts.

Another antioxidant commonly used in dogs with chronic hepatitis is milk thistle *(Silybum marianum)*. The active ingredients are flavonoids, commonly referred to as silymarin; the most effective of these is believed to be silybin. There are few studies on the use of flavonoids in dogs, and the only clinical studies are in regard to acute toxic hepatitis. Silybin may have the potential to be a helpful adjunct to therapy in some cases, but much more information on absorption, availability, and ideal dosage is necessary. Silybin

TABLE 36.2

Dietary Considerations for Dogs With Liver Disease*

DIETARY COMPONENT	RECOMMENDATIONS
Protein	Normal amount – avoid low and high protein foods High-quality (optimal amounts of all essential amino acids) Highly digestible Ideal protein source may be dairy or vegetable (Reduced aromatic amino acids and increased branched-chain amino may reduce hepatic encephalopathy—evidence lacking.) Ornithine aspartate may reduce hepatic encephalopathy—one small pilot study in dogs (Ahn et al., 2016) Proprietary liver diets or GI diets or hypoallergenic diets are ideal
Fat	No special advice for liver disease—fat restriction usually unnecessary even with biliary tract disease. Optimizing omega-3–omega-6 may help reduce inflammation (more research is needed).
Carbohydrate	No special advice for liver disease except highly digestible as a calorie source, reducing the need for hepatic gluconeogenesis from fat and protein.
Fiber	Ideal is moderate amount of mixed fiber source Fermentable fiber (e.g., lactulose) may reduce hepatic encephalopathy (conflicting evidence in humans, little evidence in dogs)—broken down to short-chain fatty acids in the colon, trapping ammonia as ammonium, increasing nitrogen incorporation into bacteria and reducing ammonia production. Nonfermentable fiber prevents constipation, a potential predisposing factor for development of encephalopathy
Minerals	
Zinc	Zinc indicated in copper storage disease—reduces copper absorption from gut and copper availability in the liver. Do not supplement when dog is on copper chelators as zinc will compete with copper for chelation. Zinc supplementation may be helpful in chronic hepatitis with hepatic encephalopathy—extrapolated from humans and no evidence in dogs
Copper	Animals with copper storage disease should be maintained on a low-copper, high-zinc diet.
Vitamins	
Fat-soluble	Vitamin E supplementation may be cytoprotective, especially in copper toxicity, because of its antioxidant effect. Vitamin K supplementation may be necessary if clotting times are prolonged, especially in cats and particularly if considering biopsies. Vitamins A and D should not be supplemented. Vitamin A can cause hepatic damage, and vitamin D supplementation can cause calcification in tissues.
Water-soluble	B vitamins may be supplemented because there is potential increased loss in polydipsia/polyuria associated with liver disease. Vitamin C should not be supplemented because ascorbate can increase the tissue damage associated with copper and iron in liver disease.

*The diet should be fed little and often (four to six times daily) and needs to be palatable. A good and sufficient diet is essential for hepatic regeneration and optimal hepatic function.

is included in many nutraceuticals marketed for dogs with liver disease. One study (Filburn et al., 2007) showed that it had very poor absorption alone but was more bioavailable when complexed with phosphatidylcholine. Denamarin (Nutramax Laboratories) contains both SAM-e and silybin in reportedly bioavailable forms, although published data supporting this are currently lacking.

Antioxidant nutraceuticals have great potential benefits for the treatment of chronic liver disease in dogs as well as vacuolar and toxic hepatopathies in dogs and cats, and can be safely used without a biopsy. However, the clinician must be aware of the emerging nature of the information about their bioavailability and efficacy, and choose products carefully with this in mind.

Copper chelators

Any dog with chronic hepatitis and an excess of copper on biopsies should be treated with copper chelators and a low copper diet (see "Copper Storage Disease" section for

more details). Pathologists may describe a copper distribution suggestive of secondary rather than primary copper buildup (predominantly zone 1, periportal) but nevertheless, copper within the liver is toxic and has the potential to worsen the disease and should be removed. As a guideline, if copper buildup is described as moderate to marked on histology, and is associated with raised ALT and histologic evidence of hepatitis, it should be chelated. Antioxidants should also be used (SAM-e and Vitamin E).

Glucocorticoids

Glucocorticoids are commonly used in dogs with idiopathic chronic hepatitis but should never be used without having the results of a biopsy available and a strong suspicion of autoimmune etiology. Biopsies are necessary not only to confirm the presumptive diagnosis but also to rule out any contraindications. Glucocorticoids have traditionally been used in this context for their putative antiinflammatory and antifibrotic actions, rather than as immunosuppressives. However there is very little evidence for their efficacy as nonspecific antifibrotics, and their use should be confined to suspected autoimmune hepatitis cases (see earlier). The most effective antifibrotic and antiinflammatory intervention in chronic hepatitis is to remove the underlying cause (Fig. 36.4), and nonspecific use of glucocorticoids in unrecognized chronic infectious, toxic, or metabolic cases of chronic hepatitis may do more harm than good in perpetuating or worsening the cause.

In suspected autoimmune hepatitis, prednisone/prednisolone should be dosed at 1 to 2 mg/kg once a day, with a gradually reducing dose over weeks to months while monitoring efficacy with repeat liver enzyme measurements. Effective treatment should be accompanied by a reduction in ALT levels, but ALP may increase due to steroid induction. Nevertheless, in one study of the efficacy of steroid treatment in English Springer Spaniels with suspected immune-mediated hepatitis, successful treatment was accompanied by a surprising reduction in ALP as well as ALT (Bayton et al., 2018). Some dogs can be weaned slowly off all therapy, whereas other dogs require long-term maintenance at a lower dose.

Glucocorticoids are contraindicated later in the disease, when there is portal hypertension and end-stage fibrosis, or in conditions with noninflammatory fibrosis (e.g., noncirrhotic portal hypertension), in which there is no rationale for their use. In these circumstances they are also likely to shorten the life expectancy by increasing the risk of serious GI ulceration. Hence, glucocorticoids should never be used without a histopathologic diagnosis and staging of disease.

Other immunosuppressive drugs

Other immunosuppressive drugs are sometimes used in dogs with suspected autoimmune hepatitis. Cyclosporine has been reported to be efficacious in one study of dogs with chronic hepatitis and is the author's first choice as an alternative to prednisolone. Cyclosporine is particularly indicated for long-term management in animals that cannot be weaned off steroids and also in dogs where the adverse effects of steroid therapy are a problem, for example, dogs with portal hypertension and ascites but suspected ongoing autoimmune hepatitis. As with corticosteroids, cyclosporine should never be used without biopsy confirmation of suspected autoimmune hepatitis. Azathioprine has been used alone or in combination with prednisolone, and mycophenolate mofetil has also been used in dogs with chronic hepatitis. However, there is no evidence in support of the use of these two potent drugs in dogs with chronic hepatitis, and the author would

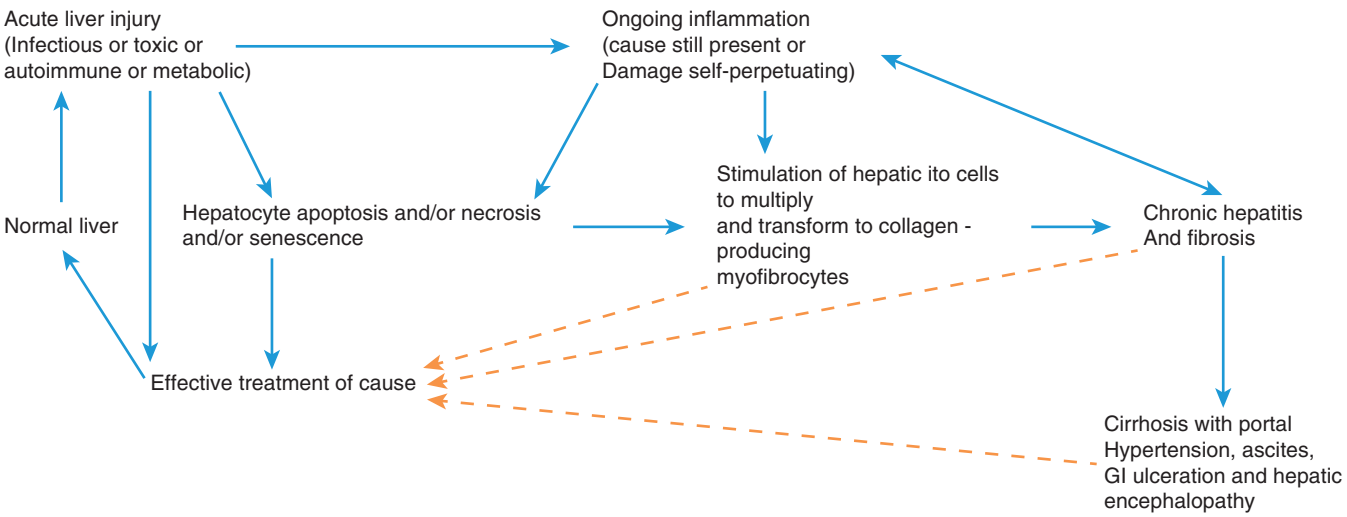


FIG 36.4
Chain of events in acute and chronic liver disease. In the face of ongoing inflammation and insult, progressive fibrosis will lead to cirrhosis and liver failure. However, if the inciting cause is effectively treated, fibrosis and even early cirrhosis might be reversed as indicated by orange arrows. This has been convincingly demonstrated in humans but not yet dogs.

generally avoid them because of the lack of evidence and potential side effects.

Antifibrotics

The most effective antifibrotic treatment in the context of chronic hepatitis is to effectively treat the underlying cause. Fig. 36.4 illustrates the potential for reversal of fibrosis and even early cirrhosis if the underlying cause is treated. This has been well described in human medicine but poorly documented in canine chronic hepatitis. Later in the disease process, when there is extensive fibrosis, the direct antifibrotic agent colchicine can be used. However, the author does not recommend its use as there is no good evidence of efficacy and it has a high incidence of side effects. It is difficult to believe that colchicine is an effective antifibrotic in the liver of dogs given that no effective hepatic antifibrotic has been identified in humans, in spite of years of research (Friedman, 2010). Spironolactone may also have some antifibrotic activity. This has been demonstrated in rats with chronic hepatitis, so there is an argument to use it.

Antibiotics

There is a primary indication for the use of antibiotics in dogs with ascending biliary tract infections or suspected bacterial infection as a cause of chronic hepatitis. The latter is rarely proven, but if an atypical leptospiral infection might be present (e.g., if chronic granulomatous hepatitis is seen in a dog with access to sources of infection, such as rivers or ditches), a course of appropriate antibiotics would be wise to rule this out. The recommended therapy for leptospiral infections is to start with intravenous (IV) amoxicillin, 22 mg/kg q12h, to terminate replication and reduce potentially fatal liver and kidney complications. If leptospiral infection is subsequently confirmed by rising titers on serology, dark field microscopy, PCR assay of the urine or blood for organisms, or fluorescent in-situ hybridization of live biopsies, this should be followed by doxycycline therapy (5 mg/kg PO q12h, for 2 weeks) once liver function has normalized to eliminate the chronic renal carrier state. For additional information on leptospirosis, see Chapter 94. *Bartonella* spp. have occasionally been associated with chronic liver disease in dogs, but the optimal treatment for *Bartonella* infection in dogs has not been established. Macrolides (e.g., erythromycin) or alternatively fluoroquinolones or doxycycline have been shown to have some efficacy against some *Bartonella* spp. in dogs. It has been suggested that 4 to 6 weeks of treatment might be necessary to eliminate infection (see Chapter 94).

Antibiotics are also used as part of supportive treatment in dogs with HE caused by acquired PSS in end-stage chronic hepatitis; they are given in a similar way as to dogs with congenital PSS to reduce toxin absorption from the gut and risk of systemic infections (see later). Ampicillin or amoxicillin is often used long term in these cases, 10 to 20 mg/kg PO q8-12h.

As with other drugs, the clinician should avoid any antibiotics that increase hepatic work or the risk of hepatotoxicity. Thus tetracyclines, potentiated sulfonamides, nitrofurantoin, and erythromycin should be avoided unless necessary (e.g., with confirmed leptospirosis or bartonellosis) because they are potentially hepatotoxic.

Treatment of portal hypertension

Dogs with chronic hepatitis presenting with clinical signs of portal hypertension (ascites, gut wall congestion, and potentially acquired PSS) have specific management considerations. The treatment of HE associated with acquired PSS is the same as the treatment of HE associated with congenital PSS (see later in this chapter).

The treatment of ascites associated with portal hypertension in chronic hepatitis revolves around the use of diuretics, first aldosterone antagonists (spironolactone, 1-2 mg/kg PO q12h) and then the addition of furosemide (2 mg/kg PO q12h) if necessary in refractory cases. The reason spironolactone is the diuretic of choice in these dogs is due to the underlying pathophysiology with increase in aldosterone and fluid retention described in Chapter 33. Spironolactone usually takes 2 or 3 days to reach full effect, and the resolution of ascites can be monitored by weighing the patient daily; any acute changes in weight will be caused by fluid shifts. Dietary sodium restriction has also been recommended, although it is unclear how effective or important this is. However, it is certainly wise to refrain from feeding the patient high-salt snacks and treats.

It is important to monitor serum electrolyte concentrations, mainly sodium and potassium, daily during the first few days of treatment and every few weeks to months thereafter, depending on how stable the dog and drug doses are. Hypokalemia should be avoided because it can precipitate HE (see later), but it is less likely in a dog on aldosterone antagonists and loop diuretics than in a dog on furosemide alone. Hyponatremia can also occur; if it is marked, the diuretics should be stopped and the patient given careful IV replacement until the sodium level is normalized. Therapeutic paracentesis is indicated only for patients with ascites that is severe enough to compromise breathing. This is actually unusual and is manifested by severe ascites with a tense abdomen and the dog is unable to settle and lie down. Paracentesis should be accompanied by concurrent IV administration of a colloid plasma expander, plasma, or albumin; removal of a large volume of fluid containing albumin can result in a precipitous hypoalbuminemia and decrease in oncotic pressure, leading to pulmonary edema. This is a real problem in dogs with chronic liver disease in which the liver's capacity to manufacture albumin is reduced.

Dogs with portal hypertension are at risk of GI ulceration due to splanchnic congestion, as described earlier and in Chapter 33. The clinician must be aware that GI ulceration may occur acutely in dogs with splanchnic congestion, and serious clinical deterioration may occur before melena is apparent because it takes several hours for the blood to pass from the small to large intestine. Before this occurs, it is possible for the animal to show sudden onset and marked signs of HE because blood is a high-protein meal in the small intestine (see earlier) or even for the ulcer to perforate and cause peritonitis (Fig. 36.5).

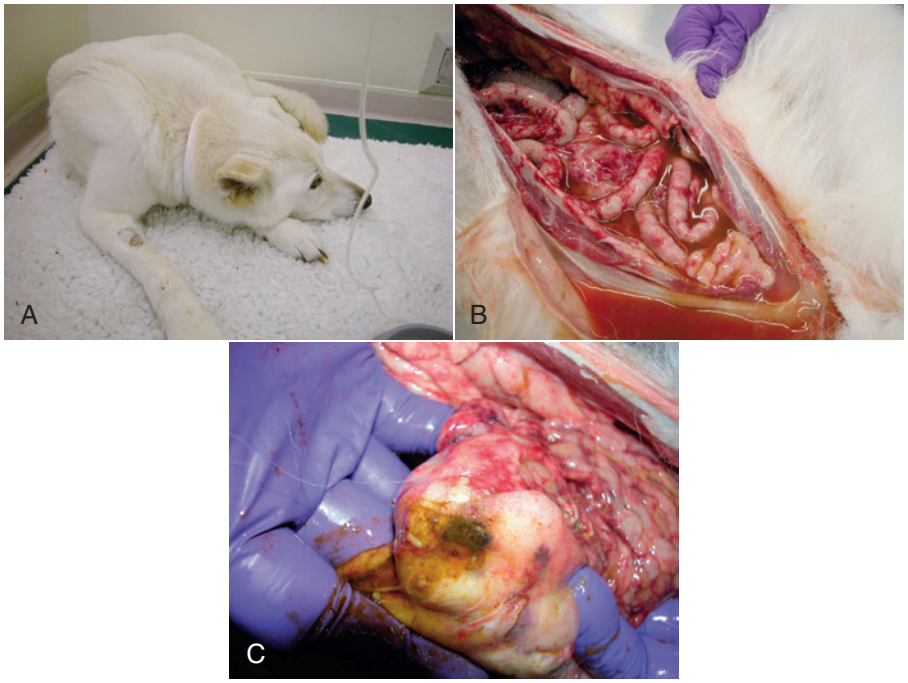


FIG 36.5
(A) Nine-year-old neutered female German Shepherd dog with previously stable noncirrhotic portal hypertension treated medically for 8 years presented very depressed, with a week-long history of anorexia (same dog as Fig. 36.13). **(B)** and **(C)** In spite of immediate institution of tube feeding on admission, the dog rapidly developed fatal septic peritonitis as a result of rupture of an ulcer at the gastroduodenal junction. It was found that the dog had developed asymptomatic pyelonephritis. The referring veterinarian had recognized the hepatic encephalopathy but tried to manage it by starvation for a week, which likely increased rather than decreased ammonia production through breakdown of muscle and also increased the risk of GI ulceration because of a lack of intraluminal gut nutrition.

Treatment of GI ulceration largely revolves around its prevention (i.e., avoiding triggers as much as possible, such as prolonged fasting and the use of steroids or NSAIDs, and avoiding hypotension during any surgery). It is particularly important that any dog with portal hypertension that undergoes a prolonged period of anorexia is fed because they will be at high risk of GI ulceration if they do not receive nourishment (see Fig. 36.5). Parenteral nutrition is not an effective alternative in these dogs because it does not supply luminal nutrients for enterocyte healing—upper GI ulceration is a common adverse effect of total parenteral nutrition in humans, even in those without portal hypertension, and some form of enteral support should be instituted as soon as possible. The use of gastric acid secretory inhibitors (H_2 blockers or proton pump inhibitors) is of questionable benefit in patients with portal hypertension because it is usually the duodenum that is ulcerated (rather than the stomach); also, there have been reports that the gastric pH in dogs with liver disease may already be higher than normal as a result of changes in gastrin metabolism, although a recent study of dogs with newly diagnosed liver disease found no difference in gastrin concentration compared with control dogs (Mazaki-Tovi et al., 2012). However, in the face of active ulceration and melena, gastric acid secretory inhibitors are often used in the hope that they will help. In these circumstances, cimetidine is contraindicated because of its effect on hepatic P450 enzymes; therefore ranitidine (2 mg/kg administered orally or via slow IV administration q12h) or famotidine (0.5-1 mg/kg administered PO q12-24h) are recommended. The proton pump inhibitor omeprazole is likely to be more effective in the face of overt bleeding and should be dosed at 1 mg/kg q12h. Likewise, sucralfate (Carafate™) is of questionable efficacy; it is most effective against gastric ulceration (i.e., in association with a low pH), but it is often used (at a dosage of 500 mg-1 g per dog PO q8h). Hemostasis profiles should also be evaluated, and any coagulopathy treated with vitamin K (see the later section on coagulopathy) or plasma transfusions.

Treatment of coagulopathies

Despite the presence of hemostatic abnormalities, spontaneous bleeding is uncommon in patients with chronic liver disease but relatively common in those with acute disease (see later). Because dogs with portal hypertension and GI hemorrhage (see previous section) may also have a coagulopathy predisposing to their bleeding, they should be thoroughly evaluated. However, the risk of hemorrhage increases

after a challenge to hemostasis, such as liver biopsy; therefore it is very important to evaluate hemostasis before performing liver biopsy. If coagulation times are prolonged, it is worth trying vitamin K1 (phytomenadione) therapy (0.5–1 mg/kg SC × 3 doses at 12 hour intervals). However, this is much less effective in dogs than cats, so administration of fresh or fresh frozen plasma may be indicated to replenish depleted clotting factors. A starting dose of 10 mL/kg given slowly is recommended; the dose of plasma is titrated on the basis of the results of the one stage prothrombin time (OSPT) and activated partial thromboplastin time (APTT).

COPPER STORAGE DISEASE

Pathogenesis and Etiology

Copper storage disease has been recognized as a cause of acute and chronic hepatitis in several breeds, the best researched of which is the Bedlington Terrier (see Box 36.1). Other breeds in which copper storage disease has been reported are Dalmatians (in the United States and Canada), Labrador Retrievers (in the United States and Holland), and some Doberman Pinschers (in Holland), although individual members of all these breeds have also been reported with chronic hepatitis without copper accumulation. In addition, copper storage disease has been suspected but not extensively investigated in West Highland White Terriers. The previously reported copper storage disease in Skye Terriers is now believed to be a congenital ductal plate abnormality (see later). In one study of several dog breeds in Holland, hepatitis was ascribed to copper storage disease in 36% and was idiopathic and not copper associated in 64% of 101 dogs studied with acute and chronic liver disease (Poldervaart et al., 2009). It is also possible for seemingly normal dogs without a recognized copper storage disease to develop copper-associated chronic hepatitis if fed a diet very high in copper, such as dry calf feed (Van den Ingh et al., 2007).

Copper is excreted in the bile and can build up as a secondary phenomenon in any type of chronic hepatitis associated with cholestasis. In these cases, the accumulation is usually mild, often in zone 1 (peribiliary), and the amount of copper does not correlate with the severity of the disease. An early study demonstrated that dogs were resistant to copper accumulation in cholestasis unless they were also copper-loaded in the diet (Azumi, 1982). Copper buildup in the liver is therefore likely to be an interaction between genetic susceptibility and environment (i.e., dietary copper concentration and concurrent biliary stasis). Dietary copper concentration heavily affects hepatic copper accumulation in all breeds, not just those predisposed to copper storage disease. An increase in hepatic copper has been observed in dogs since the 1980s, and it is hypothesized this is due to the change in formulation of copper added to commercial food to a more bioavailable chelate (Gagne et al., 2013). The peribiliary distribution and lack of correlation between amount of copper buildup and clinical signs helps distinguish these cases from "true" copper storage disease, in which the copper accumulation is the cause rather than an epiphenomenon of the disease, and accumulation is usually marked, progressive, correlated with disease severity, and in zone 3 (perivenous; see Fig. 33.7 for an explanation of hepatic zonation). Copper chelation is recommended in any dog with chronic hepatitis with significant copper buildup, whether it is primary or secondary, because copper is a potent oxidizing toxin. Therefore distinguishing primary from secondary copper accumulation may not change treatment recommendations, except for informing a search for an underlying primary cause other than the copper.

True copper storage disease likely represents a genetic defect in copper transport and/or storage. The breed in which this has been best defined is the Bedlington Terrier. In this breed it is inherited as an autosomal recessive trait, and up to 60% of Bedlington Terriers in some countries have been affected in the past, although the prevalence is now decreasing as a result of selective breeding. The disease is confined to the liver, and there appears to be a specific defect in hepatic biliary copper excretion, probably in transport from the hepatocyte lysosomes to the biliary tract. Studies have identified at least one genetic defect associated with the disease, a deletion in the *MURR1* gene (now *COMMD1;* Van de Sluis et al., 2002), which codes for a protein of unknown function. However, Bedlington Terriers with copper storage disease but without a *COMMD1* deletion have been reported in the United States, United Kingdom, and Australia (Coronado et al., 2003; Haywood, 2006; Hyun et al., 2004), suggesting that there are additional mutations involved in the breed. A recently published study identified an association between copper storage disease in Bedlington Terriers and an alternative mutation in metal transporter ABCA 12, which is functionally similar to the ATPase 7B that is mutated in humans with Wilson's disease (Haywood et al., 2016).

In Labrador Retrievers, a missense mutation in the ATPase 7B gene itself has been associated with copper accumulation, whereas a missense mutation in ATPase 7A protects against copper accumulation (Fieten et al., 2016).

Clinical Features

Affected Bedlington Terriers can present with acute or chronic clinical signs, depending on individual factors, such as the amount of copper in the diet, and other possible factors, including concurrent stress and disease. If there is rapid and marked buildup, dogs may present with acute fulminant hepatic necrosis and no previous clinical signs. This is usually seen in young to middle-aged dogs and is often accompanied by acute intravascular hemolytic anemia caused by the rapid release of copper into the circulation. The prognosis is poor, and most animals die within a few days. Fortunately, this is uncommon; most dogs have a more chronic, protracted course, with several years of copper buildup and persistently high ALT activity, culminating in the development of chronic hepatitis with piecemeal necrosis, inflammation, and bridging fibrosis. Clinical signs are therefore recognized in these individuals only late in the disease process and are usually those of canine chronic

hepatitis. These dogs usually present at about 4 years of age, but may be younger (Fig. 36.6). Eventually, if not treated, affected dogs will develop cirrhosis.

The clinical signs and progression in other breeds with copper storage disease are similar to those in Bedlington Terriers. The disease in Dalmatians is associated with acute onset, rapid progression, and very high levels of hepatic copper in the absence of significant clinical, clinicopathologic, or histologic evidence of cholestasis. Affected dogs usually present as young adults with acute onset of GI signs and PU-PD, by which time severe liver disease is already present. Labrador Retrievers with copper storage disease have an average age at presentation of 7 to 9 years (range, 2.5–14 years). The clinical signs are relatively mild and include anorexia, vomiting, and lethargy. Doberman Pinschers appear to have a long phase of subclinical disease culminating, in untreated cases, in an acute-on-chronic disease and rapidly progressive deterioration. However, it is unclear how many of the clinically affected Doberman Pinschers described in the literature had copper storage disease and how many had idiopathic or potentially immune-mediated chronic hepatitis, so the actual presenting signs of copper storage disease in this breed are unclear. Most published studies on copper storage disease in Doberman Pinschers have described the diagnosis and treatment of subclinical disease.

Occasionally, dogs with copper storage disease also present with renal signs typical of Fanconi syndrome with normoglycemic glycosuria and proteinuria. This has not been reported in Bedlington Terriers but in a variety of breeds including two West Highland White Terriers (Appleman et al., 2008; Hill et al., 2008) and nine Labrador Retrievers (Langlois et al., 2013). Most but not all cases have been associated with increased copper accumulation in the kidneys on histology.



FIG 36.6
Bedlington Terrier with copper storage disease. (From Hall EJ et al., editors: *BSAVA manual of canine and feline gastroenterology,* ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

Diagnosis

The magnitude of increase in liver enzyme activities and the diagnostic imaging findings in dogs with chronic copper storage disease are very similar to those of dogs with idiopathic chronic hepatitis. Therefore a definitive diagnosis requires a liver biopsy and determination or estimation of the copper concentration in the liver. This can be done qualitatively on formalin-fixed sections using rhodanine or rubeanic acid staining to detect copper; correlations between the quantitative and qualitative estimations of copper accumulation have been published (Shih et al., 2007). Digital scanning of rhodanine-stained sections is a more objective qualitative measure of hepatic copper (Center et al., 2013). The finding of large accumulations of copper in hepatocytes on cytology with rubeanic acid is also suggestive of copper storage disease (Fig. 36.7; Teske et al., 1992). Quantitative measurement of copper content can also be performed, but this requires a large biopsy specimen carefully taken and stored in copper-free tubes. The concentration of copper that is considered pathologic is controversial but > 1000 µg/g dry weight liver is generally considered significant. The clinician should also be aware that there can be considerable variation in copper concentration between liver lobes due to patchy fibrosis and regeneration. Further details on diagnosis of copper storage disease can be found in Webster et al., 2019. In addition to estimating copper content, the liver biopsy will give an indication of the chronicity and extent of liver damage, which will affect treatment decisions similarly to that for chronic hepatitis. Bedlington Terriers can be tested for the *COMMD1* deletion before breeding or when newly acquired to assess their risk for this disease, but an absence of the *COMMD1* deletion does not guarantee that the dog

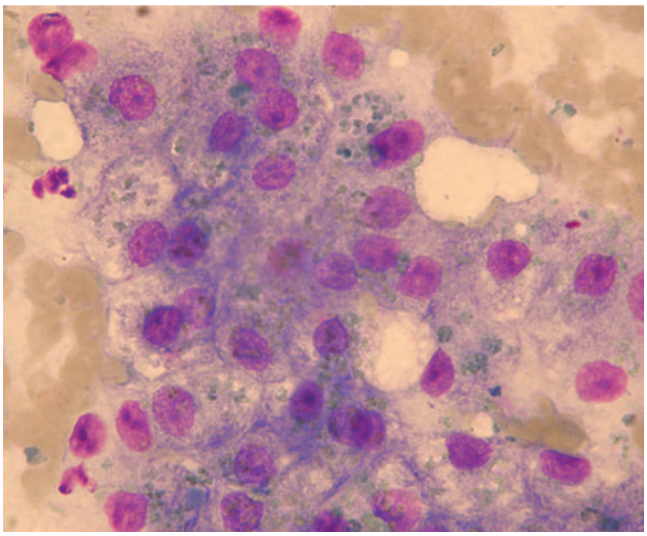


FIG 36.7
Cytology of hepatocytes from Bedlington Terrier with copper storage disease demonstrating copper granules (rubeanic acid stain). (Courtesy Elizabeth Villiers; from Hall EJ et al., editors: *BSAVA manual of canine and feline gastroenterology,* ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

will not be affected. The genetic test is currently offered via mouth swabs at the Animal Health Trust in Newmarket, England (details at https://www.ahtdnatesting.co.uk) and by VetGen in the United States (www.vetgen.com). To rule out copper storage disease through a liver biopsy in a breeding animal, clinicians should obtain a biopsy when the dog is about 12 months old, by which time there will be sufficient copper buildup to diagnose the disease. In much older animals, cirrhosis with nodular regeneration can develop, and the nodules will have a lower copper content than the rest of the liver, confusing diagnosis if a regenerative nodule is inadvertently biopsied.

A genetic test for copper storage disease in Labrador Retrievers has recently become available in the United States (https://www.vetgen.com/canine-ct-lab.html). This is based on the ATP7B mutation. However, the laboratory notes that the prevalence of this mutation is high in Labradors so they do not recommend breeding away from it completely but rather avoiding homozygous pairings.

Treatment

The ideal treatment for a dog known to be affected is prevention. Bedlington Terriers homozygous for the *COMMD1* mutation should be fed a low-copper, high-zinc diet. The proprietary liver diets formulated for dogs (Royal Canin Hepatic Support or Hill's canine l/d) have low copper and high zinc concentrations but are also moderately protein-restricted, so it would be wise to supplement with a low-copper protein source (e.g., cottage cheese) in growing dogs. Purina Proplan Veterinary HP hepatic diet (Produits Nestlé SA, Vevey, Switzerland), available in Europe but not the United States, has low copper with a slightly higher protein concentration than the other diets. It is also important to avoid giving the dog tap water from copper pipes in soft water areas; bottled water should be used instead. Box 36.3 lists common high-copper foods that should be avoided and high-zinc foods that could be supplemented.

Dogs that present with an acute crisis should be treated with intensive support in exactly the same way as dogs with acute hepatitis (Box 36.4). Blood transfusion may be necessary if hemolysis is severe, but until cupremia is controlled, the patient will likely continue to hemolyze the transfused red blood cells. Copper chelation is unlikely to be beneficial acutely, but chelation with 2,2,2-tetramine (trientine) could be considered (or 2,3,2-tetramine if obtainable) because this can chelate rapidly. Trientine is available as a drug licensed for humans (Syprine, Valeant Pharmaceuticals, Bridgewater, NJ). The recommended dose in dogs is 10 to 15 mg/

BOX 36.3

Foods Rich in Copper and Zinc

Copper

- Shellfish*
- Liver*
- Kidney, heart
- Cereals
- Cocoa
- Legumes
- Soft tap water (copper pipes)

Zinc

- Red meat
- Egg yolks
- Milk
- Beans, peas
- Liver
- Whole grains, lentils
- Rice
- Potatoes

*Particularly high in copper.

BOX 36.4

Treatment Recommendations for Acute Fulminant Hepatitis

- Identify and treat cause, if possible:
  - Remove drugs implicated.
  - Treat leptospirosis.
  - Treat acetaminophen toxicity: give *N*-acetylcysteine (150 mg/kg by IV infusion in 200 mL 5% glucose over 15 min, followed by 50-mg/kg IV infusion in 500 mL over 4 hours, then 100-mg/kg IV infusion in 1000 mL over 16 hours), ± cimetidine (5–10 mg/kg IV, IM, or PO, q8h)
- Fluids:
  - Careful IV fluid therapy—dextrose saline with added potassium often most appropriate.
  - Measure blood glucose and electrolyte concentrations every few hours and adjust appropriately.
  - Use peripheral catheter and monitor renal function; use central catheters only when confirmed that there is no coagulopathy or high risk of unnoticed bleeding around catheter.
  - Monitor carefully. Ensure adequate urine output and reversal of dehydration, but do not overinfuse or worsen fluid retention.
- Treat coagulopathy as necessary. Consider fresh-frozen plasma and vitamin K (see text).
- Treat acute hepatic encephalopathy (see text later in chapter). Consider propofol infusions and lactulose-neomycin enemas. Regularly monitor blood glucose and potassium levels, and supplement as necessary.
- Treat any gastrointestinal ulceration. Consider acid secretory inhibitors (ranitidine or omeprazole).
- Treat any ascites with spironolactone ± furosemide.
- Consider antibiotics in all cases to protect against infectious complications, particularly septicemia of gut origin. Give antibiotics to all pyrexic cases intravenously. Use broad-spectrum agents that are safe in liver disease such as amoxicillin-clavulanate.
- Food—nothing by mouth for first 1–2 days until fluid balance has been restored and dog can swallow; then feed diet based on dairy or soy protein, high-quality protein, not restricted. Tube feed if necessary.

kg PO q12h, 30 minutes before a meal. 2,3,2-Tetramine is difficult to obtain. Penicillamine is not helpful in an acute crisis because chelation takes weeks to months. However, it should be noted that there is much less information available about the pharmacokinetics, drug interactions, and toxicity of trientine in dogs than there is for D-penicillamine. Reported adverse effects include nausea, gastritis, abdominal pain, melena, and weakness. On recovery, the animal should continue on long-term treatment, as outlined in the following sections.

Treatment of dogs that already have high hepatic copper concentrations documented by biopsy but are not in an acute crisis consists of active copper chelation, zinc supplementation once chelation is completed, and a low-copper diet and additional supportive therapy. The chronic hepatitis secondary to copper storage disease should be treated the same way as in dogs with idiopathic chronic hepatitis, using antioxidants, ursodiol, and other supportive medication (see earlier, "Idiopathic Chronic Hepatitis"). There is a particular role for antioxidants such as vitamin E and SAM-e in metal-induced liver injury. Chelation can be achieved using D-penicillamine or trientine. D-Penicillamine takes months to have a significant effect on the copper content of the liver but is easily available and its pharmacokinetics and toxicity in dogs are well documented; it also has weak antifibrotic and antiinflammatory properties. The recommended dosage is 10 to 15 mg/kg PO q12h, 30 minutes before meals. Starting at the lower end of the dosage range and increasing the dose after 1 week (or dividing the dose and giving it more frequently) can reduce the common adverse effects of vomiting and anorexia. It has also been reported rarely to cause nephrotic syndrome, leukopenia, and thrombocytopenia in dogs, so a complete blood count (CBC) and urine samples should be monitored regularly during therapy. A decrease in liver copper content of about 900 µg/g dry weight/year can be anticipated in dogs treated with D-penicillamine. Trientine (2,2,2-tetramine) is another efficacious copper chelator that may be used; it can remove copper from the liver more rapidly than D-penicillamine. Details of dosage and potential adverse effects have been presented earlier.

Copper chelation treatment is continued until a normal liver copper concentration is reached; this is best determined by liver biopsy and copper quantification or cytologic estimate. An alternative is to monitor serum liver enzyme activities every 2 to 3 months until they return to normal. Treatment should then be stopped to prevent copper deficiency, which can occur after prolonged, overzealous copper chelation and can result in severe effects of copper deficiency, with weight loss and hematemesis. The regimen can then be changed to a preventive protocol consisting of a copper-restricted diet and zinc administration throughout the animal's life span.

ACUTE HEPATITIS

Etiology and Pathogenesis

Acute hepatitis is much less common than chronic hepatitis in dogs but, when severe, carries a much poorer prognosis. Treatment focuses on providing supportive measures and allowing the liver to recover. Dogs with acute hepatitis are at high risk of disseminated intravascular coagulation (DIC). Severe loss of liver function is also fatal because it cannot be replaced artificially while awaiting recovery; there is no such treatment as liver dialysis. However, because of the remarkable regenerative capacity of the liver, animals that survive the acute phase of the disease can recover completely, with no permanent hepatic injury, as long as they are fed and supported properly.

Most causes of acute fulminating hepatitis in dogs are infectious or toxic (see Box 36.5). In unvaccinated dogs, CAV-1 and leptospira are important differential diagnoses. Dogs with copper storage disease can present acutely, often associated with high serum copper concentration in addition to acute hepatic necrosis. Xylitol, an artificial sweetener, has been reported to cause acute hepatic necrosis and an associated coagulopathy in dogs (Dunayer et al., 2006), with a high mortality. Aflatoxin in contaminated food has also caused acute and subacute hepatitis with a high mortality in dogs (Newman et al., 2007). The most common drugs implicated in causing acute hepatic necrosis in dogs

BOX 36.5

Potential Causes of Acute Fulminant Hepatitis in Dogs

Infections

- Canine adenovirus type 1
- Neonatal canine herpesvirus
- *Leptospira interrogans* (various serovars)
- Endotoxemia
- *Yersinia*
- Sarcocystic hepatitis (neospora; sarcocystitis and hammondia) rarely (Irvine et al., 2016).

Thermal

- Heat stroke

Metabolic

- Acute necrosis associated with copper storage disease in Bedlingtons, Dalmatians, and some Labradors and Dobermans (see Box 36.1)

Toxic or Drug-Induced

- Acetaminophen
- Phenobarbital or primidone
- Carprofen (especially Labrador Retrievers)
- Mebendazole
- Thiacetarsamide
- Mercury
- Potentiated sulfonamides
- Mebendazole
- Cyanobacteria (blue-green algae) in seawater and fresh water
- Xylitol
- Aflatoxin
- Nitrofurantoin
- Lomustine (CCNU)

are listed in Box 36.5, but any drug could cause idiosyncratic hepatic necrosis in an individual dog. A case of destructive cholangitis (termed *disappearing bile duct syndrome*) was reported in a dog as a suspected drug reaction to amoxicillin-clavulanate, amitraz, and milbemycin oxime or a combination of these (Gabriel et al., 2006); the author has seen this in a clinical case likely caused by an idiosyncratic reaction to amoxicillin-clavulanate.

Clinical Features

The clinical features of acute fulminating hepatitis, independent of the cause, relate to the acute loss of hepatic function together with the effects of generalized cell necrosis and release of inflammatory cytokines and tissue factors. Dogs usually present with an acute onset of one or more of the following—anorexia, vomiting, PD-PU, dehydration, HE with depression progressing to seizures and/or coma, jaundice, fever, cranial abdominal pain, coagulopathy with petechiae and possible hematemesis and melena, and, in some cases, ascites and splenomegaly resulting from acute portal hypertension. In dogs and cats with severe acute liver disease, spontaneous bleeding may result from depletion of clotting factors or from DIC. Renal failure is a severe complication in some cases, with both prerenal and intrinsic renal components. In humans with acute hepatic failure, hypotension, cardiac arrhythmias, cerebral and pulmonary edema, and pancreatic inflammation also have been reported; these may occur in some dogs, although they have not been specifically reported.

Diagnosis

The diagnosis is usually made on the basis of history, clinical signs, and clinicopathologic findings. Liver histopathology should be confirmatory, but results are often not obtained until recovery (or postmortem) because of the severe, acute nature of the disease. A history of recent drug or toxin exposure is important in implicating these as a cause; vaccination status is an important consideration for infectious causes.

On clinical pathology, dogs with acute hepatitis often have early marked increases in hepatocellular enzyme ALT and AST activities (10-fold to >100-fold). Jaundice and increases in markers of cholestasis may also occur; the rare cases of destructive cholangitis are characterized by early severe jaundice, marked increases in ALP activities, and hyperbilirubinemia. Hypoglycemia and hypokalemia are common in dogs with acute hepatitis, and azotemia is seen in some cases as a result of both prerenal and renal causes. Hemostatic abnormalities, with prolonged clotting times and thrombocytopenia, are frequently present and can be a sign of developing DIC (see Chapter 87). In patients with DIC, APTT and OSPT may be prolonged, but it is impossible to distinguish this from reduced hepatic production of clotting factors. However, measurement of increased D-dimers and/or fibrin degradation products, combined with decreases in platelet count and schistocytosis, increases the index of suspicion for DIC. D-dimer concentrations are often mildly to moderately increased in dogs with liver disease because of reduced clearance in the liver, and this does not necessarily mean that the dog has a thrombus or DIC. More marked elevations are suggestive of DIC. Diagnostic imaging is not usually helpful in dogs with acute hepatitis. There may be hepatomegaly and a diffuse change in hepatic echogenicity; in some cases there may be splenic congestion and/or ascites, but these changes are not specific and do not help define the cause or extent of the damage. In some patients, the ultrasonographic examination is unremarkable.

Treatment and Prognosis

Treatment of acute fulminant hepatitis in dogs is largely supportive, outlined in Box 36.4. Every attempt should be made to identify and treat the primary cause at the same time that supportive therapy is instituted. Corticosteroid treatment is not indicated in these cases and may worsen the prognosis by increasing the risk of GI ulceration and thrombosis. DIC is a high risk in these cases, and the treatment of DIC is difficult and usually unsuccessful. The most effective treatment is to remove the inciting cause, which in acute liver failure in humans means rapid liver transplant. Without this option in dogs and cats, the mortality in DIC of acute fulminant hepatitis is likely to be 100%. Recommended therapies include plasma transfusion to replace depleted clotting factors and careful heparin therapy during the hypercoagulable phase. However, the efficacy of heparin therapy in DIC has recently been called into question in humans, and there are no clinical data supporting its use in dogs and cats (see Chapter 87).

The owner should be warned of the poor prognosis for recovery in spite of intensive support, and in severe cases, early referral to an intensive care unit should be considered. However, dogs that recover from the acute phase have a good chance of complete recovery. Some research in humans and animals has suggested that chronic liver lesions are less likely to develop if a single-protein milk or soybean-based diet is fed during the recovery phase.

BILIARY TRACT DISORDERS

Biliary tract disorders are less common in dogs than in cats, but primary biliary tract disorders and extrahepatic bile duct obstruction (EBDO) are recognized in dogs. In addition, destructive cholangitis caused by drug reactions leading to severe cholestasis and icterus has been recognized occasionally in dogs but not cats. Dogs occasionally develop congenital hepatic and renal cysts, similar to Caroli's disease in humans, which are discussed in the section on ductal plate disorders later.

CHOLANGITIS AND CHOLECYSTITIS

Primary cholangitis has been considered to be less common in dogs than in cats, although recent reports suggest it has been underestimated (Tamborini et al., 2016; Harrison et al., 2018). Histologically, cholangitis is defined as inflammation confined to the portal region with either inflammatory cell infiltration of the bile duct wall or within the lumen of the bile duct. The clinical signs and diagnostic evaluation are

similar to those in cats with neutrophilic cholangitis (see Chapter 35). Dogs can be of any age or breed, and the typical presentation is acute onset of anorexia, jaundice, and vomiting, with or without pyrexia, although not all affected dogs are jaundiced. In some cases there may have been a previous history of acute enteritis or pancreatitis, suggesting a potential cause for ascending biliary infection from the gut. Mechanical obstruction and gallbladder mucocele (see later) should be ruled out first, usually by ultrasonography, and then liver and bile and/or gallbladder mucosa specimens should be obtained for histopathology and microbial culture and sensitivity testing, preferably before antibiotic treatment is initiated. Concurrent cholecystitis is common in those cases in which it is investigated (Harrison et al., 2018).

Liver biopsies and bile samples can be obtained by direct visualization during surgery, laparoscopy, or ultrasonographic guidance. The latter method carries a greater risk of bile leakage; to minimize this, a 22-gauge needle attached to a 12-mL syringe is used for cholecystocentesis (bile retrieval), and an attempt is made to evacuate the gallbladder. The procedure is best performed under general anesthesia rather than heavy sedation to minimize the chance of patient motion during aspiration. The risk of iatrogenic bile or septic peritonitis is low but greatest with patients with a severely diseased gallbladder wall (determined ultrasonographically); surgical treatment is necessary if bile peritonitis occurs. Enteric organisms similar to those found in cats are usually found; the most common isolate in several studies is *Escherichia coli.* Other organisms reported are all of gut origin and include *Enterococcus, Klebsiella, Clostridium,* fecal *Streptococcus, Corynebacterium,* and *Bacteroides* spp. *Clostridium* may be a gas-forming species causing emphysematous changes in the gallbladder wall visible radiographically or ultrasonographically. Antibiotic resistance is relatively common among isolates and can also develop during therapy, underscoring the importance of obtaining bile samples for culture and sensitivity whenever possible. Choleliths can be found in association with cholecystitis or cholangitis; the cause and effect relationship is not always clear.

Treatment involves 4 to 6 weeks of antibiotics, preferably based on the results of culture and sensitivity, together with antioxidants and choleretics. As in cats, amoxicillin is a good initial choice at a dose of 15 to 20 mg/kg PO q8h combined with ursodeoxycholic acid at a dose of 15 mg/kg PO every 24 hours or split into two doses q12 hours. One recent study showed cholecystectomy reduced the risk of death in affected dogs, so this should be seriously considered, particularly when gallbladder abnormalities are found on ultrasound (Harrison et al., 2018).

GALLBLADDER MUCOCELE

Gallbladder mucocele has been reported as a common cause of clinical signs of biliary tract disease in dogs (Fig. 36.8). The cause is unclear, but it is most common in middle-aged to older dogs; there appears to be a breed predisposition in Shetland Sheepdogs in the United States. Other suggested breed associations are Cocker Spaniels and Miniature Schnauzers. There is a suggested association with endocrinopathies, particularly hypothyroidism, hyperadrenocorticism, and hyperlipidemia, and affected dogs show a variety of metabolic changes (Gookin et al., 2015; Gookin et al., 2018). Prior use of imidacloprid also shows an association in one study (Gookin et al., 2015). Sterile or septic inflammation of the gallbladder wall and/or disordered gallbladder

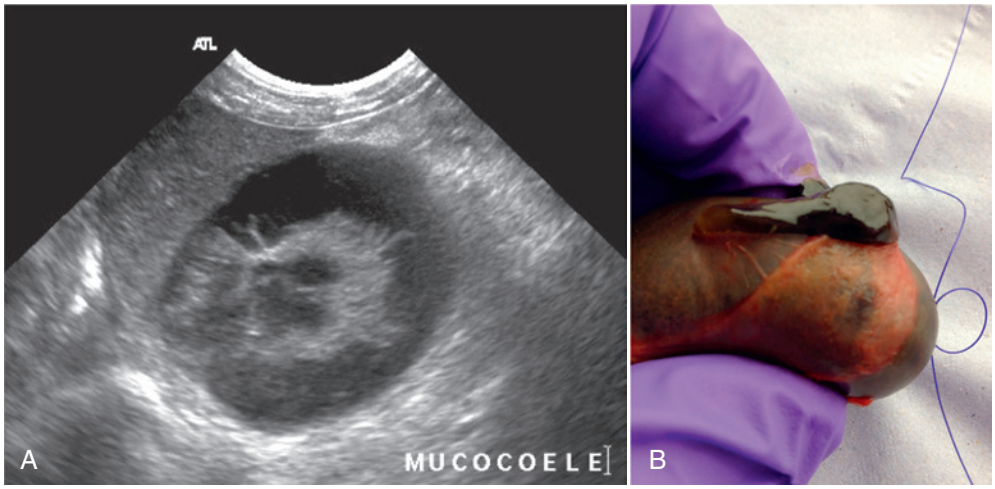


FIG 36.8
(A) Ultrasonographic image of the gallbladder of a dog with a mucocele. Note the stellate pattern to the bile. The mucinous material does not move with change in patient position. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.) **(B)** Appearance of the gallbladder with mucocele after surgical removal from a Border Terrier. Note gelatinous material exuding from cut surface. (Courtesy Queen's Veterinary School Hospital, University of Cambridge, England.)

motility may also predispose to mucocele formation. A mutation in biliary phosphatidylcholine transporter was proposed as a cause in affected Shetland Sheepdogs and also a few dogs of other breeds with mucocele (Mealey et al., 2010) but later disputed (Cullen et al., 2014).

Clinical signs vary. In some dogs mucocele is clinically silent and is an incidental finding on abdominal ultrasonography (see Fig. 36.8). In others nonspecific clinical signs are seen, similar to those of other biliary tract diseases with anorexia, lethargy, vomiting, and icterus. Some dogs present acutely because of gallbladder rupture and bile peritonitis. A recent study demonstrated that ultrasonography has a high specificity but low sensitivity of only 56% for gallbladder rupture and bile peritonitis for dogs with mucocele (Jaffey et al., 2018). Therefore, if gallbladder rupture is suspected clinically, surgery should be undertaken even if the ultrasound is negative.

Treatment is usually surgical for clinically affected dogs; cholecystectomy with or without biliary diversion is the technique of choice. Biliary diversion increases perioperative mortality and is rarely necessary. Gallbladder rupture also increases the risk of death. However, those that survive the perioperative period have a good long-term prognosis. Medical management of subclinical mucoceles has been reported in two dogs with hypothyroidism that were successfully treated (Walter et al., 2008) and in Shetland Sheepdogs (Aguirre et al., 2007). In the shelties, medical management consisted of a low-fat diet (e.g., Hill's i/d low fat; Royal Canin Waltham Gastrointestinal Low Fat; Eukanuba Intestinal Diet, Procter & Gamble Pet Care, Mason, OH) with a choleretic (ursodeoxycholic acid, 10–15 mg/kg PO total daily dosage, preferably split twice) and antioxidant (SAM-e, 20 mg/kg PO q24h). In one dog this resulted in resolution of the mucocele; in two dogs the mucocele remained static; one dog died as a result of gallbladder rupture and one as a result of pulmonary thromboembolism, both within 2 weeks of diagnosis; and two dogs were lost to follow-up. It would also seem sensible to address the underlying cause of the dyslipidemia in all cases, whether surgically or medically managed.

EXTRAHEPATIC BILE DUCT OBSTRUCTION

The causes of EBDO in dogs are similar to those in cats (see Box 35.4) with the exception of liver flukes, which are uncommon in dogs. The most common cause of EBDO in dogs is extraluminal obstruction from acute-on-chronic pancreatitis (see Chapter 37), but intestinal foreign bodies, neoplasia, bile duct involvement in a diaphragmatic hernia, and other processes can also cause EBDO (Fig. 36.9). Bile duct injuries that heal and result in stricture formation several weeks later are also seen in dogs; the common bile duct (CBD) may be compressed when carried with the liver into the thorax in dogs with diaphragmatic hernia. Extraluminal compressive lesions, such as pancreatic, biliary, or duodenal neoplasms, are less common causes, and cholelithiasis as a cause of EBDO is rare. To be considered as EBDO, a pathologic process must exist at the level of the CBD that impedes bile flow into the duodenum. Only if bile flow has been completely interrupted for several weeks are acholic feces, vitamin K–responsive coagulopathy, and repeated absence of urobilinogen in properly processed urine specimens found. If obstruction is incomplete, these features are not present and the constellation of signs and clinicopathologic test results resembles those of other, nonobstructive biliary tract disorders.

Clinical Features

Presenting clinical signs and clinicopathologic and physical examination findings of all these disorders may not differ greatly unless the underlying condition has caused EBDO or bile peritonitis. Regardless of the underlying disorder, typical clinical signs are jaundice, acute or chronic vomiting, anorexia, depression, weight loss, and occasionally vague cranial abdominal pain. Because of the protected location of the gallbladder in the abdomen, it is rarely possible to be



FIG 36.9
Jaundiced ocular **(A)** and oral mucous membranes **(B)** in a 6-year-old English Springer Spaniel with extrahepatic biliary obstruction caused by acute-on-chronic pancreatitis. The jaundice resolved uneventfully with medical management.

able to palpate it in a dog with EBDO unless the gallbladder is greatly enlarged.

Diagnosis

Affected dogs often show hyperbilirubinemia, high serum ALP, GGT, fasting and postprandial serum bile acid (SBA), and cholesterol concentrations, and less severe changes in serum ALT activity. SBA concentrations increase early in dogs with biliary stasis; in these circumstances, the degree of SBA level elevation gives no indication of liver function. Generally, more severe cholestatic lesions are associated with more severe clinicopathologic changes. Radiographically, there may be evidence of hepatomegaly and a mass effect in the area of the gallbladder on survey abdominal films. Gas shadows associated with the gallbladder and other biliary tract structures could be ascribed to ascending infection with gas-forming organisms. The cause of cholelithiasis in dogs is unclear, and they may also be found in asymptomatic dogs. These concretions are radiolucent unless they contain calcium, which occurs about 50% of the time. Inflammatory abdominal effusion is expected in dogs with bile peritonitis but not in those with most causes of EBDO, except for effusions associated with pancreatitis or pancreatic cancer.

Ultrasonography helps differentiate medical from surgical causes of EHBO, although this imaging modality is certainly not foolproof. Dilated and tortuous hepatic bile ducts and CBD, as well as gallbladder distention, are convincing ultrasonographic evidence of EBDO at the CBD or sphincter of Oddi. When dilated biliary structures are seen, it might be difficult to distinguish EBDO that requires surgical intervention from resolving transient EBDO associated with severe acute-on-chronic pancreatitis or from nonobstructive biliary disease (e.g., bacterial cholecystitis or cholangitis) unless a source of obstruction is specifically identified (e.g., pancreatic mass, cholelith in the CBD). Prolonged fasting causes gallbladder enlargement because of delayed evacuation and should not be overinterpreted. In addition, cystic hyperplasia and epithelial polyp formation are common lesions in older dogs and should not be confused with choleliths in the gallbladder. A stellate appearance to the contents of the gallbladder is characteristic of gallbladder mucocele (see Fig. 36.8). Monitoring the serum bilirubin concentration to determine when to intervene surgically is not worthwhile because it begins to decline over days to weeks, without relief of obstruction, in cats and dogs with experimentally induced EBDO. Conversely, in some dogs a significant proportion of bilirubin becomes irreversibly bound to albumin in the circulation (biliprotein), resulting in delayed clearance and continued elevation of the serum bilirubin concentration for up to 2 weeks after the initial insult has resolved.

Treatment and Prognosis

If the distinction between medical and surgical causes of jaundice is not clear, it might be safer to proceed surgically to avoid excessive delays in diagnosis, particularly if bile peritonitis is suspected. The previously established principle is that cases with complete, persistent EBDO should be operated on as quickly as possible because of the fear that refluxed bile acids will inevitably lead to cirrhosis unless the obstruction is relieved rapidly. However, more recent evidence suggests that medical management can be safely undertaken in otherwise clinically well dogs for days to weeks while transient biliary tract obstruction resolves, and clinicians should not be too quick to go in surgically in a dog with EBDO secondary to pancreatitis. There is no evidence in the veterinary literature to guide clinicians on how often cirrhosis ensues and how long a complete biliary obstruction should be allowed to continue before surgical intervention. However, in a review of biliary tract obstruction caused by chronic pancreatitis (CP) in humans, Abdallah et al. (2007) pointed out that as few as 7% of cases developed subsequent biliary cirrhosis. Biliary obstruction caused by CP in humans is considered to be transient if it resolves within 1 month; most cases are transient because the biliary obstruction resolves as the edema of the acute-on-chronic inflammation resolves. In the absence of marked pain or a mass, the patient will be monitored for 1 month and only treated surgically if the jaundice is persistent after this or there is suspicion of neoplasia.

As with any other form of liver disease, it is important to stabilize the patient with fluids and electrolytes, and to perform a hemostasis profile and platelet count before surgery. Prolonged coagulation times may respond to vitamin K_1 injections 0.5–1 mg/kg SC × 3 doses at 12-hour intervals prior to surgery (to be consistent with earlier recommendations), but if not, a fresh-frozen plasma transfusion is advisable before surgery to replace clotting factors. If the site of obstruction or biliary injury is not identified, at least tissue (e.g., liver, gallbladder mucosa) and bile specimens can be obtained for histopathologic and cytologic evaluation, bacterial culture, and sensitivity testing. Any abdominal fluid should be analyzed cytologically and cultured for aerobic and anaerobic bacteria. A liver biopsy specimen should also be obtained in all cases. Typical hepatic histopathologic findings in dogs with early EBDO are canalicular bile plugs and bile ductular proliferation, with degrees of periportal inflammation and fibrosis in chronic cases. Confounding biliary infection can incite a stronger inflammatory reaction in the periportal region. However, it is impossible to diagnose a primary biliary tract infection from a liver biopsy alone.

Surgical goals are to relieve biliary obstruction or leakage and restore bile flow. Reconstructive procedures to divert bile flow can be performed if the cause of EBDO cannot be corrected. However, because these carry a poor long-term prognosis, less invasive procedures such as stenting are preferred whenever possible.

In cases without complete biliary obstruction (e.g., some choleliths) or with transient obstruction (e.g., most cases of acute-on-chronic pancreatitis), medical management alone is indicated. The choleretic ursodiol is indicated as treatment in these cases, provided that complete EBDO has been ruled out. Choleliths may also move using this drug. The recommended dosage is 10 to 15 mg/kg total, PO daily, preferably split into two doses. In addition, all cases (both medical and

surgical) should receive antioxidant therapy, preferably with vitamin E (400 IU PO for a 30-kg dog, scaled appropriately to the size of the dog; tablets usually come as 100, 200, or 400 IU) and SAM-e (20 mg/kg PO q24h) because it has been demonstrated that bile reflux in the liver is a potent oxidant toxin. Dogs should be fed a high-quality diet that is not protein-restricted: usually, a diet designed for critical care feeding is more appropriate than a manufactured liver support diet because the dog is suffering an inflammatory and/or septic process, but hepatocyte function is usually good.

The prognosis for dogs with EBDO depends on the underlying cause. If the cause can be addressed without surgical reconstruction, the prognosis is fair to good. If extensive biliary reconstruction is needed, the prognosis is guarded.

Bile Peritonitis

Bile peritonitis usually results from abdominal trauma damaging the CBD (e.g., penetrating injury, horse kick, automobile accident) or pathologic rupture of a severely diseased gallbladder, particularly with gall bladder mucocele but also which sometimes occurs after diagnostic ultrasonography-guided aspiration. Early signs of bile peritonitis are nonspecific, but with progression, jaundice, fever, and abdominal effusion are seen. When bile, which is normally sterile, comes into contact with the peritoneal surface, there are resultant cell necrosis and changes in permeability, which predispose to infection with bacteria that move across the intestinal wall. Hypovolemia and sepsis may occur in animals with undetected bile peritonitis. Surgery is essential in bile peritonitis, both to identify and treat the cause and to lavage the abdomen. Presurgical considerations are the same as for EBDO. If surgery for bile peritonitis is to be delayed, peritoneal drainage should be established to remove noxious, bile-containing abdominal fluid and for lavage.

CONGENITAL VASCULAR DISORDERS

Congenital disorders of hepatic vasculature, intrahepatic and extrahepatic, are more common in dogs than in cats. There are some breed-related tendencies, suggesting a genetic basis to some disorders, but it is also assumed that most of them result from some type of (as yet undefined) insult in utero. Experimental reduction in flow in the umbilical vein in sheep and other species can result in the development of PSSs and asymmetry of hepatic lobular and vascular supplies; this is likely also true in dogs. This would explain why it is relatively common to see dogs with more than one coexistent congenital vascular disorder in the liver (e.g., a congenital PSS combined with intrahepatic portal vein hypoplasia or microvascular dysplasia [MVD]) and would also explain why dogs with congenital PSSs have a higher prevalence of other congenital defects, such as cryptorchidism and cardiac disorders.

For ease of categorization, and because they have different clinical presentations, congenital vascular disorders have been divided into disorders associated with low portal pressure and those with high portal pressure. However, it is important to remember than when two or more congenital hepatic defects occur concurrently, the differentiation will be less obvious.

DISORDERS ASSOCIATED WITH LOW PORTAL PRESSURE: CONGENITAL PORTOSYSTEMIC SHUNT

Etiology and Pathogenesis

Congenital PSSs are the most common congenital portovascular disorder in dogs. The etiology and pathogenesis are similar to those in cats; see Chapter 35 for more details. Many different types of congenital portovascular anomalies have been reported in dogs; sometimes they coexist with intrahepatic or extrahepatic portal vein hypoplasia or intrahepatic MVD (see later). However, a distinguishing feature of isolated congenital PSS is that it results in a low portal pressure because some blood is shunted away from the sinusoidal circulation by the shunting vessel(s). Dogs with isolated congenital PSS therefore do not present with ascites unless they are severely hypoalbuminemic. This allows differentiation from the congenital vascular disorders associated with increased portal pressure and therefore acquired PSS (see later) in which portal hypertension and associated ascites are common at presentation.

Canine congenital PSSs can be extrahepatic or intrahepatic. Extrahepatic PSSs are anomalous vessels connecting the portal vein or one of its contributors (left gastric, splenic, cranial or caudal mesenteric, or gastroduodenal vein) to the caudal vena cava or azygos vein. They are most commonly recognized in small-breed dogs and have a high prevalence in Cairn Terriers, Yorkshire Terriers, West Highland White Terriers, Maltese, Havanese, other terriers, and Miniature Schnauzers (Fig. 36.10). Intrahepatic PSSs may be left-sided, in which case they are thought to represent persistence of the fetal ductus venosus, or they can be right-sided or central, in which case they likely have a different embryologic origin. An intrahepatic PSS is usually seen in large-breed dogs, but Collies tend to have extrahepatic PSSs, despite being large dogs. Increased breed prevalence suggests a genetic basis to the disease, but this has only been investigated in Irish Wolfhounds, in which an inherited basis of patent ductus venosus has been demonstrated, in Cairn Terriers with extrahepatic PSSs, in which an autosomal polygenic inheritance or monogenic inheritance with variable expression is suspected (van Straten et al., 2005), and in Maltese dogs, in which a partially penetrant recessive mode of inheritance has been proposed (O'Leary et al., 2014). Affected Irish Wolfhounds tend to have smaller litters and can also produce more than one puppy with a PSS in a litter.

One study reported that dogs from breeds that were not usually recognized as having a high risk of PSS were more likely to present with unusual anatomic forms of PSS that were less often amenable to surgical management (Hunt, 2004).



FIG 36.10
Typical small-breed dogs with congenital extrahepatic portosytemic shunts. **(A)** Eight-month-old female Border Terrier. **(B)** Nine-month-old female Miniature Schnauzer.

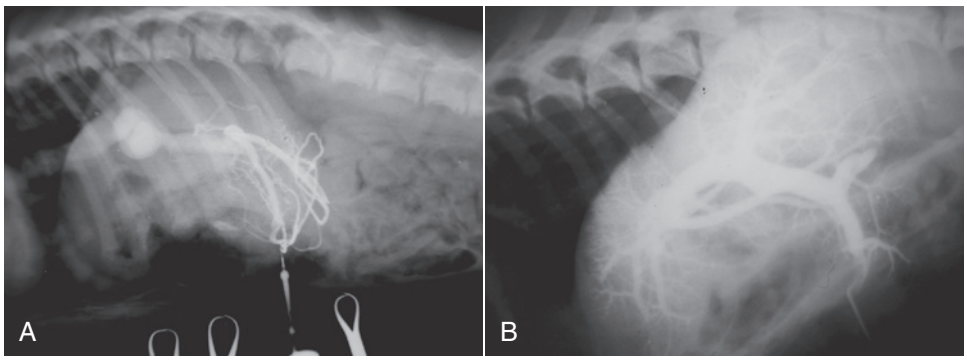


FIG 36.11
(A) Portovenogram in a 1-year-old Golden Retriever with an intrahepatic portosystemic shunt. This was a central divisional shunt, which had a venous sinus–like structure, as demonstrated well in this radiograph. **(B)** Normal portovenogram in a dog for comparison with **A.** (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

Clinical Features

Clinical signs are similar to those in cats; neurologic, GI, and urinary tract signs predominate (see Chapter 35 for more details). About 75% of dogs present before 1 year of age, but some present at an older age, with some as old as 10 years before signs are recognized. There is a spectrum of severity of neurologic signs, ranging from severely affected young puppies that persistently circle, become centrally blind, and can even have seizures or become comatose, to very mildly affected or asymptomatic individuals. It is likely that this variation reflects differences in shunt fraction and dietary and other environmental differences among dogs. Concurrent inflammation is an important trigger for HE in affected dogs, so clinicians should look carefully in affected animals for inflammatory disease such as urinary tract infections. PU-PD with hyposthenuric urine are relatively common; this is probably multifactorial in etiology and partly caused by reduced renal medullar concentrating gradient (see Chapter 33). Urate uroliths are also common and can be cystic or renal. Anecdotally, urate renal calculi seem to be more common in terriers, and dogs presenting with calculi often do not have prominent neurologic signs. On physical examination, animals are often but not always smaller than their litter mates and may have nonlocalizing neurologic signs and, in some cases, palpable renomegaly. The latter is caused by circulatory changes and is not a reflection of renal disease or uroliths; it is of no clinical significance and regresses after shunt ligation. Other congenital defects may be apparent, particularly cryptorchidism, which is reported in up to 50% of male dogs with congenital PSSs.

Diagnosis

The diagnosis of congenital PSS in dogs is the same as in cats (see Chapter 35) and relies on visualizing the shunting vessel ultrasonographically, with computed tomography (CT) angiography or portovenography (Fig. 36.11, or

grossly at surgery. Scintigraphy can demonstrate shunting but is not helpful for differentiating congenital from acquired PSS, so some other imaging method is necessary for treatment decisions. See Chapter 34 for more information on imaging PSSs.

If possible, it is important to try to estimate how well developed the remaining hepatic portal vasculature is by repeating the portovenography after ligation and/or by evaluating the histologic findings on liver biopsies taken at the time of ligation. This is a work in progress, but there is a strong suspicion that the postligation prognosis may depend on the potential for the intrahepatic vasculature to open up after surgery, and dogs that do poorly postoperatively may have concurrent portal vein hypoplasia and/or MVD (see later).

Nonspecific clinicopathologic findings in more than 50% of affected dogs, regardless of the type of vascular anomaly, are microcytosis, hypoalbuminemia, mild increases in serum AP and ALT activities, hypocholesterolemia, and low blood urea nitrogen concentration. Fasting bile acid concentrations may be normal or high, but postprandial bile acid concentrations are high in all cases. However, this does not distinguish congenital PSS from acquired PSS or early cholestasis, which also causes increases in bile acid concentration. The postprandial ammonia concentration can also be measured and will be high, whereas fasting ammonia concentration may be high or normal (see Box 34.3 for details of how to perform an ammonia challenge test). Ammonia tolerance or challenge tests are potentially dangerous because they can precipitate an encephalopathic crisis. Other tests have been evaluated for their sensitivity and specificity in the diagnosis of PSS. The level of protein C, a liver-derived anticoagulant, is also decreased in dogs with PSS and increases after ligation; this can help differentiate PSS from MVD.

Puppies of high-risk breeds could be screened for congenital PSS by measuring bile acid or ammonia concentrations before they are placed into homes, but there are potential false-positives with both of these tests; no puppy should be euthanized or labeled as having a definite congenital PSS on the basis of a high bile acid and/or ammonia concentration without further evidence. Normal Irish Wolfhounds can have a transiently high blood ammonia concentration between the ages of 6 to 8 weeks; this normalizes at 3 to 4 months of age. Zandvliet et al. (2007) have demonstrated that this is caused by a clinically insignificant urea cycle defect. Postprandial bile acid concentrations can be falsely elevated in Maltese puppies without PSS for unknown reasons, again confusing any efforts at screening tests in this breed (Tisdall et al., 1995).

On diagnostic imaging, the liver is frequently but not always small. Ultrasonography now has a high sensitivity and specificity for the diagnosis of both intrahepatic and extrahepatic PSS; furthermore, their anatomy can usually also be described ultrasonographically. Bubble studies may help visualization of a PSS with ultrasonography (Gómez-Ochoa et al., 2011). If the shunting vessel cannot be fully visualized or characterized by ultrasonography, CT angiography is now the imaging technique of choice, replacing portovenography wherever possible (see Chapter 34 for more details).

Overview of Treatment Options and Prognosis

Surgical occlusion of the anomalous vessel to restore normal portal circulation has long been recommended as the treatment of choice. In many cases this will restore normal or near-normal liver function. However, owners need to be aware of the small but definite risk of postoperative mortality as a result of portal hypertension and/or refractory seizures, and of the potential that the PSS may be only partially and not totally ligated. It is more common to be able to ligate the PSS partially at the first surgery, because the portal vasculature cannot initially accommodate all the shunting blood. In some cases it is possible to repeat the surgery at a later date to ligate the PSS further, but this is often unnecessary to control clinical signs. A few dogs with partially ligated shunts develop portal hypertension and multiple acquired PSSs with a recurrence of their clinical signs. There are several different surgical procedures described for ligation of PSS, but they are outside the scope of this text. In addition to surgical ligation, a PSS may be attenuated with ameroid constrictors (Fig. 36.12) or embolized with coils. Laparoscopic ligation of PSS has been reported in two dogs (Miller et al., 2006). As a general rule, ligation of a PSS requires an experienced surgeon.

Medical treatment is required to stabilize the patient before surgery and for about 8 weeks after surgery while the hepatic vasculature and mass recover. This involves careful dietary management combined, in many cases, with antibiotics and soluble dietary fiber. In some cases medical management may continue successfully over the course of

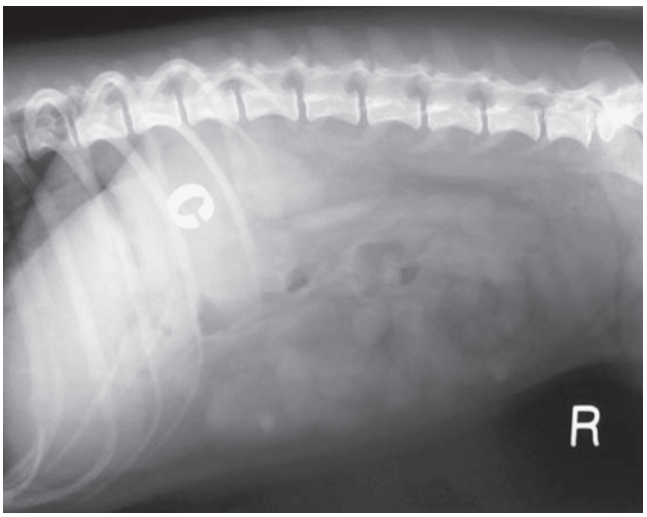


FIG 36.12
Lateral abdominal radiograph of a 3-year-old Miniature Schnauzer that had an extrahepatic portosystemic shunt ligated with an ameroid constrictor 2 years previously. Note that the ameroid is visible as a radiodense ring in the craniodorsal abdomen. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

the patient's life as an alternative to surgery. This is usually because the client cannot afford referral, is unhappy about the risks associated with surgery, or because the patient has multiple or intrahepatic shunts. Mildly affected and older animals are good candidates for medical management, but generally these are dogs with smaller shunting fractions. Dogs (particularly terriers) that present at an older age with urate stones but no neurologic signs are also good candidates for medical management alone. In addition, dogs with concurrent portal vein hypoplasia and/or MVD tend to have a higher surgical risk and are best managed medically. Medical management does not reverse the underlying disorder but can result in good long-term results. A recent prospective study of 126 dogs with congenital PSSs comparing surgical with medical management found that surgically managed dogs had a higher probability of survival over the course of the study (Greenhalgh et al., 2010). However, only 18 dogs had died by the end of the study, and survival time was long for the dogs remaining alive in both groups (mean, 729 days). Age at the time of surgery did not appear to affect prognosis. Once the dog has reached adulthood, there is no evidence that the liver progressively atrophies throughout life. Ultimately, more studies are needed to identify the factors that are most important in determining prognosis after medical and/or surgical management and to help preoperatively identify the small number of animals that will have a poor outcome after surgery. The specific details of medical management of hepatic encephalopathy are given below.

Management of Hepatic Encephalopathy

Whether caused by congenital or acquired PSS, the treatment of HE in dogs is similar (Fig. 36.13). The main difference is that acquired PSSs are usually the result of portal hypertension, so treatment of its other manifestations and the underlying liver disease will also be necessary in these cases (see earlier). Controlled trials have not been conducted in animals to determine the optimal treatment for HE and for each stage (mild, moderate, severe) of HE. Therefore current recommendations are based on human studies and on anecdotal reports in dogs.

The goal of treatment in dogs with HE is to restore normal neurologic function by decreasing the formation



FIG 36.13
Female German Shepherd Dog with noncirrhotic portal hypertension. **(A)** At 14 months of age, with ascites and in poor body condition, but remarkably alert. **(B)** 5 years later on medical management only—very stable and in good body condition, with no detectable ascites. The dog lived for 8 years with a good quality of life before developing a gastroduodenal ulcer (see Fig. 36-5). **(C)** Drugs that the dog received long term, in addition to dietary management. (**B** and **C** reproduced by permission from Watson PJ: Treatment of liver disease in dogs and cats. Part 2: Treatment of specific canine and feline liver diseases, *UK Vet* 9:39, 2004.)

of gut-derived and peripherally derived encephalotoxins, eliminating precipitating factors, and correcting acid-base and electrolyte abnormalities. A variety of encephalotoxins are implicated as causes of HE (see Chapter 33), but the most important from the point of view of treatment is ammonia. It was once believed that the most important source of ammonia was undigested protein in the colon metabolized by gut bacteria, but emphasis has now shifted to interorgan metabolism of ammonia and small intestinal enterocyte glutamine catabolism in patients with HE rather than production of ammonia in the large intestine from dietary protein itself, which is considered a less important source (see Chapter 33 for more details). There are high amounts of ammonia in the portal circulation, particularly after a meal, but the main source is obligate catabolism of glutamine by small intestinal enterocytes as their main energy source; intestinal glutaminase concentrations seem to increase for unknown reasons in humans with cirrhosis, increasing gut ammonia production. There are no published studies showing the relative contribution of small and large intestine–derived ammonia to HE in dogs, but the observed tendency for dogs to show signs of HE 1 to 2 hours after feeding would support a small intestinal origin. Dogs with experimental PSS and animals and humans with acquired PSS actually have a higher dietary protein requirement than do normal animals or people. Inflammatory mediators are also thought to be important precipitators of HE. It is known that clinically relevant episodes of HE in dogs with congenital or acquired PSS are often precipitated by stress and infections, not just by feeding, emphasizing the role of hypermetabolism, inflammation, and breakdown of body protein in the development of HE (see Chapter 33). HE is also triggered by negative nitrogen balance and breaking down of muscle mass (see Fig. 36.5), particularly in dogs with acquired PSS and protein-calorie malnutrition, and in these cases starvation and protein restriction will worsen the HE.

A combination of careful dietary manipulation, locally acting agents that discourage the formation of readily absorbable ammonia and hasten evacuation of the intestinal tract (lactulose), antibiotics to suppress bacterial populations that generate ammonia and other gut-derived encephalotoxins, and treatment of any precipitating cause is the standard approach for the long-term management of chronic HE (Box 36.6). Dietary management and treatment of the



BOX 36.6

Long-Term Medical Management of Hepatic Encephalopathy

Dietary Management

- Feed normal amounts (if possible) of high-quality, highly digestible protein to minimize the chance that any protein will reach the colon to be converted into NH_3. Some veterinarians recommend increasing branched chain amino acids and reducing aromatic amino acids such as tryptophan, but there is no evidence that changing the dietary levels affects cerebrospinal fluid levels. Consider adding ornithine aspartate, which provides substrates for conversion of NH_3 to urea (ornithine) and glutamine (aspartate). Restrict protein only if absolutely necessary to control neurologic signs and monitor muscle mass and blood protein concentrations carefully.
- Prevent protein-calorie malnutrition by avoiding prolonged fasting and/or excessive protein restriction because this will lead to hyperammonemia from the breakdown of body protein.
- Feed small amounts often to reduce the amount of liver work required, reduce energy demands and thus glutamine metabolism in small intestine, and lessen the potential for undigested food to reach the colon.
- Fat needs no special recommendations, although it should be fed in normal amounts and not restricted unless clinical steatorrhea develops (rare). Avoid diets that are very high in fats, particularly with cholestasis or portal hypertension, in which GI signs may be exacerbated.
- Carbohydrates should be highly digestible as a primary calorie source, reducing the need for hepatic gluconeogenesis from fat and protein.
- Fermentable fiber reduces hepatic encephalopathy in the same way as lactulose. Nonfermentable fiber is also important because it prevents constipation and therefore reduces contact time for colonic bacteria to act on feces and produce ammonia.
- Zinc supplementation may reduce encephalopathy because zinc is used in many metalloenzymes in the urea cycle and in the muscle metabolism of ammonia.

Lactulose

- Lactulose is a soluble fiber that acidifies colonic contents, reducing ammonia absorption, and also increases colonic bacterial cell growth, therefore incorporating ammonia into the bacterial cell walls. Cats should be given 2.5–5 mL PO q8h, and dogs, 2.5–15 mL PO q8h. Start at the low dose, and titrate to effect (two or three soft stools daily).

Antibiotics

- Give amoxicillin (22 mg/kg PO q12h) to reduce gastrointestinal flora and also protect against bacteremia.

Identify and Treat Concurrent Infections and Inflammation

- Pay particular attention to identifying and treating any urinary tract infections (pyelonephritis or cystitis).

underlying cause are the most important approaches, but guidelines have changed over the last few years with respect to protein restriction, and it is now clear that many dogs with congenital or acquired PSS have higher protein requirements than do normal animals. Long-term feeding of a protein-restricted diet is contraindicated and will result in protein-calorie malnutrition. The emphasis has shifted to feeding a digestible protein in small amounts and often to reduce the work of the small intestine and thus glutamine metabolism. There is preliminary evidence that soybean or dairy protein may be preferable to other protein sources.

Most, if not all, dogs with congenital or acquired PSS can tolerate normal protein concentrations if other measures are also implemented, as outlined later and in Box 36.6. A few require more marked restriction in the short term, but every effort should be made to increase to a normal protein concentration over the long term. The body condition score and serum protein concentrations should be carefully monitored to avoid negative nitrogen balance.

Lactulose (β-galactosidofructose) is a semisynthetic disaccharide that is not digestible by mammals and therefore passes into the colon, where it is degraded by bacteria into short-chain fatty acids (SCFAs), particularly lactic and acetic acid. These SCFAs help control signs of HE by acidifying the intestinal contents, which traps ammonium ions in the colon, and by promoting osmotic diarrhea. In addition, SCFAs are used as an energy source by colonic bacteria, allowing them to grow and thus incorporate colonic ammonia into their own bacterial protein, which is subsequently lost with the bacteria in the feces (a type of bacterial ammonia trap).

The dose is adjusted until there are two to three soft stools per day (see Box 36.6); overdosing results in watery diarrhea. There are no known complications of chronic lactulose use in animals other than diarrhea. However, the efficacy of lactulose has never been critically evaluated in dogs and cats with HE. Recent studies in humans have been contradictory with one meta-analysis suggesting no benefit, but a more recent meta-analysis suggested some benefit in HE. Lactulose can also be given by enema in animals with acute HE (see Box 36.7). Many dogs object strongly to the sweet taste of lactulose; an attractive alternative is lactitol (β-galactosidosorbitol), which is related to lactulose and can be used as a powder (500 mg/kg/day in three to four doses, adjusted to produce two to three soft stools daily). Currently, lactitol is available in the United States as a food sweetener but has not been studied in dogs with HE.

If dietary therapy alone or in combination with lactulose is insufficient to control signs of HE, antibiotics may be added. Usually, amoxicillin is used at 22 mg/kg PO q12h. Traditionally, antibiotic therapy was believed to work simply by reducing colonic bacterial metabolism. However, recent studies implicating inflammatory mediators in triggering HE provide an alternative explanation for the efficacy of antibiotics in some animals with HE where they may also be treating undetected urinary tract or other infections. Antibiotics effective for gram-negative, urea-splitting organisms (neomycin sulfate, 20 mg/kg PO q12h) may also be used, although neomycin is more useful for acute HE rather than long-term use because intestinal bacteria tend to become resistant to neomycin. In addition, it is not systemically absorbed and remains in the GI tract, which will not help any systemic infection.

Other therapeutic strategies investigated in humans with chronic HE include ornithine aspartate supplementation (see Box 36.6) and probiotics to increase the numbers of beneficial bacteria. These may show benefit in dogs in the future, but there are currently no published studies documenting their use in small animals.

Certain conditions are known to accentuate or precipitate HE and should be avoided or treated aggressively when detected (see Box 33.2). In many cases it is the precipitating factors, rather than the diet, that are most important in triggering HE. It is particularly important to identify and treat any concurrent inflammatory disease that can trigger HE episodes in susceptible animals.

Management of Acute Hepatic Encephalopathy

Acute HE is a true medical emergency. Fortunately, it is much less common than chronic waxing and waning HE. Animals may present in status epilepticus or comatose, and although HE initially causes no permanent brain damage, prolonged seizures, status epilepticus, or coma will; prolonged severe HE by itself may lead to serious cerebral edema as a result of accumulation of the osmolyte glutamine (from ammonia detoxification) in astrocytes. In addition, the systemic effects of acute HE, particularly hypoglycemia, can be fatal if not recognized and treated. The treatment of acute encephalopathic crises is outlined in Box 36.7. Intensive management is required. However, treatment is worthwhile because some animals can go on to complete recovery and successful long-term medical management, particularly if the acute crisis was triggered by a definable event (e.g., acute GI bleeding in a dog with chronic liver disease and portal hypertension). Nothing by mouth (NPO), administration of enemas, and IV fluid therapy constitute the basic therapeutic approach. Warm water cleansing enemas may be useful simply by removing colonic contents and preventing absorption of intestinal encephalotoxins. Lactulose or dilute vinegar may be added to acidify the colon and decrease absorption of ammonia. The most effective enema contains three parts lactulose to seven parts water at a total dose of 20 mL/kg. The solution is left in place, with the aid of a Foley catheter, as a retention enema for 15 to 20 minutes. For lactulose to be beneficial, the pH of the evacuated colon contents must be 6 or lower. These enemas can be given every 4 to 6 hours. Because lactulose is osmotically active, dehydration can occur if enemas are used too aggressively without careful attention to fluid intake. Fluids chosen for the replacement of losses, volume expansion, and maintenance should not contain lactate, which is converted to bicarbonate, because alkalinizing solutions may precipitate or worsen HE by promoting the formation of the more readily diffusible form of ammonia. Half-strength (0.45%) saline solution in 2.5% dextrose is a good empirical

BOX 36.7

Treatment of Acute Encephalopathic Crisis

- Remove or treat any identified precipitating cause.
- Give nothing by mouth for 24–48 hours and IV fluids.
- Avoid fluid overload; measure central venous pressure or monitor carefully clinically.
- Avoid or treat hypokalemia (triggers hepatic encephalopathy).
- Avoid or treat hypoglycemia (monitor blood glucose level every 1–2 hours, particularly in small breeds, in which hypoglycemia is common and can cause permanent cerebral damage).
- Monitor body temperature, and warm gently or cool as necessary if hyperthermic after seizures.
- Administer enemas to remove ammonia from colon—warm water, lactulose, or dilute vinegar.
- Instill a neomycin retention enema after the colon is clear and administer IV ampicillin.
- Treat any seizures:
  - Carefully rule out treatable causes (e.g., electrolyte imbalances, hypoglycemia, hypertension, idiopathic epilepsy).
  - Maintain other intensive care measures (as earlier).
  - Treat with anticonvulsant—exact protocol controversial. Options are:
    - Levetiracetam 20 mg/kg bolus. Repeat as necessary every 20 minutes to maximum 60 mg/kg followed by 20 mg/kg tid. Unlikely to work for postligation seizures if dog already on levetiracetam.
    - Propofol bolus (3.5 mg/kg dogs; 1 mg/kg cats) followed by infusions (0.1–0.25 mg/kg/min) often effective.
    - Phenobarbitol, ketamine, or dexmedetomidine may also be used.
    - Diazepam of very limited efficacy.

choice, with potassium added according to its serum concentration. Serum electrolyte concentrations in dogs with HE are extremely variable; until the results become available, 20 mEq KCl/L in the fluids administered is a safe amount to add. Seizuring dogs can be stabilized with a loading dose of levetiracetam intravenously (see Box 36.7) or low-dose propofol infusions (Fig. 36.14). The dose of propofol is calculated by giving an initial bolus to effect, usually about 1 mg/kg, timing how long it takes for the animal to show mild signs of seizures, such as mild limb paddling again, and then dividing the dose by the time required to calculate an infusion rate. For example, if after a bolus of 1 mg/kg of propofol the dog shows signs of seizure activity again after 10 minutes, the infusion rate would be 1/10 = 0.1 mg/kg/min. In practice, the dose of propofol to be given by constant rate infusion is usually about 0.1 to 0.2 mg/kg/min. Dogs sometimes need to remain on the infusion for hours or days, but the rate can be gradually reduced to control seizures while still allowing the dog to regain consciousness—in some cases, even



FIG 36.14
Miniature Schnauzer with a congenital portosystemic shunt that had postligation seizures and was stabilized with a propofol infusion.

enough to start eating. Propofol infusions can result in Heinz body hemolytic anemia in dogs and cats. Levetiracetam has been reported to be effective at reducing the risk of postoperative seizures and death in dogs undergoing surgical attenuation of extrahepatic PSS with ameroid constrictors when the dogs were pretreated with 20 mg/kg PO q8h, for a minimum of 24 hours before surgery (Fryer et al., 2011). However, a recent large multicenter study did not support the use of preoperative levetiracetam as protective against seizures, leaving clinicians unclear as to whether to use it or not (Mullins et al., 2019). There are no studies describing the use of levetiracetam IV in dogs with PSS that are already seizuring, but there are anecdotal reports of its efficacy in this situation.

In spite of some early promising reports, there is still no convincing evidence in support of other pharmacologic treatments for HE, apart from antibiotics and lactulose, so other drugs cannot currently be recommended for use in dogs. Trials of the benzodiazepine receptor antagonist flumazenil in human patients with refractory acute HE have had mixed results. Although flumazenil has been studied in animals for its ability to reverse the action of benzodiazepine tranquilizers, there have been no clinical studies on its use in acute HE in animals.

DISORDERS ASSOCIATED WITH HIGH PORTAL PRESSURE

There are a number of less common congenital vascular disorders of the liver in dogs that present with normal or high portal pressure, rather than the low portal pressure seen in association with a congenital PSS. Because of the portal hypertension, the affected dog may present with the constellation of typical clinical signs (see Chapter 33), including ascites, and the potential for GI ulceration in addition to multiple acquired PSSs and HE. With the exception of arteriovenous fistulae, none of these conditions can be treated surgically, but some of them have a good long-term prognosis with medical management.

Primary Hypoplasia of the Portal Vein, Microvascular Dysplasia, and Noncirrhotic Portal Hypertension

Etiology and Pathogenesis

There have been several reports of vascular disorders in young dogs associated with portal hypertension, usually ascites, and characteristic histopathologic changes in the liver, including a reduction in smaller portal vein branches, increased numbers of arterioles, and a variable amount of mild fibrosis. There are some reports of overt hypoplasia of the extrahepatic portal vein, but most studies of noncirrhotic portal hypertension and MVD appear to describe portal vein hypoplasia confined to the intrahepatic vasculature. These diseases may all be different abnormalities or may represent different spectra of the same abnormalities, but their clinical presentation, treatment, and prognosis are similar. A lack of intrahepatic or extrahepatic portal vein branches results in portal hypertension, with the same potential consequences as those of chronic hepatitis (see earlier), including ascites, gut wall edema, and often GI ulceration and acquired PSSs (Fig. 36.13). Dogs with MVD often do not present with notable portal hypertension; despite this, MVD has been grouped with these diseases by the World Small Animal Veterinary Association (WSAVA) Liver Standardization Group (Cullen et al., 2006). Dogs reported with MVD typically have shunting at the level of the hepatic lobule but no clinical signs of overt portal hypertension.

Any breed can be affected, but MVD particularly affects small-breed dogs; Yorkshire Terriers and Cairn Terriers show a particularly high prevalence, whereas noncirrhotic portal hypertension often affects large-breed dogs.

Clinical Signs

Dogs with all these conditions typically present at a young age with a combination of signs of portal hypertension and PSS, the severity of which depends on that of their lesions. Because of the acquired PSS seen in these patients, some of the clinical signs and clinicopathologic findings overlap with those of congenital PSS, particularly because all these disorders typically present in young dogs. Therefore the presence of other signs of portal hypertension (e.g., ascites) is an important clinical clue that one of these disorders with acquired PSS may be present, rather than a congenital PSS.

Dogs with portal vein hypoplasia or idiopathic noncirrhotic portal hypertension typically present between 1 and 4 years of age and are often purebreds of either gender; large breeds predominate. Early reports of congenital or juvenile hepatic fibrosis in German Shepherd Dogs may also have represented a form of noncirrhotic portal hypertension. Presenting signs are typically those of portal hypertension, with abdominal distention associated with effusion, GI signs, polydipsia, weight loss, and, less consistently, signs of HE. Dogs are often surprisingly alert (Fig. 36.14).

Dogs with MVD present with similar clinicopathologic findings but usually without overt evidence of portal hypertension or ascites. MVD tends to affect terriers and thus overlaps with breeds at high risk for congenital PSSs. In addition, some dogs may have both congenital PSS and MVD or portal vein hypoplasia, further confusing the diagnosis. Cairn Terriers and Yorkshire Terriers in particular have been reported with MVD. In one breed (Cairn Terrier), the site of anatomic abnormality has been identified as the terminal portal veins. In this breed it is believed to be an autosomal inherited trait, but the specific mode of inheritance has not been established. Typical signs include vomiting, diarrhea, and signs of HE, although the clinical signs, particularly the HE, are notably milder in dogs with MVD than in those with congenital PSS unless both disorders occur concurrently. Dogs with only MVD are somewhat older, and many have mild to no signs of illness. In the case of young purebred dogs that have been screened for congenital PSS before sale or that are ill for nonhepatic reasons, a high SBA concentration may be the only finding.

Diagnosis

The diagnosis of MVD or intrahepatic portal vein hypoplasia and noncirrhotic portal hypertension relies ultimately on liver biopsy findings of intrahepatic portal vein hypoplasia in the absence of a grossly demonstrable shunting vessel. The liver biopsy findings alone can be indistinguishable from the changes that occur secondary to congenital PSSs, so the clinical findings of concurrent portal hypertension and ruling out a shunting vessel are important parts of the final diagnosis. Clinicopathologic findings are similar to those in dogs with congenital PSS and include evidence of hepatic dysfunction (e.g., hypoalbuminemia) and hyposthenuria.

Microcytosis is much less common with MVD than with congenital PSS. One study suggested that having a normal protein C concentration (>70% activity) had a high sensitivity and specificity for differentiating MVD from a congenital PSS, in which the protein C concentration is usually low (Toulza et al., 2006). Microhepatia and hypoechogenic abdominal fluid are the notable abdominal ultrasonographic findings in dogs with noncirrhotic portal hypertension; it may be possible to visualize multiple acquired PSSs ultrasonographically. Dogs with MVD alone tend not to have ascites and have less marked increases in SBA concentrations than dogs with a true congenital PSS.

The most important aspects of identifying a dog with MVD, portal vein hypoplasia, and/or noncirrhotic portal hypertension are ruling out a surgically correctable PSS, identifying portal hypertension (which requires treatment; see earlier), and obtaining a liver biopsy for confirmation or exclusion of other hepatopathies. Portal vein hypoplasia is similar clinically, on clinical pathology, and on diagnostic imaging to end-stage chronic hepatitis with cirrhosis; the only way to differentiate the two is on liver histology. In general, portal vein hypoplasia–noncirrhotic portal hypertension carries a much better long-term prognosis than cirrhosis, so the differentiation is important prognostically.

Treatment and Prognosis

The prognosis for all these conditions appears to be relatively good, provided that the clinical signs can be controlled. They are nonprogressive, and there is no surgical treatment for any

of them. Symptomatic therapy for HE, ascites, and GI ulceration (if present) is usually successful (see earlier). It should be noted that glucocorticoid therapy is absolutely contraindicated in these dogs and is likely to worsen the outcome because of the associated portal hypertension and high risk of GI ulceration. This underlines the importance of liver biopsy in these dogs, allowing differentiation from chronic hepatitis.

One study of dogs with noncirrhotic portal hypertension concluded that affected dogs might live as long as 9 years after diagnosis with appropriate symptomatic therapy (Bunch et al., 2001). A few dogs were euthanized because of problems related to persistent portal hypertension (e.g., duodenal ulceration). Dogs with MVD tend to have milder clinical signs than dogs with congenital PSSs and can be managed medically with success over the long term. Affected dogs seem to live comfortably, in good to excellent condition, for at least 5 years.

Congenital Ductal Plate Abnormalities

Etiology

Ductal plate abnormalities are congenital diseases of the liver causes by abnormalities in development of the ductal plate (see later). There are a variety of phenotypes depending on the stage in embryologic development when the abnormality occurs, and there may be some overlap with portal vein abnormalities. Traditionally, these conditions were considered rare in dogs, but with increasing awareness of the condition, more cases are being identified. The commonest phenotypes in dogs are Caroli's disease, where bile ducts are large, and cystic and congenital hepatic fibrosis, where there are multiple small bile ductules and associated fibrosis. The latter can be confused with cirrhosis on pathology and hence potential underdiagnosis. The differentiation is important because dogs with congenital hepatic fibrosis generally have a better prognosis than those with cirrhosis if appropriately treated.

The ductal plate is the embryonic precursor of the interlobular and intralobular bile ducts. It is a double layer of embryonic epithelium surrounding the portal veins. Bile duct development involves many signaling molecules, and abnormalities in this development result in a wide variety of presentations in human medicine, with persistence of embryonic bile ducts and varying amounts of periportal fibrosis. The drivers of fibrosis in this context remain incompletely understood. There are a variety of genetic mutations involved in humans, many of them autosomal dominant, and affected individuals may have concurrent renal cysts or skeletal abnormalities. The disease phenotype in the liver depends on which bile ducts are affected; maturation arrest of small interlobular bile ducts results in congenital hepatic fibrosis, whereas maturation arrest of medium intrahepatic bile ducts results in Caroli's disease. The genetics of ductal plate anomalies are currently unknown in dogs. The first report of congenital hepatic fibrosis in dogs in the veterinary literature was in 2010 (Brown et al., 2010). Since that time, cases have been reported in Boxer dogs and Skye Terriers and anecdotally in other breeds. Pillai et al. in 2016 reported 30 Boxer dogs with ductal plate malformations, suggesting an increased prevalence in this breed. Interestingly, there was a high prevalence of concurrent congenital hepatic abnormalities such as atrophy of liver lobes or gallbladder or vascular abnormalities. Two dogs also had Caroli's disease. Recent work at the University of Cambridge in the UK suggests that Skye Terrier hepatitis may in fact also be a congenital ductal plate abnormality.

Clinical Features

Dogs with congenital hepatic fibrosis usually present at a young age, with most being under 1 year of age at presentation, but occasionally dogs present as old as 10 years of age. Clinical signs are typical of portal hypertension (see earlier) including ascites, vomiting, and diarrhea, and also in some cases melena. Some dogs present with HE.

Diagnosis

Clinicopathologic abnormalities are very similar to chronic liver disease. Affected dogs usually have elevated liver enzymes but very rarely elevated bilirubin. Bile acids are often elevated, associated with development of acquired PSSs. Some dogs have microcytic red cells. Diagnostic imaging findings are generally indistinguishable from cirrhosis: dogs usually have a small hyperechoic liver and free abdominal fluid. Some cases may have other congenital abnormalities such as atresia of the gallbladder or a liver lobe, or large liver cysts that would increase the index of suspicion of ductal plate abnormality. However, confirmation of diagnosis requires a liver biopsy. Congenital hepatic fibrosis typically appears as abnormal, expanded portal tracts with multiple small bile duct profiles and bands of fibrosis both periportally and extending into the liver. These tracts of fibrosis can sometimes resemble lobular dissecting hepatitis. There may also be areas of fibrosis and multiple small bile ducts underneath the liver capsule, similar to Meyenburg complexes reported in humans. Bile ducts typically have cuboidal rather than columnar epithelium. Increased copper accumulation is common in affected boxers and Skye Terriers, and is assumed to be secondary to abnormal excretion. The disease is often patchy affecting individual liver lobes more than others.

Treatment and Prognosis

Treatment of affected animals is symptomatic because there is no cure for the congenital abnormality. Nonetheless, many dogs have a good long-term prognosis with supportive care; a reported median survival in one study in Boxers was 8.8 years in dogs without acquired PSS and 7.5 years in dogs with PSS. Anecdotally, Skye Terriers and other breeds can also do well long term. Management is the same as for dogs with portal hypertension, with symptomatic treatment of ascites with spironolactone and careful dietary and other management for HE (see Box 36.6). It is particularly important that affected dogs are fed sufficient dietary protein for maintenance because long-term survival is anticipated.

Arterioportal Fistula

Intrahepatic arterioportal fistula, causing marked volume overload of the portal circulation and resulting in portal hypertension, acquired PSSs, and ascites, is seen occasionally. Abdominal Doppler ultrasonography can frequently detect the tortuous tubular structures representing the connection between an artery and overperfused portal vein or veins; sometimes the turbulent blood flow through the fistula can be auscultated through the body wall. If only one lobe of the liver is affected, the lobe containing the arterioportal fistula can be removed surgically. Assuming that there is adequate intrahepatic portal vasculature, acquired PSSs regress once portal overcirculation subsides. More often, multiple liver lobes are involved, making surgical treatment impossible.

FOCAL HEPATIC LESIONS

ABSCESSES

Etiology

Hepatic abscesses are usually the result of septic embolization from an intraabdominal bacterial infection. In puppies they are frequently a consequence of omphalophlebitis, whereas in adult dogs they arise most often subsequent to inflammatory conditions of the pancreas or hepatobiliary system. Adult dogs with certain endocrine diseases (e.g., diabetes mellitus, hyperadrenocorticism) are also at risk. Hepatic abscesses have also been reported secondary to liver fluke infection in a dog (Lemetayer et al., 2016). Occasionally, infection arising from a location other than the abdominal cavity, such as the endocardium, lung, or blood, may disseminate to the liver, causing abscessation.

The most common isolates in published studies are aerobic gram-negative organisms, particularly *E. coli,* which can be multiresistant, and the anaerobic *Clostridium* spp. *Staphylococcus* spp. have also been identified.

Clinical Features

The typical signalment and physical examination findings in dogs with hepatic abscesses depend on the underlying cause. Dogs older than 8 years are most often affected because the predisposing causes of liver abscesses are seen more commonly in older dogs. Regardless of the initiating event, anorexia, lethargy, and vomiting are consistent presenting complaints. Expected physical examination findings include fever, dehydration, and abdominal pain. Hepatomegaly may be detected in dogs with diabetes mellitus or hyperadrenocorticism and in some dogs with primary hepatobiliary disease.

Diagnosis

Neutrophilic leukocytosis with a left shift, with or without toxic changes, and high serum ALP and ALT activities are dependable but nonspecific clinicopathologic abnormalities. Survey abdominal radiographs may reveal evidence of an irregular hepatomegaly, mass, or gas opacities within the area of the hepatic parenchyma (Fig. 36.15), but ultrasonography is the imaging modality of choice. One or more hypoechoic or anechoic hepatic masses and perhaps a hyperechoic rim surrounding the mass or masses are characteristic findings. If there are multiple masses that would preclude surgical removal, or if the owner declines surgery, FNA

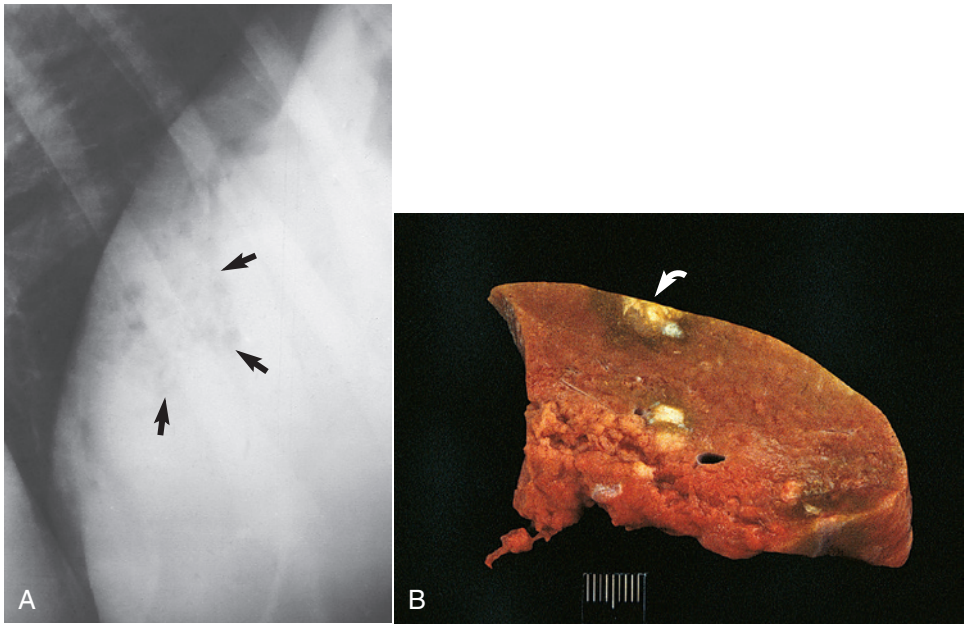


FIG 36.15
(A) Lateral abdominal radiograph of a 1-year-old female Great Dane with a liver abscess *(arrows)* caused by *Clostridium* spp. The cause was undetermined. **(B)** Gross appearance of the resected liver lobe containing an abscess *(arrow)*.

cytology analysis of the contents of a representative lesion will distinguish an abscess from nodular hyperplasia, neoplasm (e.g., hemangiosarcoma), or granuloma. Ideally, material should be obtained for cytologic analysis and aerobic and anaerobic bacterial cultures from a representative lesion deep in the liver parenchyma to prevent abscess rupture and abdominal contamination. Abscess material should also be obtained by this approach during surgery so that antibiotic treatment can be initiated postoperatively. Ultrasound-guided drainage of the abscess can also be used as treatment in combination with appropriate antibiotics (see later). Results of the preliminary clinicopathologic and radiographic evaluation should be scrutinized for evidence of previously noted comorbidities.

Treatment and Prognosis

Treatment for liver abscesses consists of surgical removal of infected tissue, administration of appropriate antibiotics, supportive care, and resolution of underlying predisposing conditions. Infected liver tissue should be removed, if possible, and submitted for histopathologic examination and bacterial culture if this was not done preoperatively. Fluid, electrolyte, and acid–base abnormalities are addressed. Administration of a combination of antibiotics with a gram-negative and anaerobic spectrum is initiated until culture and sensitivity test results are available. Because staphylococci and clostridia are the most common isolates, amoxicillin (10–20 mg/kg IV q8h) combined with metronidazole (10 mg/kg PO q12h, or 7.5 mg/kg PO q12h for dogs with hepatic dysfunction) or clindamycin (10 mg/kg IV or PO q12h) is a good empiric choice. Surgery is not indicated for animals with multiple abscesses; ultrasound-guided centesis and abscess evacuation may be a reasonable adjunct to treatment. This has been described combined with saline lavage and alcohol infusion. For more details, see Lemetayer et al. (2016). Antibiotic treatment is continued on a long-term basis, usually for 6 to 8 weeks or until clinicopathologic and ultrasonographic indicators of abscessation are resolved. From the limited information available about this rare condition, it seems that with aggressive medical and surgical treatment, the prognosis for dogs with liver abscesses may not be as poor as once thought.

NODULAR HYPERPLASIA

Hepatic nodular hyperplasia is a benign condition of older dogs that does not cause clinical illness; clinicians should be aware of it, however, because hyperplastic nodules may be misinterpreted as a more serious condition, such as primary or metastatic malignancy or regenerative nodules associated with cirrhosis. The prevalence increases with age, and as many as 70% to 100% of dogs older than 14 years have some microscopic or macroscopic hyperplasia. Affected dogs have high serum ALP activities (usually a 2.5-fold elevation but possibly as high as 14-fold), which prompts an investigation for hyperadrenocorticism. There is no evidence of hepatic dysfunction on serum biochemical analysis. Many dogs have multiple macroscopic nodules found ultrasonographically or at surgery, ranging in size from 2 to 5 cm in diameter; some dogs have a single nodule.

Micronodular changes occur much less frequently and are identified only in liver biopsy specimens. The lesion consists of increased numbers of normal to vacuolated hepatocytes with more mitotic figures and fewer binucleate cells than expected in normal liver; components of normal lobular architecture (e.g., portal tracts, central vein) remain. The adjacent parenchyma is compressed by growth of the nodules; fibrosis, necrosis, inflammation, and bile ductule hyperplasia are absent. Because the prognosis for each of these nodular conditions is different and the margin of the lesion with adjacent hepatic tissue is important to establish a diagnosis, a wedge biopsy is recommended. Needle specimens are likely to be too small to confidently differentiate nodular hyperplasia from primary hepatocellular carcinoma or adenoma. The cause of this lesion is unknown; on the basis of the experimental development of nodular hyperplasia in rodent species, some have speculated a dietary role (low protein).

NEOPLASIA

Etiology

Primary hepatic neoplasms are rare in dogs, accounting for fewer than 1.5% of all canine tumors. Unlike in cats, malignant tumors are more common than benign tumors, and metastatic tumors are 2.5 times more common than primary tumors in dogs. Metastases particularly arise from primary neoplasms in the spleen, pancreas, and GI tract (Fig. 36.16); the liver can also be involved in systemic malignancies such as lymphoma, malignant histiocytosis, and mastocytosis.

Although certain chemical agents can induce hepatic neoplasms experimentally, and chronic hepatitis, steatohepatitis, and chronic biliary tract disease are also predisposing causes in other species, the cause of naturally occurring canine hepatic neoplasms is unknown. The types of primary

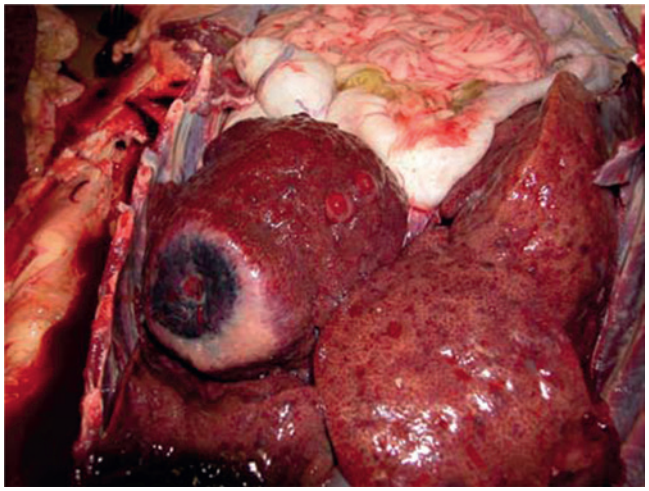


FIG 36.16
Gross appearance of liver postmortem from a 2-year-old male Siberian Husky with a metastatic carcinoma.

hepatic tumors seen in dogs and their relative importance and metastatic potential are outlined in Table 36.3.

Clinical Features

Clinical signs and physical examination findings in dogs with primary or secondary liver tumors are nonspecific, except for diffuse or nodular hepatomegaly. Even this can be confused with other conditions, such as macronodular cirrhosis or benign nodular hyperplasia, which are also common in older dogs. Therefore no dog should be euthanized on the basis of a presumptive diagnosis of a liver mass on clinical examination or diagnostic imaging without supportive histology. The left liver lobes are often affected by hepatocellular carcinoma, which can occur in three different patterns—massive (single, large nodule; most common), nodular (multiple smaller nodules), and diffuse (indistinct nodules throughout). The behavior of each type of tumor tends also to be different, as outlined in Table 36.3.

Clinicopathologic abnormalities are similarly not specific for neoplasia, and blood test results may be normal, even in dogs with extensive involvement. Dogs with lymphoma infiltrating the liver usually have marked increases in ALT and ALP activities but are rarely jaundiced; moreover, although the liver usually looks abnormal on ultrasonography, they may have normal liver echotexture. The authors occasionally see dogs with marked hepatic involvement with large cell lymphoma that have normal liver enzyme activities. Hypoglycemia has been described in association with hepatocellular carcinoma in dogs and can be caused by paraneoplastic production of insulin-like growth factor. Cytology usually allows the distinction of solitary hepatocellular carcinomas from nodular hyperplasia. Massive forms of hepatocellular carcinoma have a low metastatic rate. Metastases from other diffuse and nodular forms of hepatocellular carcinoma or biliary carcinoma usually occur early; the most common sites are the liver, regional lymph nodes, lung, and peritoneal surfaces. Hepatocellular adenoma (hepatoma) is a benign tumor that usually occurs as a single mass that is typically smaller than the massive form of hepatocellular carcinoma but can be multifocal. Histologic features of hepatocellular adenoma are similar to those of nodular hyperplasia (or normal liver), except for the presence of a fine rim of reticulin surrounding the adenoma and lack of apparent normal architecture—that is, few portal tracts and no central veins.

TABLE 36.3

Primary Liver Tumors in Dogs*

TYPE OF TUMOR	COMMENTS
Hepatocellular Tumors	
Hepatocellular carcinoma (HCC)	HCC most common primary liver tumor in dogs (50%)
Hepatocellular adenoma, hepatoma	Most are massive; some nodular or diffuse
Hepatoblastoma—very rare	Miniature Schnauzers, male dogs may be at increased risk MR, 0%–37% for massive forms, 93%–100% for nodular and diffuse forms Adenoma uncommon and usually incidental
Biliary Tract Tumors	
Biliary carcinoma (including cystadenocarcinoma)	Bile duct carcinomas second most common primary tumor in dogs (22%–41% of malignant canine liver tumors)
Biliary adenoma	Labrador Retrievers, females may be at increased risk
Gallbladder tumors	Usually aggressive MR up to 88% Adenomas uncommon, gallbladder tumors very rare
Neuroendocrine Tumor	
Hepatic carcinoid	Very rare, but always diffuse or nodular, and very aggressive
Primary Hepatic Sarcomas	
Hemangiosarcoma, leiomyosarcoma, gastrointestinal stromal tumors, others	Uncommon Most locally aggressive, diffuse, or nodular; high MR

MR, Metastatic rate.
*Note that malignant tumors are more common than benign tumors and that metastases to the liver are more common than primary liver tumors in dogs.

Treatment and Prognosis

When a single large hepatic mass is identified, it can be difficult to distinguish a well-differentiated hepatocellular carcinoma from nodular hyperplasia and hepatocellular adenoma from ultrasonography, CT imaging, or gross appearance; however, as noted, cytology is usually helpful. Surgical resection is the treatment of choice for primary hepatic neoplasms and massive hepatocellular carcinoma. In the latter, it usually carries a good prognosis provided the tumor can be fully resected because these have a lower metastatic rate than the more diffuse and nodular forms of the tumor, and the local recurrence rate after liver lobectomy is reportedly less than 13%. Long-term (2- to 3-year) survival rates after surgical resection are common in dogs with massive hepatocellular carcinoma. Surgical excision is therefore the treatment of choice for single tumors involving one liver lobe because this allows diagnosis and, in many cases, cure.

The prognosis for diffuse and nodular hepatocellular carcinomas and other forms of primary malignant liver tumors

is poor because there is no effective therapy. Hepatic tumors also respond poorly to chemotherapy, likely partly because of the development of rapid drug resistance by neoplastic hepatocytes. The response of secondary (metastatic) liver tumors depends on the type and location of the primary tumor; responses in dogs with hepatic lymphoma as part of the multicentric form are very good to excellent, whereas presumed primary hepatic lymphoma had a poor response to chemotherapy in one recent study, with dogs not achieving complete remission and dogs with a low serum albumin concentration having particularly poor responses (Dank et al., 2011). Hemangiosarcoma metastases respond well to vincristine, doxorubicin, and cyclophosphamide (VAC) chemotherapy (see Chapter 81). Metastatic carcinomas or carcinoids of the liver rarely respond to chemotherapy. (See "Oncology" for additional information on metastatic tumors.)

HEPATOCUTANEOUS SYNDROME AND SUPERFICIAL NECROLYTIC DERMATITIS

Etiology and Pathogenesis

Hepatocutaneous syndrome (also known as *superficial necrolytic dermatitis, metabolic epidermal necrosis*, and *necrolytic migratory erythema*) is a skin condition reported in association with certain liver diseases that usually carries a poor prognosis. The pathophysiology and underlying causes in dogs remain unclear, and it is likely multifactorial. It occurs in association with certain typical findings on hepatic ultrasonography and histopathology, and often no underlying cause is found. However, because it is likely that many cases represent a hepatic reaction to an underlying endocrine tumor or disorder, superficial necrolytic dermatitis represents an intermediate disorder between primary liver disease and secondary hepatopathies.

The underlying pathogenesis in the skin appears to be caused by abnormally low circulating amino acid concentrations and thus malnutrition of the skin, particularly in areas of poor blood supply, such as the extremities. Zinc deficiency may also be involved because the histologic appearance of the skin is similar to that in dogs with zinc-responsive dermatosis; fatty acid deficiencies have also been implicated. In humans the disorder is usually associated with a glucagon-secreting tumor of the pancreas. However, glucagonomas are rarely reported in affected dogs, and circulating glucagon concentrations are usually normal, although they may be occasionally high. Plasma amino acid concentrations have been reported to be very low in all affected dogs in which they have been measured, both in dogs with pancreatic tumors and dogs without. It has been proposed that canine superficial necrolytic dermatitis represents a metabolic hepatopathy with increased hepatic catabolism of amino acids, which decreases their peripheral availability.

Superficial necrolytic dermatitis secondary to chronic phenobarbital administration for epilepsy has been reported in 11 dogs (March et al., 2004). The median age of the affected dogs was 10 years, and the median duration of phenobarbital therapy was 6 years. No other underlying cause could be found. Plasma amino acid concentrations were markedly decreased in the only dog in which they were measured.

Whatever the underlying pathogenesis, dogs with superficial necrolytic dermatitis are at high risk of becoming diabetic, which is reported in 25% to 40% of cases. This is easy to explain if blood glucagon concentrations are high, because glucagon is a diabetogenic hormone but is difficult to explain on the basis of simple amino acid level changes.

Clinical Findings

Idiopathic superficial necrolytic dermatitis is usually reported in older dogs of small breeds; in one study 75% of the affected dogs were male (Outerbridge et al., 2002). Most dogs present because of their skin disease rather than their primary liver disease. Typically, there is erythema, crusting, and hyperkeratosis affecting the footpads, nose, and periorbital, perianal, and genital areas, and often pressure points on the limbs. The paw lesions can be extremely painful because of associated fissures and may result in lameness and secondary infection. Signs of liver disease may also be present, although not usually, and diabetes mellitus often develops later in the disease process, especially if the animal is given diabetogenic drugs such as glucocorticoids in an attempt to control the skin disease.

Diagnosis

Definitive diagnosis is based on skin biopsy findings that are characteristic and unique. The only syndrome with a similar appearance on skin histopathology is zinc-responsive dermatosis. There is a marked parakeratotic hyperkeratosis with intercellular and intracellular edema and hyperplastic basal cells, producing a characteristic red, white, and blue appearance on hematoxylin and eosin (H&E) staining.

The associated hepatic findings are more nonspecific, except for the ultrasonographic findings. There are usually increases in liver enzyme activities, and there may be hypoalbuminemia in some cases. In dogs that are diabetic, there is hyperglycemia and glycosuria. The typical ultrasonographic appearance is a so-called Swiss cheese liver consisting of multiple hypoechoic regions with hyperechoic borders (Fig. 36.17). Hepatic histology in all cases is remarkably similar, showing what has been described as a distinctive form of macronodular cirrhosis. The liver is divided into regenerative hyperplastic nodules with fibrous septa and bordered by characteristic ballooned vacuolated hepatocytes but with minimal or no inflammation or necrosis.

Treatment and Prognosis

The prognosis is very poor unless the underlying cause can be identified and treated; most dogs live for less than 6 months. There have been reports of disease resolution if a pancreatic tumor is identified and removed. Dogs with phenobarbital-associated hepatocutaneous syndrome may

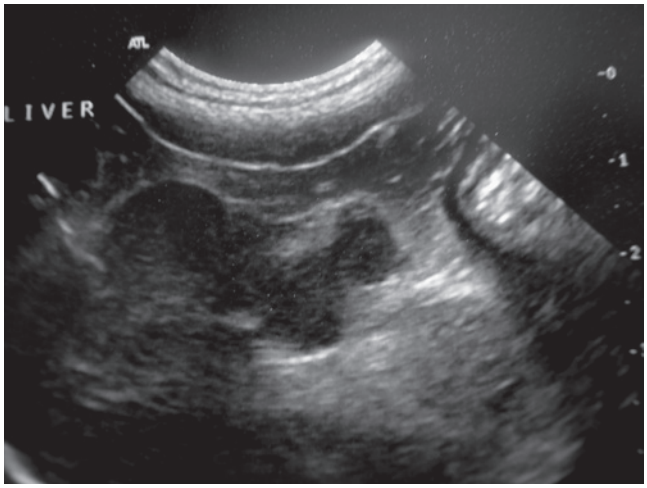


FIG 36.17
Ultrasonographic appearance of the liver of a 6-year-old Border Terrier with hepatocutaneous syndrome secondary to chronic phenobarbital medication for idiopathic epilepsy. Note the typical hypoechoic holes in the liver parenchyma on the left. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

improve when the drug is withdrawn, although this has not yet been demonstrated. An alternative nonhepatotoxic therapy for their epilepsy will need to be instituted; potassium bromide might be an alternative choice, but it takes weeks to reach a steady state. Imepitoin is another alternative choice. Gabapentin might also be used, although this is only effective in some dogs and does undergo some hepatic metabolism. For more details, see Chapter 62.

When an underlying cause cannot be identified and treated, therapy is symptomatic and supportive. The most important aspect is amino acid and protein supplementation; in a few cases this may lead to long-term survival. There are single case reports of humans with resolution of the disease after amino acid infusions and/or regular dietary supplementation of egg protein; feeding egg yolks has also been reported as resulting in a clinical improvement in some dogs. It is unclear whether eggs are beneficial simply because they are a high-quality amino acid supplement or whether there are other beneficial micronutrients in the eggs. Dogs with hepatocutaneous syndrome should not be fed proprietary diets for liver disease because these are protein-restricted. Other supportive therapy includes antibiotics for secondary skin infections (e.g., cephalexin, 20 mg/kg PO q12h) and antioxidants (see earlier, "Chronic Hepatitis: Treatment"). In addition, zinc and fatty acid supplementation may be helpful in some cases. Glucocorticoids should be avoided because they will precipitate diabetes mellitus. Our group has treated two dogs with hepatocutaneous syndrome that survived for several years on a high-quality digestible diet, marketed for GI disease, with extra egg and vitamin E and SAM-e supplementation with antibiotics; however, one dog did become diabetic 1 month after diagnosis.

SECONDARY HEPATOPATHIES

Secondary (reactive and vacuolar) hepatopathies are common in dogs. In pathology studies it is clear that they are more common than primary hepatic disease. Many of these hepatopathies result in elevations in liver enzyme activities, but usually the liver changes are not clinically relevant and do not result in compromised liver function. However, they are often confused with primary liver disease, and it is important to rule out secondary hepatopathies as much as possible in the workup of dogs with elevated liver enzyme activities to allow identification and treatment of the underlying primary disease (e.g., endocrine disease or inflammatory disease elsewhere in the splanchnic bed). High liver enzyme activities in older dogs have many other causes in addition to primary liver disease, and it is also important to resist the urge to put them on a protein-restricted diet and other medications for liver disease before working up the case properly. Many dogs with secondary hepatopathies will not have hepatic histopathology performed because the primary cause will be identified with other tests. However, it is convenient from a classification point of view to split secondary hepatopathies into three groups on the basis of their appearance histopathologically—secondary hepatopathies associated with hepatocyte swelling and/or vacuolation, hepatic congestion or edema, and reactive hepatitis.

HEPATOCYTE VACUOLATION

Secondary hepatopathies associated with hepatocyte vacuolation are divided into steroid-induced hepatopathy and hepatocellular steatosis (lipidosis, fatty changes). Steroid-induced hepatopathy is characterized by hepatocellular glycogen accumulation, which is distinctive from steatosis, in which fat (rather than glycogen) accumulates in hepatocytes. The difference can be demonstrated with special stains (periodic acid–Schiff for glycogen and Oil Red O or Sudan black for fat), but there are also some differences on routine H&E staining that help with differentiation. Glycogen vacuoles tend not to displace the nucleus from the center of the cell and often contain strands of eosinophilic material, whereas classic steatosis is associated with clear empty vacuoles because the fat is lost in processing, and the nucleus is often displaced to the edge of the cell (Fig. 36.18).

Both types of vacuolar hepatopathies are reversible when the underlying cause is eliminated. The most common causes are endocrine diseases (see Table 36.1). Steroid-induced hepatopathy is seen in hyperadrenocorticism and dogs being given exogenous corticosteroids. It has also been associated with other hormone therapies and the administration of some other drugs, such as D-penicillamine or barbiturates. There have been reports of idiopathic vacuolar hepatopathy in Scottish Terriers causing marked elevations in ALP levels, but the underlying cause is unknown. A large study of Scottish Terriers with vacuolar hepatopathy at Cornell (Sepesy et al., 2006) suggested that these dogs had an overproduction of androgenic hormones, perhaps as a result of a genetic defect in 21-hydroxylase. It is worrisome that 30% of the Scottish Terriers in that study also developed

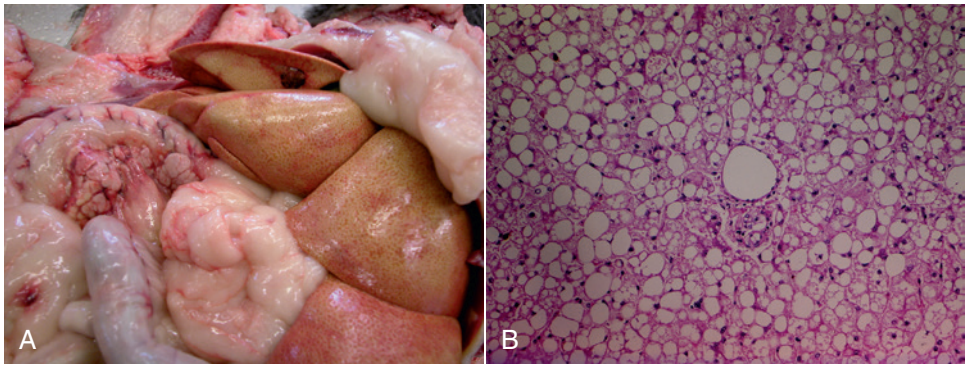


FIG 36.18
Gross **(A)** and histologic **(B)** appearance of the liver postmortem in a middle-aged Miniature Poodle with poorly controlled diabetes mellitus. Note the pale yellowish appearance of the liver associated with generalized hepatic steatosis. Histologically, the hepatocytes are markedly swollen with fat that displaces the nuclei to the edge of the cells. The portal triad is seen in the center (H&E, ×200). (Courtesy Pathology Department, Veterinary Medicine, University of Cambridge, Cambridge, England.)

hepatocellular carcinoma, suggesting that chronic vacuolar hepatopathy may predispose to tumors in dogs as it can in humans. The vacuolation seen as part of the hepatocutaneous syndrome looks similar to glycogen vacuolation. Steatosis is generally associated with diabetes mellitus in dogs, in which it starts centrilobularly and then spreads. It has also been reported in juvenile hypoglycemia of small-breed dogs. However, although hepatic steatosis can sometimes appear very marked in dogs, it does not appear to become a clinically significant disease in its own right, unlike in cats, in which primary or secondary hepatic lipidosis are important clinical syndromes (see Chapter 35).

HEPATIC CONGESTION AND EDEMA

Hepatic congestion is a common finding with right-sided congestive heart failure and other causes of posthepatic venous congestion, such as heartworm disease. Again, this results in elevation in liver enzyme levels. It is usually reversible, but in a few chronic cases of congestion associated with heart disease, it can result in fibrosis and permanent compromise (so-called cardiac cirrhosis).

NONSPECIFIC REACTIVE HEPATITIS

Nonspecific reactive hepatitis is a nonspecific hepatic response to a number of extrahepatic processes, particularly inflammatory processes in the splanchnic bed, such as pancreatitis and inflammatory bowel disease. There is a mild inflammatory infiltrate in the sinusoids and portal areas and/or parenchyma but no associated hepatocyte necrosis or fibrosis and therefore no evidence of primary (significant) hepatitis. This could be viewed as the hepatic equivalent of a reactive lymph node and should prompt a search for an underlying cause.

Diagnosis

The diagnosis of all types of secondary hepatopathies relies on diagnosing the underlying cause. The clinical signs will be those of the primary cause and are not related to the liver. However, sometimes there will be an overlap in clinical signs, notably with hyperadrenocorticism or diabetes mellitus in which the PU-PD and abdominal enlargement, together with raised liver enzyme levels, might increase the suspicion of primary liver disease. Recognizing that there is a secondary hepatopathy involves initial pattern recognition of the enzyme level elevation and clinical signs—for example, in a dog with PU-PD, a potbelly, dermatologic signs, a pattern of a very marked elevation in the ALP activity, and a less marked elevation in the ALT activity should raise the suspicion of hyperadrenocorticism. This is followed by appropriate diagnostic tests for the underlying condition. Liver biopsies are usually not indicated. However, there will inevitably be cases with mild or nontypical changes of the primary condition in which liver biopsies will be taken on suspicion of primary hepatopathy. Finding nonspecific secondary changes in the liver should then stimulate a repeat search for an underlying cause.

Suggested Readings

Abdallah AAL, et al. Biliary tract obstruction in chronic pancreatitis. *HPB (Oxford)*. 2007;9:421.

Adamus C, et al. Chronic hepatitis associated with leptospiral infection in vaccinated beagles. *J Comp Pathol*. 1997;117:311.

Aguirre AL, et al. Gallbladder disease in Shetland Sheepdogs: 38 cases (1995-2005). *J Am Vet Med Assoc*. 2007;231:79.

Ahn JO, et al. Hyperammonemic hepatic encephalopathy management through L-ornithin-L-aspartate administration in dogs. *J Vet Sci*. 2016;17:431.

Appleman EH, et al. Transient acquired fanconi syndrome associated with copper storage hepatopathy in 3 dogs. *J Vet Intern Med*. 2008;22:1038.

Azumi N. Copper and liver injury—experimental studies on the dogs with biliary obstruction and copper loading. *Hokkaido Igaku Zasshi*. 1982;57:331.

Bayton W, et al. Prednisolone therapy for chronic hepatitis in the English Springer Spaniel: A prospective study of 14 cases. Research communications of the 27th ECVIM Congress. *J Vet Intern Med*. 2018;32:574.

Bexfield NH, et al. Breed, age and gender distribution of dogs with chronic hepatitis in the United Kingdom. *Vet J*. 2012;193:124.

Bexfield NH, et al. Canine hepacivirus is not associated with chronic liver disease in dogs. *J Viral Hepat*. 2013;[Epub ahead of print].

Bexfield NH, et al. Chronic hepatitis in the English Springer Spaniel: clinical presentation, histological description and outcome. *Vet Rec*. 2011;169:415.

Bigge LA, et al. Correlation between coagulation profile findings and bleeding complications after ultrasound-guided biopsies: 434 cases (1993-1996). *J Am Anim Hosp Assoc*. 2001;37:228.

Boomkens SY, et al. PCR screening for candidate etiological agents of canine hepatitis. *Vet Microbiol*. 2005;108:49.

Brown DL, et al. Congenital hepatic fibrosis in 5 dogs. *Vet Pathol*. 2010;47:102.

Bunch SE, et al. Idiopathic noncirrhotic portal hypertension in dogs: 33 cases (1982-1988). *J Am Vet Med Assoc*. 2001;218:392.

Center SA, et al. Digital image analysis of rhodanine-stained liver biopsy specimens for calculation of hepatic copper concentrations in dogs. *Am J Vet Res*. 2013;74:1474.

Center SA, et al. Evaluation of the influence of S-adenosylmethionine on systemic and hepatic effects of prednisolone in dogs. *Am J Vet Res*. 2005;66:330.

Christiansen JS, et al. Hepatic microvascular dysplasia in dogs: a retrospective study of 24 cases (1987-1995). *J Am Anim Hosp Assoc*. 2000;36:385.

Coronado VA, et al. New haplotypes in the Bedlington terrier indicate complexity in copper toxicosis. *Mamm Genome*. 2003;14:483.

Cullen JM, et al. Lack of association of ABCB4 insertion mutation with gallbladder mucoceles in dogs. *J Vet Diagn Invest*. 2014;26:434.

Cullen JM, et al. Morphological classification of circulatory disorders of the canine and feline liver. In: Rothuizen J, et al, eds. *WSAVA standards for clinical and histological diagnosis of canine and feline liver disease*. Oxford: Saunders Elsevier; 2006.

Dank G, et al. Clinical characteristics, treatment, and outcome of dogs with presumed primary hepatic lymphoma: 18 cases (1992-2008). *J Am Vet Med Assoc*. 2011;239:966.

Dunayer EK, et al. Acute hepatic failure and coagulopathy associated with xylitol ingestion in eight dogs. *J Am Vet Med Assoc*. 2006;229:1113.

Fieten H, et al. The Menkes and Wilson disease genes counteract in copper toxicosis in Labrador retrievers: a new canine model for copper-metabolism disorders. *Dis Model Mech*. 2016;9:25.

Filburn CR, et al. Bioavailability of a silybin-phosphatidylcholine complex in dogs. *J Vet Pharmacol Ther*. 2007;30:132.

Fox JA, et al. *Helicobacter canis* isolated from a dog liver with multifocal necrotizing hepatitis. *J Clin Microbiol*. 1996;34:2479.

Friedman SL. Evolving challenges in hepatic fibrosis. *Nat Rev Gastroenterol Hepatol*. 2010;7:425.

Gabriel A, et al. Suspected drug-induced destructive cholangitis in a young dog. *J Small Anim Pract*. 2006;47:344.

Gagne JW, et al. Evaluation of calcium, phosphorus, and selected trace mineral status in commercially available dry foods formulated for dogs. *J Am Vet Med Assoc*. 2013;243:658.

Gillespie TN, et al. Detection of *Bartonella henselae* and *Bartonella clarridgeiae* DNA in hepatic specimens from two dogs with hepatic disease. *J Am Vet Med Assoc*. 2003;222:47.

Gómez Selgas A, et al. Total serum bilirubin as a negative prognostic factor in idiopathic canine chronic hepatitis. *J Vet Diagn Invest*. 2014;26:246.

Gómez-Ochoa P, et al. Use of transsplenic injection of agitated saline and heparinized blood for the ultrasonographic diagnosis of macroscopic portosystemic shunts in dogs. *Vet Radiol Ultrasound*. 2011;52:103.

Gookin JL, et al. Qualitative metabolomics profiling of serum and bile from dogs with gallbladdermucocele formation. *PLoS ONE*. 2018;13:e0191076.

Gookin JL, et al. Association of gallbladder mucocele histologic diagnosis with selected drug use in dogs: a matched case-control study. *J Vet Intern Med*. 2015;29:1464.

Görlinger S, et al. Congenital dilatation of the bile ducts (Caroli's disease) in young dogs. *J Vet Intern Med*. 2003;17:28.

Greenhalgh SN, et al. Comparison of survival after surgical or medical treatment in dogs with a congenital portosystemic shunt. *J Am Vet Med Assoc*. 2010;236:1215.

Harrison JL, et al. Cholangitis and cholangiohepatitis in dogs: a descriptive study of 54 cases based on histopathologic diagnosis (2004-2014). *J Vet Intern Med*. 2018;32:172.

Haywood S. Copper toxicosis in Bedlington terriers. *Vet Rec*. 2006;159:687.

Haywood S, et al. Copper toxicosis in non-COMMD1 Bedlington terriers is associated with metal transport gene ABCA12. *J Trace Elem Med Biol*. 2016;35:83.

Hoffmann G, et al. Copper-associated chronic hepatitis in Labrador Retrievers. *J Vet Intern Med*. 2006;20:856.

Hunt GB. Effect of breed on anatomy of portosystemic shunts resulting from congenital diseases in dogs and cats: a review of 242 cases. *Aust Vet J*. 2004;82:746.

Hyun C, et al. Evaluation of haplotypes associated with copper toxicosis in Bedlington terriers in Australia. *Am J Vet Res*. 2004;65:1573.

Irvine KL, et al. Sarcocystid organisms found in bile from a dog with acute hepatitis: a case report and review of intestinal and hepatobiliary Sarcocystidae infections in dogs and cats. *Vet Clin Pathol*. 2016;45:57.

Jaffey JA, et al. Gallbladder mucocele: variables associated with outcome and the utility of ultrasonography to identify gallbladder rupture in 219 dogs (2007-2016). *J Vet Intern Med*. 2018;32:195.

Jarrett WF, O'Neil BW. A new transmissible agent causing acute hepatitis, chronic hepatitis and cirrhosis in dogs. *Vet Rec*. 1985;15:629.

Jarrett WFH, et al. Persistent hepatitis and chronic fibrosis induced by canine acidophil cell hepatitis virus. *Vet Rec*. 1987;120:234.

Kapoor A, et al. Characterization of a canine homolog of hepatitis C virus. *Proc Natl Acad Sci USA*. 2011;108:11608.

Kitchell BE, et al. Peliosis hepatis in a dog infected with *Bartonella henselae*. *J Am Vet Med Assoc*. 2000;216:519.

Langlois DK, et al. Acquired proximal renal tubular dysfunction in 9 Labrador Retrievers with copper-associated hepatitis (2006-2012). *J Vet Intern Med*. 2013;27:491.

Lee KC, et al. Association of portovenographic findings with outcome in dogs receiving surgical treatment for single congenital portosystemic shunts: 45 cases (2000-2004). *J Am Vet Med Assoc*. 2006;229:1122.

Lemetayer JD, et al. Multiple liver abscesses in a dog secondary to the liver fluke Metorchis conjunctus treated by percutaneous transhepatic drainage and alcoholization. *Can Vet J*. 2016;57:605.

Mandigers PJ, et al. Improvement in liver pathology after 4 months of D-penicillamine in 5 doberman pinschers with subclinical hepatitis. *J Vet Intern Med*. 2005;19:40.

March PA, et al. Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002). *J Vet Intern Med*. 2004;18:65.

Mazaki-Tovi M, et al. Serum gastrin concentrations in dogs with liver disorders. *Vet Rec*. 2012;171:19.

McKallum KE, et al. Hepatic leptospiral infections in dogs without obvious renal involvement. *J Vet Intern Med*. 2019;33:141.

Mealey KL, et al. An insertion mutation in ABCB4 is associated with gallbladder mucocele formation in dogs. *Comp Hepatol*. 2010;9:6.

Miller JM, et al. Laparoscopic portosystemic shunt attenuation in two dogs. *J Am Anim Hosp Assoc*. 2006;42:160.

Mullins RA, et al. Effect of prophylactic treatment with levetiracetam on the incidence of postattenuation seizures in dogs undergoing surgical management of single congenital extrahepatic portosystemic shunts. *Vet Surg*. 2019;48:164.

Newman SJ, et al. Aflatoxicosis in nine dogs after exposure to contaminated commercial dog food. *J Vet Diagn Invest*. 2007;19:168.

O'Leary CA, et al. The inheritance of extra-hepatic portosystemic shunts and elevated bile acid concentrations in Maltese dogs. *J Small Anim Pract*. 2014;55:14.

O'Neill EJ, et al. Bacterial cholangitis/cholangiohepatitis with or without concurrent cholecystitis in four dogs. *J Small Anim Pract*. 2006;47:325.

Outerbridge CA, et al. Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis. *Vet Dermatol*. 2002;13:177.

Pike FS, et al. Gallbladder mucocele in dogs: 30 cases (2000-2002). *J Am Vet Med Assoc*. 2004;224:1615.

Pillai S, et al. Ductal plate malformation in the liver of er dogs: clinical and histological features. *Vet Pathol*. 2016;53:602.

Poldervaart RP, et al. Primary hepatitis in dogs: a retrospective review (2002-2006). *J Vet Intern Med*. 2009;23:72.

Raffan E, et al. Ascites is a negative prognostic indicator in chronic hepatitis in dogs. *J Vet Intern Med*. 2009;23:63.

Schermerhorn T, et al. Characterization of hepatoportal microvascular dysplasia in a kindred of cairn terriers. *J Vet Intern Med*. 1996;10:219.

Seguin MA, et al. Iatrogenic copper deficiency associated with long-term copper chelation for treatment of copper storage disease in a Bedlington Terrier. *J Am Vet Med Assoc*. 2001;15:218.

Sepesy LM, et al. Vacuolar hepatopathy in dogs: 336 cases (1993-2005). *J Am Vet Med Assoc*. 2006;229:246.

Shih JL, et al. Chronic hepatitis in Labrador Retrievers: clinical presentation and prognostic factors. *J Vet Intern Med*. 2007;21:33.

Skorupski KA, et al. Prospective randomized clinical trial assessing the efficacy of Denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. *J Vet Intern Med*. 2011;25:838.

Tamborini A, et al. Bacterial cholangitis, cholecystitis, or both in dogs. *J Vet Intern Med*. 2016;30:1046.

Teske E, et al. Cytological detection of copper for the diagnosis of inherited copper toxicosis in Bedlington terriers. *Vet Rec*. 1992;131:30.

Tisdall PL, et al. Post-prandial serum bile acid concentrations and ammonia tolerance in Maltese dogs with and without hepatic vascular anomalies. *Aust Vet J*. 1995;72:121.

Tobias KM, et al. Association of breed with the diagnosis of congenital portosystemic shunts in dogs: 2,400 cases (1980-2002). *J Am Vet Med Assoc*. 2003;223:1636.

Toulza O, et al. Evaluation of plasma protein C activity for detection of hepatobiliary disease and portosystemic shunting in dogs. *J Am Vet Med Assoc*. 2006;229:1761.

Van de Sluis B, et al. Identification of a new copper metabolism gene by positional cloning in a purebred dog population. *Hum Mol Genet*. 2002;11:165.

Van den Ingh TSGAM, et al. Morphological classification of parenchymal disorders of the canine and feline liver. In: Rothuizen J, et al, eds. *WSAVA standards for clinical and histological diagnosis of canine and feline liver disease*. Oxford: Saunders; 2006.

Van den Ingh TSGAM, et al. Possible nutritionally induced copper-associated chronic hepatitis in two dogs. *Vet Rec*. 2007;161:728.

van Straten G, et al. Inherited congenital extrahepatic portosystemic shunts in Cairn terriers. *J Vet Intern Med*. 2005;19:321.

Walter R, et al. Nonsurgical resolution of gallbladder mucocele in two dogs. *J Am Vet Med Assoc*. 2008;232:1688.

Watson PJ, et al. Medical management of congenital portosystemic shunts in 27 dogs—a retrospective study. *J Small Anim Pract*. 1998;39:62.

Watson PJ. Canine chronic liver disease: a review of current understanding of the aetiology, progression and treatment of chronic liver disease in the dog. *Vet J*. 2004;167:228.

Webb CB, et al. Copper-associated liver disease in Dalmatians: a review of 10 dogs (1998-2001). *J Vet Intern Med*. 2002;16:665.

Webster CRL, et al. ACVIM consensus statement on the diagnosis and treatment of chronic hepatitis in dogs. *J Vet Intern Med*. 2019;33:1173.

Zandvliet MM, et al. Transient hyperammonemia due to urea cycle enzyme deficiency in Irish wolfhounds. *J Vet Intern Med*. 2007;21:215.

CHAPTER 37

The Exocrine Pancreas



GENERAL CONSIDERATIONS

The pancreas is located in the cranial abdomen, with the left limb positioned between the transverse colon and the greater curvature of the stomach, and the right limb running next to the proximal duodenum. Any or all of these neighboring structures can be affected when there is pancreatic inflammation. The exocrine acini make up about 90% of pancreatic tissue, and the endocrine islets interspersed among the acini make up the remaining 10% (Fig. 37.1). The close anatomic association between the acini and islets allows subtle signaling between them to coordinate digestion and metabolism, but it also means that there is a complex cause and effect relationship between diabetes mellitus (DM) and pancreatitis. The major function of the exocrine pancreas is to secrete digestive enzymes, bicarbonate, and intrinsic factor (IF) into the proximal duodenum. Pancreatic enzymes are responsible for the initial digestion of larger food molecules and require an alkaline pH to function—hence the concurrent bicarbonate secretion by pancreatic duct cells. The pancreas secretes several proteases, phospholipases, ribonucleases, and deoxyribonucleases as inactive precursors (zymogens), and α-amylase and lipase as intact molecules. The pancreas is the only significant source of lipase, and hence steatorrhea (fatty feces) is a prominent sign of exocrine pancreatic insufficiency (EPI). Trypsin is central to the pathogenesis of pancreatitis, as discussed later, and inappropriate early activation of the zymogen trypsinogen to trypsin within the pancreatic acini is the final common pathway triggering pancreatic inflammation. In the normal animal, pancreatic secretion is triggered by the thought of food and stomach filling, and most potently by the presence of fat and protein in the small intestinal lumen. The vagus nerve, local enteric nervous system, and hormones secretin and cholecystokinin from the small intestine stimulate pancreatic secretion. Trypsinogen is activated in the small intestine by the brush border enzyme enterokinase, which cleaves a peptide (the trypsin activation peptide [TAP]) from trypsinogen. Activated trypsin then activates the other zymogens within the intestinal lumen. IF, which is necessary for vitamin B_{12} absorption in the ileum, is secreted only by the pancreas in the cat. In the dog the pancreas is the main source of IF, but a small amount is also secreted by the gastric mucosa.

Diseases of the exocrine pancreas are relatively common but often misdiagnosed in dogs and cats because of nonspecific clinical signs, relative difficulty in accessing the organ for diagnostic imaging and biopsies, and lack of sensitive and specific clinicopathologic tests. Pancreatitis is the most common disease of the exocrine pancreas in cats and dogs; EPI, although less common, is also recognized frequently. Uncommon diseases of the pancreas include pancreatic abscess, pseudocyst, and neoplasia.

Recent advances in the understanding of the pathophysiology, prevalence, and potential causes of pancreatitis in dogs and cats may provide clues about treatment in the future, although treatment of acute pancreatitis remains largely nonspecific and supportive in all species.

Important differences in the anatomy of the pancreas and associated areas between the dog and cat are outlined in Table 37.1.

PANCREATITIS

Pancreatitis may be acute or chronic. As with acute and chronic hepatitis, the difference is histologic and not necessarily clinical (Table 37.2; Fig. 37.2), and there is often clinical overlap between the two. Chronic disease may present initially as an acute-on-chronic episode; in postmortem studies of fatal acute pancreatitis in dogs and cats, up to half of the cases were actually acute-on-chronic disease. Differentiation of acute disease from an acute flare-up of chronic disease is not important for initial management, which is the same in all cases, but is important to allow recognition of the potential long-term sequelae of chronic disease (see later). The causes of acute and chronic pancreatitis may be different, but there may also be some overlap between them.

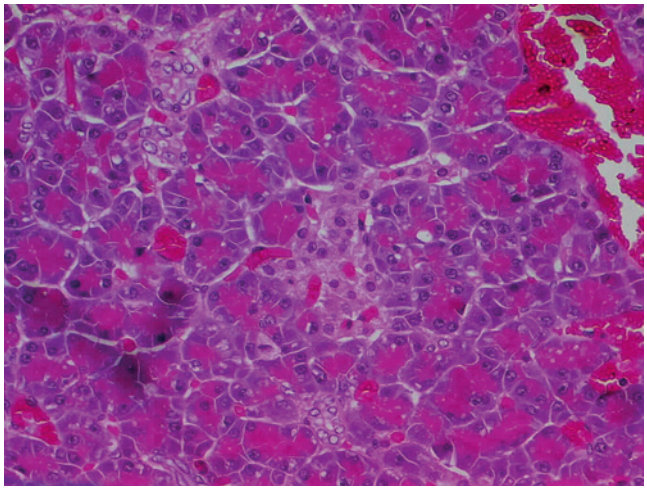


FIG 37.1
Histopathology of a section of normal canine pancreas showing two paler staining islets of Langerhans and exocrine acini surrounding them. Note that the islets make up only 10% to 20% of the volume of the pancreas.

ACUTE PANCREATITIS

Etiology and Pathogenesis

Understanding of the pathophysiology of acute pancreatitis in humans has increased in recent years with the discovery of hereditary mutations of trypsin, which predispose to pancreatitis; the pathophysiology of this disease is believed to be similar in dogs and cats. The final common pathway in all cases is the inappropriate early activation of trypsinogen in the pancreas as a result of increased autoactivation of trypsinogen and/or reduced autolysis of prematurely activated trypsin. Trypsin is the major protease secreted by the pancreas, and inappropriate early activation in the acinar cells would obviously cause autodigestion and severe inflammation. Protective mechanisms therefore exist to prevent early activation. Trypsin is stored in zymogen granules in the pancreatic acini as the inactive precursor trypsinogen. Up to 10% of trypsinogen gradually autoactivates normally within the granules but is inactivated by the action of other trypsin molecules and by the cosegregating protective molecule, pancreatic secretory trypsin inhibitor (PSTI; also known as serine protease inhibitor Kazal type 1, or *SPINK1*). Genetic mutations of trypsinogen, which make it resistant to hydrolysis, and/or of PSTI predispose to pancreatitis in people and are also likely to occur in some dogs (Table 37.3). A variety of mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene also predispose to pancreatitis in humans. Studies of mutations predisposing to acute pancreatitis in dogs have focused on Miniature Schnauzers. Initial studies showed no mutations in the cationic trypsinogen gene in individuals with pancreatitis in this breed but did find variations in the gene coding *SPINK1* (Bishop et al., 2004, 2010). However, a more recent study questioned the significance of this finding because *SPINK1* mutations were found in Miniature and Standard Schnauzers, both with and without pancreatitis (Furrow et al., 2012). Another study identified several mutations of the canine CFTR gene in dogs both with and without pancreatitis but no significant association with disease (Spadafora et al., 2010). More studies are necessary to elucidate the role of mutations in pancreatitis in dogs.

If too much trypsin autoactivates in the pancreas, the protective mechanisms are overwhelmed and a chain reaction occurs whereby activated trypsin activates more trypsin and the other enzymes in the pancreas. This results in pancreatic autodigestion, inflammation, and peripancreatic fat necrosis, which leads to focal or more generalized sterile peritonitis. There is an associated systemic inflammatory response (SIR) in even the mildest cases of pancreatitis. Many other organs may be involved, and in the most severe cases there is multiorgan failure (MOF) and diffuse intravascular coagulation (DIC). The circulating protease inhibitors α_1-antitrypsin (α_1-protease inhibitor) and α-macroglobulin play a role in removing trypsin and other proteases from the circulation. Saturation of these protease inhibitors by excessive amounts of circulating proteases contributes to the systemic inflammation, but generalized neutrophil activation and cytokine release are probably the primary cause of SIR.

The previous paragraph has described the final common pathway of acute pancreatitis in dogs and cats, but the underlying cause of the disease is often unknown (see Table 37.3). There appears to be a strong breed relationship for pancreatitis in dogs, so hereditary causes are likely to be a factor. Many of the previously reported supposed causes in dogs are likely triggers for disease in genetically susceptible individuals.

Clinical Features

Acute pancreatitis typically affects middle-aged dogs and cats, although very young and very old individuals may also be affected. Terrier breeds, Miniature Schnauzers, and domestic short-haired cats appear to be at increased risk for acute pancreatitis, although any breed or cross-breed can be affected. Some dog breeds appear to be underrepresented in clinical studies, particularly large and giant breeds, although Labrador Retrievers and Husky types (the latter particularly in Australia) are often affected. Breed relationships suggest an underlying genetic tendency, mirroring the situation in humans. It is likely that the disease is multifactorial, with a genetic tendency and superimposed triggering factors. For example, eating a high-fat meal may be a trigger for a susceptible terrier. Some studies suggest a slight increase in risk in female dogs, whereas others show no gender predisposition. Obesity has been suggested as a predisposing factor in dogs, but it is unclear whether this is a cause or whether it is cosegregating with disease (i.e., breeds at high risk for acute pancreatitis may coincidentally also be breeds with a high risk for obesity). In some cases in cats there is a recognized association with concurrent cholangitis, inflammatory bowel disease, and renal disease. Cats with acute pancreatitis are also at high risk for hepatic lipidosis.

The history in dogs often includes a trigger such as a high-fat meal or engorging (see Table 37.3). Recent drug therapy

TABLE 37.1

Differences in Pancreatic Structure, Function, and Diseases in Dogs and Cats

FEATURE	DOGS	CATS
Anatomy (but many variations; some dogs are like cats, and vice versa)	Usually two pancreatic ducts—large accessory duct from right limb to minor papilla in duodenum, small pancreatic duct from left limb to major duodenal papilla in duodenum next to (but not joining) bile duct Sphincter of Oddi unlikely to be of clinical significance	Usually single major pancreatic duct joining common bile duct before entering duodenum at duodenal papilla 3 cm distal to pylorus 20% of cats have second, accessory duct; occasionally ducts remain separate Sphincter of Oddi may be as important as in humans
Pancreatic function	Intrinsic factor secreted largely by pancreas but also some in stomach; vitamin B_{12} deficiency common in exocrine insufficiency but sometimes normal	Intrinsic factor secreted entirely by pancreas so vitamin B_{12} deficiency very common in exocrine insufficiency; vitamin K deficiency also common because of concurrent liver and intestinal disease further reducing absorption
Pancreatitis—disease associations	Common association between pancreatitis and endocrine disease (see text) Association with liver and small intestinal disease not recognized Emerging association in some breeds with immune-mediated diseases, particularly keratoconjunctivitis sicca and glomerulonephritis (see text)	Common association with cholangiohepatitis and/or inflammatory bowel disease High risk of concurrent hepatic lipidosis May also be associated with renal disease
Exocrine pancreas, other pathology	Incidental pancreatic nodular hyperplasia common	Incidental pancreatic nodular hyperplasia common
Pancreatitis		
Spectrum of disease	Most cases acute at presentation Low-grade chronic disease increasingly recognized and more common than acute on postmortem studies	Most cases low-grade, chronic interstitial disease, challenge to diagnose Acute severe cases also recognized
Diagnosis (see Chapter 34)	Histology is gold standard Variety of catalytic and immunoassays available Ultrasonography quite sensitive Obvious or suggestive clinical signs in acute cases	Histology is gold standard Most catalytic assays no help Immunoassays more helpful Ultrasonography less sensitive than in dogs Clinical signs usually low grade and nonspecific, even in acute disease
Causes of exocrine pancreatic insufficiency	Often pancreatic acinar atrophy—increased prevalence in certain breeds (especially German Shepherd Dogs) End-stage chronic pancreatitis also common, underrecognized, particularly in middle-aged to older dogs of specific breeds (see text)	Most cases end-stage chronic pancreatitis Pancreatic acinar atrophy rare Occasionally due to raccoon pancreatic fluke (*Eurytrema procyonis*) in eastern United States.

TABLE 37.2

Differences Between Acute and Chronic Pancreatitis in Dogs and Cats

PARAMETER	ACUTE PANCREATITIS	CHRONIC PANCREATITIS
Histopathology	Varying degrees of acinar necrosis, edema, inflammation, with neutrophils and peripancreatic fat necrosis Potentially completely reversible, with no permanent pancreatic architectural or functional changes	Characterized by lymphocytic inflammation and fibrosis, with permanent disruption of architecture Possible to have acute-on-chronic cases with concurrent neutrophilic inflammation and necrosis
Clinical appearance	Spectrum from severe and fatal (usually necrotizing) to mild and subclinical (less common)	Spectrum from mild, low-grade intermittent gastrointestinal signs (most common) to acute-on-chronic episode indistinguishable from classic acute pancreatitis
Diagnostic challenge	Higher sensitivity of enzyme tests and ultrasonography than in chronic disease	Lower sensitivity of enzyme tests and ultrasonography than in acute disease: diagnosis much more challenging
Mortality and long-term sequelae	High immediate mortality but no long-term sequelae	Low mortality except acute-on-chronic bouts High risk of eventual exocrine and endocrine insufficiency

TABLE 37.3

Causes of Acute Pancreatitis in Dogs and Cats

RISK FACTOR	CAUSE
Idiopathic, 90%	Unknown (some may be hereditary or inherited susceptibility to environmental trigger)
Duct obstruction ± hypersecretion ± bile reflux into pancreatic duct	Experimental; neoplasia; surgery ± cholangitis + role in chronic pancreatitis
Hypertriglyceridemia	Inherent abnormal lipid metabolism (breed-related—e.g., Miniature Schnauzers) Endocrine—diabetes mellitus, hyperadrenocorticism, hypothyroidism
Breed, gender (?)	Increased risk in terriers ± spayed females—may reflect risk of hypertriglyceridemia in some (also Miniature Schnauzers; see above) and potentially other mutations (see text)
Diet	Dietary indiscretion, high-fat diet Malnutrition, obesity (?)
Trauma	Road traffic accident, surgery, high-rise syndrome
Ischemia, reperfusion	Surgery (not just pancreas), gastric dilation, volvulus; shock, severe immune-mediated hemolytic anemia (common association if anemia severe)
Hypercalcemia	Experimental (more common in cats than dogs); hypercalcemia of malignancy (uncommon association clinically); primary hyperparathyroidism
Drugs, toxins	Organophosphates, azathioprine, asparaginase, thiazides, furosemide, estrogens, sulfa drugs, tetracycline, procainamide, potassium bromide, clomipramine
Infections	Toxoplasma, others (uncommon)

Adapted from Villiers E, Blackwood L, editors: *BSAVA manual of canine and feline clinical pathology*, ed 2, Gloucestershire, Britain, 2005, British Small Animal Veterinary Association.

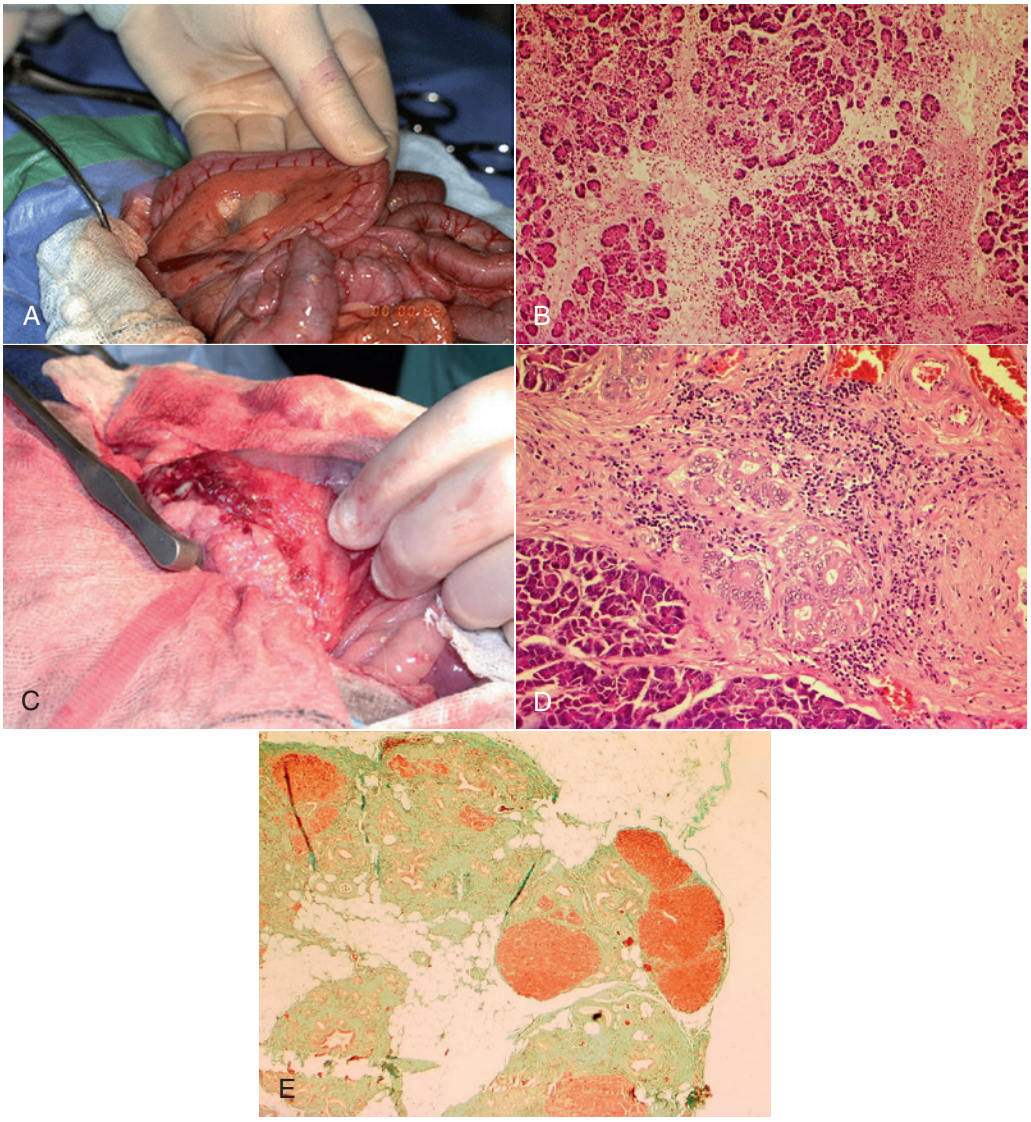


FIG 37.2
(A) Gross appearance of acute pancreatitis in a cat at laparotomy demonstrating generalized hyperemia. It is also possible for acute pancreatitis to appear normal grossly. **(B)** Histopathologic appearance of acute pancreatitis in a young adult female West Highland White Terrier. Note prominent edema and inflammation disrupting the acini. This case was fatal, but it would have been potentially completely reversible if the dog had survived the acute phase (hematoxylin and eosin [H&E], ×100). **(C)** Gross appearance of chronic pancreatitis in a middle-aged Jack Russell Terrier. Note the nodular appearance of pancreas and extensive adhesions to the duodenum obscuring the mesentery. It is also possible for chronic pancreatitis to appear normal grossly. **(D)** Histologic appearance of chronic pancreatitis from a 10-year-old male Cavalier King Charles Spaniel. Note fibrosis, mononuclear inflammatory cells, and ductular hyperplasia (H&E, ×200). **(E)** Histologic appearance of end-stage chronic pancreatitis in an 11-year-old neutered female Cavalier King Charles Spaniel with diabetes mellitus and exocrine pancreatic insufficiency. Note extensive fibrosis *(green)* and small islands of remaining acini *(red)* (Masson's trichrome, ×40). (**A** and **C,** From Villiers E, Blackwood L, editors: *BSAVA manual of canine and feline clinical pathology,* ed 2, Gloucestershire, Britain, 2005, British Small Animal Veterinary Association.)

may also be a trigger, particularly potassium bromide, azathioprine, or asparaginase in dogs. Concurrent endocrine diseases such as hypothyroidism, hyperadrenocorticism, or DM increase the risk of severe fatal pancreatitis in dogs; therefore it is important to identify these in the history. In cats the history may include features of concurrent cholangiohepatitis, inflammatory bowel disease, hepatic lipidosis, or any combination of these.

The clinical signs in dogs vary with the severity of the disease, from mild abdominal pain and anorexia to acute abdomen and potential MOF and DIC. Dogs with severe acute disease usually present with acute onset of vomiting, anorexia, marked abdominal pain, and varying degrees of dehydration, collapse, and shock. The vomiting is initially typical of delayed gastric emptying resulting from peritonitis, with emesis of undigested food a long time after feeding, progressing to vomiting only bile. The main differential diagnoses in these cases are other causes of acute abdomen, particularly intestinal foreign body or obstruction; the vomiting may be so severe that the dog may undergo an unnecessary laparotomy for a suspected obstruction if a careful workup was not performed first. Some patients may show the classic so-called praying stance, with the forelegs on the floor and the hind legs standing (Fig. 37.3), but this is not pathognomonic for pancreatitis and can be seen in association with any painful condition in the cranial abdomen, including hepatic, gastric, or duodenal pain. By contrast, cats with severe, fatal, necrotizing pancreatitis usually have surprisingly mild clinical signs, such as anorexia and lethargy; vomiting and abdominal pain occur in fewer than half of the cases. Unlike dogs, cats often demonstrate remarkably little abdominal pain on examination in spite of severe peritonitis.

At the milder end of the spectrum, dogs and cats may present with mild gastrointestinal signs, typically anorexia and sometimes some mild vomiting, followed by the passage of some colitic-like feces (e.g., tenesmus, hematochezia, frequent bowel movements) accompanied by some fresh blood because of local peritonitis in the area of the transverse colon. Inflammatory bowel disease, low-grade infectious enteritis, chronic food intolerance, and chronic hepatitis are major differential diagnoses for this presentation in dogs and cats. Animals that are still eating may show prominent postprandial discomfort.

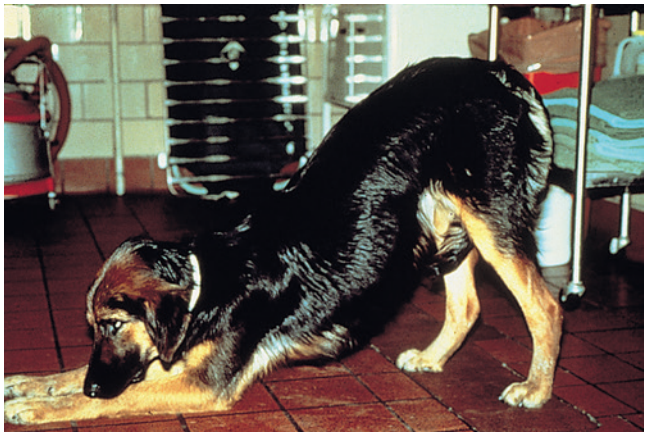


FIG 37.3
Dog exhibiting evidence of cranial abdominal pain by assuming the so-called position of relief. (Courtesy Dr. William E. Hornbuckle, Cornell University, College of Veterinary Medicine, Ithaca, NY.)

Cats and dogs with acute pancreatitis can present with jaundice at initial examination or often developing a few days later, when the initial acute signs are resolving. Most, if not all, animals with pancreatitis and jaundice have acute-on-chronic disease (see later, "Chronic Pancreatitis").

Careful clinical examination should focus on the identification of the degree of dehydration and shock, careful assessment for any concurrent diseases (particularly endocrine disease), and careful abdominal palpation. In severe cases, petechiae or ecchymoses suggestive of DIC may be identified, and there may be respiratory distress associated with acute respiratory distress syndrome. Careful clinical and clinicopathologic assessment of the degree of shock and concurrent organ damage is important for prognosis and treatment decisions (see later). Abdominal palpation should identify pancreatic pain and rule out, if possible, any palpable foreign bodies or intussusceptions, although abdominal imaging may be required to rule these out with confidence. In severe cases, generalized peritonitis will result in generalized unmistakable abdominal pain in dogs, whereas in milder cases careful palpation of the cranial abdomen is required to identify a focus of abdominal pain (Fig. 37.4); in cats, pain may not be apparent. Occasionally, a cranial abdominal mass representing a focus of fat necrosis may be palpated, particularly in cats.

Diagnosis

The clinician should be aware that there are many other diseases that produce similar clinical presentations to acute pancreatitis, and some of these might also be associated with elevations in pancreatic enzymes. Some form of diagnostic imaging is recommended together with blood sampling to rule out more serious primary diseases, such as a perforating foreign body.

Routine clinical pathology

Routine laboratory analysis (i.e., complete blood count [CBC], serum biochemical profile, and urinalysis) typically does not help in arriving at a specific diagnosis, but it is very important to perform these in all but the mildest cases because they provide important prognostic information and aid in effective treatment (see later). Typical clinicopathologic abnormalities in dogs and cats with acute pancreatitis are shown in Table 34.3.

Specific pancreatic enzyme assays

More specific tests for the pancreas are the catalytic assays for amylase and lipase, the new catalytic assay DGGR lipase and the immunoassays for trypsin-like immunoreactivity (TLI) and pancreatic lipase immunoreactivity (PLI). More



FIG 37.4
Carefully palpating a Cocker Spaniel for cranial abdominal pain. **(A)** The clinician should palpate craniodorsally under the rib cage for evidence of focal pancreatic pain, as shown in this dog by turning of the head. **(B)** With deep-chested dogs it helps to ask an assistant to elevate the head of the dog to displace the pancreas caudally (effectively achieving the opposite of the dog in Fig. 37.3).

details on these tests including the sensitivity and specificity in dogs and cats are found in Chapter 34 and Table 34.2. Overall, PLI has the highest sensitivity and likely the highest specificity in both species. DGGR lipase is also of diagnostic utility in both dogs and cats. Classical lipase has some usefulness in dogs but none in cats.

Prognostic indicators

Blood tests can give some prognostic indication in both species. TAP, the peptide removed from trypsin in the small intestine to activate it, is well conserved among species, so human enzyme-linked immunosorbent assays (ELISAs) can be used for dogs and cats. Elevations in plasma or urine TAP levels are no more sensitive or specific than currently available blood tests for the diagnosis of pancreatitis in dogs and cats, but do have some prognostic value. Of the individual diagnostic tests, the following were found to be negative prognostic indicators in dogs: high urinary TAP-to-creatinine ratio, marked increases in serum lipase activity, marked increases in serum creatinine and phosphate concentrations, and low urine specific gravity. A recent study identified hypothermia and metabolic acidosis as negative prognostic indicators in dogs with pancreatitis (Pápa et al., 2011), and another recent study also identified very marked elevations in canine PLI, thrombocytopenia, high urea or creatinine, and increased C-reactive protein concentrations on days 3 and 4 but not days 1 and 2 after admission as negative prognostic indicators in dogs with suspected but not confirmed acute pancreatitis (Sato et al., 2017). A clinical severity index with prognostic utility in dogs has been published, which takes into account renal and hepatic function, presence or absence of DM, blood pressure, and other local and systemic complications (Mansfield et al., 2008). In cats, the negative prognostic indicators found were low ionized calcium levels and leukopenia. Urinary or plasma TAP levels do not appear to be prognostically useful in cats, and neither does the degree of elevation of TLI in cats or dogs.

Diagnostic imaging

The most sensitive and easily accessible way to image the canine and feline pancreas noninvasively is by ultrasonography. Endoscopic ultrasound may be more sensitive but is only available in a small number of centers. Abdominal radiographs in patients with pancreatitis usually show mild or no changes, even in those with severe disease (Fig. 34.8). However, in patients with acute disease, abdominal radiography plays an important role in ruling out acute intestinal obstruction, which would result in obvious changes, primarily dilated, gas-filled, stacking loops of intestine and the presence of radiopaque foreign bodies. Typical radiographic changes in dogs and cats with acute pancreatitis are described in Chapter 34.

The most sensitive imaging modalities in humans with pancreatitis are magnetic resonance imaging (MRI), computed tomography (CT), and endoscopic ultrasonography (EUS). In addition, endoscopic retrograde cholangiopancreatography (ERCP) is performed in humans to image the ducts and enable tiny pancreatic biopsies to be taken via a small endoscope.

CT has so far proved disappointing in dogs and cats as detailed in Chapter 34. EUS is not widely available, although a recent study in Beagles indicated that the technique could visualize most of the pancreas, except the distal third of the right limb, and could be used to obtain fine-needle aspiration (FNA) samples (Kook et al., 2012). ERCP has been described in normal Beagles and in dogs with chronic gastrointestinal disease (Spillmann et al., 2004, 2005) but is technically difficult in dogs weighing less than 10 kg and carries a risk of worsening pancreatitis. Because all these techniques require general anesthesia, they may never become widely used in small animal patients with severe acute pancreatitis. Transcutaneous ultrasonography has a high specificity for pancreatic disease—if a lesion is found, it usually is real—but a variable sensitivity, depending on the skill of the operator and severity of the disease. Ultrasonography has a higher

sensitivity for typical acute pancreatitis in dogs and cats because associated edema and peripancreatic fat necrosis result in visible interfaces. The sensitivity is much lower for chronic and low-grade acute pancreatitis in cats and dogs (Fig. 37.5).

Fluid analysis

Some dogs and cats with pancreatitis have abdominal effusion. Fluid analysis usually reveals serosanguineous sterile exudates, although modified transudates and chylous effusions have also been reported in cats. Amylase and lipase concentrations in the fluid may be higher than in the serum, and high lipase concentrations in the effusion can be diagnostically helpful (Guija de Arespacochaga et al., 2006). Pleural effusions also occur in a small number of dogs with acute pancreatitis as a result of generalized vasculitis. More details are found in Chapter 34.

Histopathology

Definitive diagnosis of acute pancreatitis can be achieved only via histopathology of a pancreatic biopsy, but this is invasive and not indicated in most cases. However, if the animal has a laparotomy during the investigation, the clinician should always remember to inspect the pancreas visually and, preferably, to obtain a small biopsy. The pancreas usually appears grossly inflamed and may have a mass-like appearance. The latter is usually caused by fat necrosis and/or fibrosis and not neoplasia; therefore no animal should be euthanized on the basis of a tumor-like appearance in the pancreas without supportive cytology or pathology because large masses in the pancreas are very rarely tumors. Pancreatic neoplasia is usually so malignant that it will have metastasized widely and caused the animal's death before the mass becomes large. Indications and techniques for pancreatic biopsy are reviewed in Chapter 34.

However, in most cases, a biopsy will not be performed, and diagnosis is based on a combination of clinical suspicion, specific enzyme tests, and diagnostic imaging. No one noninvasive test is 100% sensitive and specific for pancreatitis in dogs and cats; in a few cases of even severe disease, all the tests may be negative.

Treatment and Prognosis

The treatment and prognosis of dogs and cats with acute pancreatitis depends on the severity of the condition at presentation. Severe acute pancreatitis is a very serious disease, has a very high mortality, and requires intensive management, whereas more moderate disease can be managed with intravenous (IV) fluids and analgesia, and patients with mild disease can sometimes be managed on an outpatient basis.

Cats with severe disease are more difficult to assess because of their mild clinical signs. It therefore seems prudent to assume that all cats have severe disease unless proved otherwise and treat them intensively, with the intent of preventing hepatic lipidosis and other fatal complications.

The inciting cause of the pancreatitis should be treated or removed in the few cases for which it is known (e.g., hypercalcemia or drug-induced), and every effort should be made during treatment to avoid further potential triggers, as outlined in Table 37.3. Most cases of pancreatitis are, however, idiopathic, and treatment is largely symptomatic. The one exception is chronic pancreatitis in English Cocker Spaniels, which may be an immune-mediated disease in which steroids and other immunosuppressive drugs may be indicated as a specific treatment (see later, "Chronic Pancreatitis," for more details). Occasionally, Cocker Spaniels with chronic pancreatitis present with acute clinical signs, and judicious corticosteroid therapy might be considered for them. However, there is no evidence that corticosteroid therapy is beneficial for other breeds of dogs, including Terriers; the

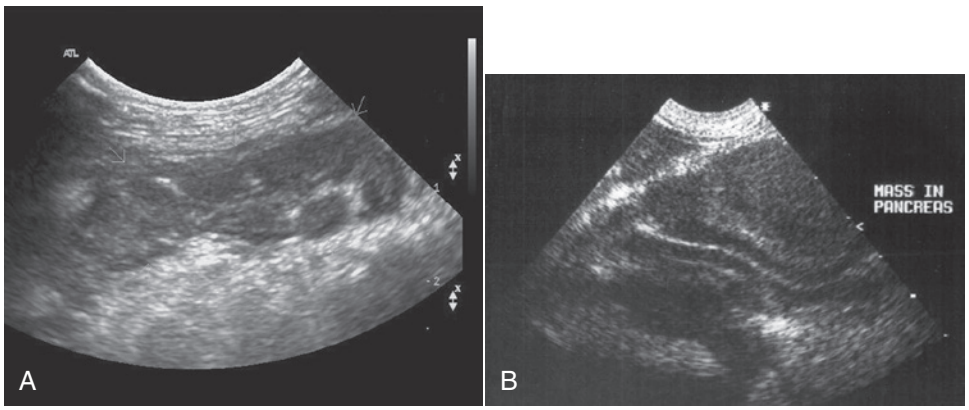


FIG 37.5
(A) Typical ultrasonographic appearance of acute pancreatitis in a Miniature Schnauzer with a diffusely hypoechoic pancreas *(gray arrows)* with surrounding hyperechoic mesentery. **(B)** Typical ultrasonographic appearance of chronic pancreatitis in an English Cocker Spaniel. There is a mass-like effect displacing the duodenum. Many dogs and cats with chronic pancreatitis have an unremarkable abdominal ultrasound. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.)

use of such drugs in them might actually worsen the prognosis by increasing the risk of gastric ulceration and reducing the activity of the reticuloendothelial system in the removal of circulating α_2-macroglobulin–protease complexes. In some cases, a dog or cat might need corticosteroid therapy for a concurrent condition, such as immune-mediated hemolytic anemia or inflammatory bowel disease, in which case the benefits of corticosteroids may outweigh their potential deleterious effects.

Severe, necrotizing pancreatitis carries a poor to very poor prognosis in cats and dogs. These patients have severe fluid and electrolyte abnormalities associated with systemic inflammatory disease, renal compromise, and a high risk of DIC. Intensive management is required, including plasma transfusions in many cases and enteral tube feeding or total parenteral nutrition (TPN) in some (see next section). These patients will likely benefit from referral to a specialist. If referral is not an option, intensive therapy can be attempted in the practice, but the owner must be warned of the very poor prognosis and expense of treatment. Severe acute pancreatitis also carries a poor prognosis in humans, but the mortality has been reduced in the last 5 years by a combination of early and aggressive IV fluid therapy and early feeding.

At the other end of the spectrum, patients with very mild pancreatitis may simply need hospitalization for 12 to 24 hours of IV fluid therapy if they are vomiting and dehydrated; if they are alert and well hydrated, they may be managed at home with 24 to 48 hours of pancreatic rest (fluids only by mouth) and analgesia, followed by long-term feeding of an appropriate diet.

It is important to give consideration to the following aspects of treatment in all patients: IV fluid and electrolyte replacement; analgesia; nutrition; and other supportive therapy, as indicated, such as antiemetics and antibiotics (see Box 37.1).

Intravenous fluids and electrolytes

IV fluid therapy is very important in all but the mildest cases of pancreatitis to reverse dehydration, address electrolyte imbalances associated with vomiting and fluid pooling in the hypomotile gastrointestinal tract, maintain adequate pancreatic circulation, and maintain effective peripheral circulation in the presence of the associated SIR. It is vital to prevent pancreatic ischemia associated with reduced perfusion because it contributes to necrosis. Replacement fluids (e.g., lactated Ringer's or Plasmalyte) are usually used at rates and volumes that depend on the degree of dehydration and shock—twice the maintenance rates (100-120 mL/kg/day) are adequate for mild to moderately affected animals (grades 0 and 1), but more severely affected animals may need initial shock rates (90 mL/kg/h for 30-60 minutes) followed by synthetic colloids. It is important to measure urine output concurrently. Rapid crystalloid infusion in severely affected animals that have a pathologic increase in vascular permeability carries an increased risk of pulmonary edema, so patients should be closely monitored; central venous pressure ideally should be measured in the most severely affected dogs and the fluid rate adjusted accordingly to maintain normal central venous pressure.

Serum electrolyte concentrations should be carefully monitored. Potential electrolyte abnormalities are outlined in Table 34.3, but the most clinically relevant is hypokalemia caused by vomiting and reduced food intake. Hypokalemia can significantly impair recovery and contribute to mortality because it causes not only skeletal muscle weakness but also gastrointestinal atony, which will contribute to the clinical signs of the disease and delay successful feeding. Aggressive fluid therapy further increases renal potassium loss, particularly in cats, so it is important to measure serum potassium concentrations frequently (at least daily while the patient is vomiting) and add supplemental potassium chloride to the fluids as necessary. A scaled approach is best, based on the degree of hypokalemia. Lactated Ringer's or Plasmalyte contains only 4 mEq/L potassium, and most cases require supplementing at least to replacement rates (20 mEq/L). Even if the serum potassium concentration cannot be measured, a vomiting anorexic dog with no evidence of renal failure should receive replacement rates of potassium in the fluids. More severely hypokalemic dogs should be supplemented more as long as serum concentrations can be measured regularly and infusion rates carefully controlled. A dog or cat with a serum potassium concentration of 2.0 mEq/L or less should receive between 40 and 60 mEq/L in the fluids at a controlled infusion rate. As a general rule, the infusion rate of potassium should still not be increased above 0.5 mEq/kg/h.

A plasma transfusion is likely indicated in dogs and cats with severe pancreatitis to replace α_1-antitrypsin and α_2-macroglobulin. It also supplies clotting factors and may be combined with heparin therapy in animals at high risk of DIC, although the efficacy of heparin therapy in DIC in humans and animals has been questioned, and there are currently no controlled trials that either support or refute its use for pancreatitis in dogs and cats (see Chapter 87).

Analgesia

Pancreatitis is usually a very painful condition. Hospitalized patients should be monitored carefully for pain, and analgesia should be administered as necessary. In practice, analgesia is indicated for almost all patients with pancreatitis and should be given routinely to cats with pancreatitis

BOX 37.1

Pillars of Treatment in Severe Acute Pancreatitis (see text for more details)

- Early, aggressive intravenous fluid therapy (monitor urine output and electrolytes)
- Analgesia (early and effective—assume pain unless proven otherwise)
- Early enteral feeding (as soon as rehydrated)

because their pain is difficult to assess. Morphine agonists or partial agonists are often used, particularly buprenorphine or butorphanol. Butorphanol also has antiemetic properties. These partial opiate agonists are effective for mild to moderate pain, but full opioid agonists are preferred in more severe pain. Morphine, methadone, meperidine, and fentanyl (IV or patches) can be used (Table 37.4). Concerns that the effects of opiates on the sphincter of Oddi might exacerbate disease have often been cited with regard to dogs and humans, but more recent studies have suggested minimal clinically relevant effects, except when high and repeated doses of morphine are used. These drugs are regularly used now in humans with pancreatitis, with no obvious problems. Fentanyl patches take time to achieve effect (on average, 24 hours in dogs and 7 hours in cats), so concurrent use of an opiate for the first few hours after application is recommended.



TABLE 37.4

Analgesics Used for Acute Pancreatitis

ANALGESIC	INDICATIONS AND CAUTIONS	DOSAGE AND ROUTE		COMMENTS
		DOGS	CATS	
Buprenorphine	Most generally useful analgesic in hospitalized patient May be dosed transmucosally at home in both dogs and cats but dog dose much higher	IV, SC, IM, 0.01-0.02 mg/kg Oral transmucosal dose 0.12 mg/kg	IV, SC, IM same as for dogs Oral transmucosal dose 0.01-0.03 mg/kg*	Concerns about effects on sphincter of Oddi largely unfounded
Butorphanol	Author has limited experience with its use; other opiates preferred in acute pancreatitis because of butorphanol's limited analgesic effect and potentially negative cardiovascular effects (see notes); however, additional antiemetic effect may be beneficial	0.05-0.6 mg/kg IM, SC, IV, q6-8h; 0.1-0.2 mg/kg/h as CRI Oral—0.5-1 mg/kg q6-12h	Same as for dogs	At analgesic doses in humans, increases pulmonary artery pressure and cardiac work, unlike other analgesics in the table, so other opiates preferred
Meperidine (Demerol)	Meperidine by injection only, hence hospitalized animals Not for IV administration (causes histamine release and results in profound hypotension)	5 mg/kg SC, IM, q2h	3-5 mg/kg SC, IM, q2h	Painful on injection Derived from atropine; therefore, in contrast to other opioids, is spasmolytic agent on smooth muscle; might be useful for the gut
Morphine	Vomiting common Useful for severe acute pain, can be given by slow IV injection to effect	0.1-0.5 mg/kg SC, IM, IV, 0.1 mg/kg/h by constant rate infusion	0.1-0.2 mg/kg SC, IM, IV	Stimulation of sphincter of Oddi reported in humans but of dubious relevance for dogs and cats
Methadone	Little nausea or vomiting, so more useful than morphine	0.2-0.4 mg/kg SC, IM, q4-6h or as required	0.2 mg/kg SC, IM, q4-6h or as required	Can produce dysphoria May get increased duration of action with repeated doses
Hydromorphone		0.05 mg/kg IV q4h; 0.1-0.4 mg/kg IM	0.1 mg/kg IM q7h	Can produce dysphoria
Fentanyl patch	Very useful, but take great care if sending home with patch	2-4 µg/kg/h patch	25 µg/h patch with half exposed	24-hour onset and 72-hour duration in dogs; 7-hour onset and 72-hour duration in cats

Continued

TABLE 37.4

Analgesics Used for Acute Pancreatitis—cont'd

ANALGESIC	INDICATIONS AND CAUTIONS	DOSAGE AND ROUTE		COMMENTS
		DOGS	CATS	
Tramadol	Author has no personal experience with this drug in acute pancreatitis but may be useful drug for home use orally for mild to moderate pain	Oral—2-5 mg/kg q8-12h	Oral—2-4 mg/kg q8-12h	Tramadol also decreases cardiac contractility; should not be used in acute phase when myocardial depressant factor may be released Published studies on pharmacokinetics in small animals suggest that should be more effective in cats than dogs due to rapid metabolism in dogs to inactive metabolites. Dysphoria more likely in cats
Ketamine infusion	Severe refractory pain in hospitalized patient	2 µg/kg/min	Same as for dogs	Useful as adjunct, probably not suitable as sole analgesic; can produce dysphoria at higher infusion rates
Lidocaine infusion	Excellent analgesic for hospitalized patients	Bolus of 1 mg/kg IV followed by 20-µg/kg/min infusion	0.1 mg/kg/h	Use with caution in cats because of lidocaine toxicity
Acetaminophen (Paracetamol)	Most widely used NSAID for human pancreatitis; often neglected in dogs, but useful because it does not have same deleterious effects on GI tract and kidneys as other nonsteroidals	10 mg/kg PO, IV, q12h	**Do not use**—toxic in cats	Should not be used if significant concurrent liver disease
Carprofen and other nonsteroidal antiinflammatory drugs (NSAIDs)	Mainly for home use; used with great care because of potential gut and renal side effects in pancreatitis; not for use in acute disease or in presence of concurrent hyperadrenocorticism or steroid treatment	Carprofen—4 mg/kg SC, IV, PO, q24h; maintain on 2 mg/kg q12h	Carprofen—2 mg/kg SC, IV, PO; maintain on 2 mg/kg	Underestimated efficacy COX 1:2 inhibition ratio of 65

COX, Cyclooxygenase; *CRI,* constant rate infusion; *GI,* gastrointestinal.

With thanks to Dr. Jackie Brearley, Senior Lecturer in Veterinary Anaesthesia, the Queen's Veterinary School Hospital, University of Cambridge, Cambridge, England.

*Robertson SA et al: Systemic uptake of buprenorphine by cats after oral mucosal administration, *Vet Rec* 152:675, 2003.

Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided, if possible, because of the increased risk of gastroduodenal ulceration in patients with pancreatitis and the potential of some NSAIDs to precipitate renal failure in animals with hypotension and/or shock. In humans, acute pancreatitis has been associated with the use of NSAIDs. Cyclooxygenase-2 (COX-2) inhibitors have a lower risk ratio than the conventional NSAIDs in this respect, as does acetaminophen if used carefully (see Table 37.4). Alternative analgesics that could be considered in severe cases include a low-dose IV ketamine infusion, which has the advantage of minimal effect on gastrointestinal motility (Fass et al.,

1995), or IV lidocaine. Details of analgesia are given in Table 37.4.

Providing analgesia that can be dispensed for the client to take home for patients with milder or resolving disease can be a challenge. The pain should not be underestimated in these patients. However, it is difficult to find effective and safe analgesia that can be dispensed for use at home. Administration of opioids during visits to the clinic is prudent, and one of the less ulcerogenic NSAIDs or acetaminophen could be used cautiously at home. Cats can be effectively dosed with buprenorphine transmucosally (Robertson et al., 2003), allowing simple home medication, but the oral route requires much larger doses in dogs (Abbo et al., 2008) (see Table 37.4). Anecdotally, tramadol has been found to be helpful for some dogs and cats, but its efficacy is variable. Feeding a low-fat diet helps reduce postprandial pain in humans and anecdotally helps some dogs. However, administering pancreatic enzymes in the food does not seem to reduce pain in dogs, and there is little evidence to support their use for pain relief in dogs or cats.

Nutrition

It is very important to consider appropriate nutritional management of the patient with pancreatitis. Complete pancreatic rest by starvation, avoiding anything by mouth (including water or barium), has traditionally been advised for patients with acute pancreatitis. Initially, it was believed that early enteral nutrition was contraindicated because it was likely to result in cholecystokinin and secretin release, with the consequent release of pancreatic enzymes and worsening of pancreatitis and associated pain. TPN seemed a more logical route early in the disease process, with jejunal tube feeding later in the disease aiming to bypass the areas of pancreatic enzyme stimulation. However, recent studies in humans and also experimental models in dogs have strongly supported early enteral nutrition over TPN; early enteral nutrition in humans with severe acute pancreatitis has been found to reduce the length of hospital stay and decrease mortality.

Current recommendations for feeding veterinary patients with acute pancreatitis are outlined in Box 37.2. It is no longer appropriate or acceptable to starve the patient for a



BOX 37.2

Best Practice for Feeding Patients With Acute Pancreatitis

Recent studies and meta-analyses of studies of nutrition in human acute pancreatitis have led to changes in advice for best-practice feeding in these cases (Al-Omran et al., 2010; Quan et al., 2011). Note that early enteral nutrition is particularly indicated for severe disease, which is perhaps unexpected and counter to recent practice in dogs.

When to Feed?

- Early enteral nutrition reduces mortality and hospitalization time in humans with severe acute pancreatitis and is supported by experimental studies in dogs and studies in canine parvovirus enteritis (Mohr et al., 2003). Start enteral nutrition within 24 to 48 hours, once the animal is rehydrated.
- In mild acute pancreatitis in humans, current best practice is to withhold food in many patients for a little longer, and this is also recommended in dogs to reduce pain and vomiting. Fluids, electrolytes, and analgesics are delivered for 2 to 5 days while the patient is fasted, and then a diet rich in carbohydrate and moderate in fat and protein is initiated with discharge on a normal diet within 4 to 7 days.
- In cats, current anecdotal recommendations are to feed immediately in mild, moderate, and severe pancreatitis because of the high risk of hepatic lipidosis.

How to Feed?

- Multiple studies show better outcomes with enteral compared with parenteral nutrition in humans and experimental dogs due to maintenance of gut wall barrier and reduced bacterial translocation, so enteral is preferred.
- Severe, acute cases will likely need tube feeding. Nasoesophageal tubes are best in the acute stages to avoid the risk of general anesthetic in a dog or cat with multiorgan failure. Longer term, most animals will eat voluntarily, but if necessary, an esophageal or gastrostomy feeding tube can be placed (see Chapter 35 for more details). Recent studies support prepyloric feeding as safe in humans and dogs—jejunostomy tube placement is not necessary (Mansfield et al., 2011).

What to Feed?

- Studies show that high dietary fat increases postprandial pain but does not worsen the pancreatitis. Dogs and cats with severe, acute pancreatitis can be fed any appropriate diet provided they are receiving sufficient analgesia. Tube feeding may require a high-fat convalescence-type diet down a tube, such as Hills a/d diet or Royal Canin convalescence support. The new Royal Canin GI low-fat liquid diet would be particularly appropriate.
- Low-fat diets are indicated in milder pancreatitis in dogs and for recovery at home, to reduce postprandial pain.
- There is no convincing evidence for addition of immune-modulating ingredients such as glutamine or omega-3 fatty acids. Probiotics are best avoided in acute disease (one study in humans showed an increase in mortality when probiotics were used in severe acute pancreatitis [Besselink et al. 2008]).
- Addition of pancreatic enzymes during the acute phase is wise, as they will not be secreted down the duct.

long period while awaiting the resolution of disease. Increasing evidence is accumulating in human medicine about the importance of early enteral nutrition in patients with pancreatitis; the more severe the pancreatitis, the earlier nutrition support should be instituted. Furthermore, recent studies suggest that prepyloric (e.g., nasoesophageal or gastrostomy tube) feeding may be as safe as jejunal feeding. There is little evidence that immunomodulating nutrients are of benefit, and data on probiotics in pancreatitis are conflicting, with one study showing increased mortality in humans (Besselink et al., 2008), so these are best avoided. There have been no studies evaluating the efficacy of early or late enteral or parenteral nutrition in naturally occurring pancreatitis in dogs or cats. Therefore the advice currently given is based on anecdotal evidence, extrapolation from humans, and experimental studies in dogs. However, a recent pilot study comparing early enteral nutrition via esophagostomy tube with parenteral nutrition in 10 dogs with severe acute pancreatitis found that prepyloric tube feeding of a low-fat canine diet, with added pancreatic enzymes and medium-chain triglycerides, was well tolerated by dogs with acute pancreatitis. The dogs receiving enteral nutrition did not show obvious postprandial pain, and a significantly greater number of dogs in the parenteral group showed vomiting and regurgitation compared with those in the enteral group (Mansfield et al., 2011).

Starvation is also contraindicated in cats with acute pancreatitis because of the high risk of concurrent hepatic lipidosis. Current advice is therefore to institute some form of enteral feeding, whenever possible, within 48 hours in dogs and cats. The more severe the disease, the more important it is to feed early. In severe cases this is best achieved with nasoesophageal tube feeding by slow continuous infusion of a critical care diet, although frequent small-volume feeds are also well tolerated by many patients. Anesthesia to place an esophagostomy or gastrostomy tube is best avoided in the acute stages of pancreatitis but is indicated for longer-term feeding, if necessary, in a more stable patient. High-fat critical-care diets are potentially associated with increased pain but are tolerated in hospitalized animals with adequate analgesia. Once the animal is eating voluntarily, it can be transitioned on to a lower-fat diet for recovery. A good initial choice is baby rice mixed with water, followed by a low-fat proprietary veterinary diet (e.g., Eukanuba Intestinal Formula, Mars Petcare; Hill's i/d Low Fat, Hill's Pet Nutrition, Topeka, KN; Royal Canin Digestive Low Fat, Royal Canin USA, St. Charles, MO; Purina EN Gastroenteric Canine Formula, Nestlé SA, Vevey, Switzerland) (Fig. 37.6). It may not even be necessary to use a low-fat diet. There is no evidence that standard diets increase the severity of disease in patients with acute pancreatitis, so a liquid critical care diet should also be tolerated if given in small amounts and often. However, there is evidence in humans that higher-fat diets increase pain and prolong hospitalization times for this reason, which also appears to be anecdotally true in dogs. Addition of pancreatic enzymes to the diet is wise in the very acute phases of the disease when the pancreas is not secreting enzymes down the duct. Concurrent antiemetics are also essential to allow effective feeding in many cases (see next section). In patients for which enteral nutrition is not possible or when only a small percentage of the daily caloric requirements can be given enterally, some form of supplemental parenteral nutrition should be considered. This is administered most practically as peripheral parenteral nutrition (Chandler et al., 2000). However, it is very clear that recovery is improved if at least some of the daily calorie intake can be given enterally.

Antiemetics

Antiemetics are often necessary to manage acute vomiting in dogs and cats with pancreatitis. The neurokinin (NK1) receptor antagonist maropitant has central and peripheral antiemetic effects, and seems to be the most effective antiemetic in dogs and cats with pancreatitis. Maropitant is



FIG 37.6
Baby rice is a good first choice for feeding dogs with moderate acute pancreatitis because it contains no fat and protein. It comes as a finely ground rice powder **(A)** that can then be mixed with water and, if desired, a gravy substitute such as Bovril **(B)** to enhance the flavor for feeding. Dogs with severe acute pancreatitis should be tube fed a critical-care diet (see text and Box 37.2).

available as Cerenia (Zoetis, Madison, NJ) in an injectable solution (10 mg/mL) or as tablets (16, 24, 60, and 160 mg). The dose of injection is 1 mg/kg (1 mL/10 kg body weight q24h for up to 5 days). The dose of the tablets is 2 mg/kg q24h for up to 5 days. Maropitant also has potential analgesic properties because substance P, which acts on the NK1 receptor, is involved in pancreatic pain, but no clinical studies have demonstrated its efficacy. It would be indicated as part of multimodal analgesia in animals with acute pancreatitis and would not be sufficient alone.

Metoclopramide has been used successfully in dogs with pancreatitis (0.5–1 mg/kg, administered intramuscularly, subcutaneously, or orally [PO] q8h, or 1–2 mg/kg, administered intravenously over 24 hours as a slow infusion), but its effect on stimulating gastric motility may increase pain and pancreatic enzyme release in some animals. It is also of limited efficacy in cats. Butorphanol, used as an analgesic in animals with pancreatitis causing mild to moderate pain, also has antiemetic properties. A phenothiazine antiemetic such as chlorpromazine may be more effective for some patients, but phenothiazines have sedative and hypotensive effects, which may be particularly marked if they are used together with opioid analgesia, so care should be taken in these cases. 5-HT_3 receptor antagonists such as ondansetron are useful for other types of vomiting in dogs (e.g., chemotherapy-induced emesis) but are best avoided in pancreatitis because they have occasionally been reported to trigger pancreatitis in humans.

Gastroprotectants

Patients with acute pancreatitis have an increased risk of gastroduodenal ulceration, probably caused by local peritonitis. They should be monitored carefully for evidence of melena or hematemesis and treated as necessary with sucralfate and acid secretory inhibitors (e.g., H_2 blockers such as cimetidine, famotidine, ranitidine, or nizatidine, or the proton pump inhibitor omeprazole). Cimetidine should be avoided in animals with concurrent liver disease because of its effect on the cytochrome P-450 system. Ranitidine can be used instead in these animals, but its additional gastric prokinetic effect can cause vomiting in some individuals; it should be discontinued if this occurs. Famotidine is preferable because it does not have these prokinetic effects.

Antibiotics

Infectious complications are reportedly rare in dogs and cats with pancreatitis, but when they occur, they can be serious; the efficacy of antibiotic therapy in preventing such complications remains contentious in humans. Nonetheless, most veterinary experts advise the use of broad-spectrum antibiotics prophylactically in dogs and cats with severe acute pancreatitis. IV potentiated amoxicillin is most often used. Fluoroquinolones penetrate the pancreas well, but responsible antibiotic use indicates that these should not be used as first-line antibiotic treatment unless there is a specific indication. Animals at the milder end of the disease spectrum do not require antibiotic therapy.

Treatment of biliary tract obstruction associated with pancreatitis

Most cases of extrahepatic biliary obstruction secondary to acute-on-chronic pancreatitis resolve with conservative management; surgical or needle decompression of the gallbladder and stenting of the bile duct are usually unnecessary in dogs and cats. In humans it has now been demonstrated that there is no advantage to surgical intervention in most patients and no difference in the severity and chronicity of secondary liver disease between those treated medically and those treated surgically, provided that there is no neoplasia and the jaundice resolves within a month (Abdallah et al., 2007). No such study has been undertaken in small animals, so treatment advice is empiric; if the feces remain colored (not white or acholic, which implies complete biliary obstruction) and the jaundice gradually resolves over a week to 10 days, then surgical intervention is not indicated and conservative management with antioxidants and ursodeoxycholic acid is advised (see Chapters 35 and 36).

CHRONIC PANCREATITIS

Etiology and Pathogenesis

Chronic pancreatitis is defined as "a continuing inflammatory disease characterized by the destruction of pancreatic parenchyma leading to progressive or permanent impairment of exocrine or endocrine function, or both" (Etemad et al., 2001). The gold standard for diagnosis is histology (see Fig. 37.2), but this is rarely indicated or performed in dogs or cats. Noninvasive diagnosis is difficult with the currently available diagnostic imaging, and clinicopathologic testing has a lower sensitivity than for acute disease.

Chronic pancreatitis has been considered a rare and not particularly important disease in dogs, whereas it is recognized as the most common form of pancreatitis in cats. However, the early literature published on canine pancreatic disease in the 1960s and 1970s recognized it as a common disease of clinical significance. It was noted that a high proportion of cases of EPI in dogs were caused by chronic pancreatitis, and it might be responsible for 30% of cases of DM or more. More recent pathologic and clinical studies in both dogs (Bostrom et al., 2013; Newman et al., 2004; Watson et al., 2007, 2011) and cats (De Cock et al., 2007) have reconfirmed it as a common and clinically relevant disease in dogs and cats. It is likely to cause intermittent and/or ongoing recurrent gastrointestinal signs and epigastric pain in many dogs and cats, but it is frequently underrecognized because of the difficulty of obtaining a noninvasive diagnosis. In dogs the postmortem prevalence of chronic pancreatitis is up to 34%, particularly in susceptible breeds, and even in studies of fatal acute pancreatitis, acute-on-chronic disease accounts for 40% of cases. In cats an even higher postmortem prevalence of chronic pancreatitis of 60% has been reported. It must be noted that postmortem studies tend to overestimate the prevalence of chronic diseases, which leave permanent

architectural changes in the organ, whereas the prevalence of acute, totally reversible diseases will be underestimated unless the animal dies during the episode. Nevertheless, it is clear that there are many more cases of chronic pancreatitis in veterinary practice than currently recognized, and a number of these are clinically relevant.

Idiopathic chronic pancreatitis

As in acute pancreatitis, the cause of chronic pancreatitis in dogs is usually unknown. Any age or breed of dog can be affected, but in Britain the most typical is a middle-aged to old dog, particularly a Cavalier King Charles Spaniel, Cocker Spaniel, Collie, or Boxer (Watson et al., 2007, 2010; Fig. 37.7). One recent study in the United States suggested that breeds defined by the American Kennel Club as toy and nonsporting breeds have a higher prevalence of chronic pancreatitis (Bostrom et al., 2013). An independent large study of EPI in Britain found an increased prevalence in older Cavalier King Charles Spaniels, supporting a breed association. Other parts of the world have also reported a high prevalence in Arctic-type breeds such as Siberian Huskies. There is likely to be some overlap with acute disease, although some cases will have a separate etiology. In humans, both genetic and environmental factors determine whether recurrent acute pancreatitis becomes more chronic with development of fibrosis. One environmental factor predisposing to fibrosis is smoking, which may also be relevant in dogs that can be passive smokers, but no studies have yet investigated this. Some cases are chronic from the outset, with an initial mononuclear infiltrate. Genetic causes are likely to be important in dogs, which explains the high risk in certain breeds. No particular breed prevalence has been reported for cats with chronic pancreatitis; domestic shorthairs are most commonly affected.



FIG 37.7
Eight-year-old neutered male English Cocker Spaniel with chronic pancreatitis.

Autoimmune chronic pancreatitis

The particular form of chronic pancreatitis recognized in English Cocker Spaniels in Britain is thought to be an immune-mediated disorder (Watson et al., 2011; see Fig. 37.7). As in human autoimmune pancreatitis, it typically affects middle-aged to older dogs, with a higher prevalence in males, and at least 50% of affected dogs subsequently develop DM, EPI, or both. Dogs also often have another concurrent autoimmune disease, particularly keratoconjunctivitis sicca and glomerulonephritis. There may also be an association with anal sacculitis and increased risk of anal sac carcinoma. There is often a mass-like lesion on ultrasonography (see Fig. 37.5, *B*). Biopsies show a typical perilobular, diffuse, fibrotic, and lymphocytic disease centered on perilobular ducts and vessels, with loss of large ducts. Immunohistochemistry shows a preponderance of duct- and vein-centered CD3+ lymphocytes (i.e., T cells). The disease in humans is believed to be a duct-centered immune reaction. Recent work has identified a strong association with plasma cells that secrete one subgroup of immunoglobulin G, IgG4. The disease in humans has been redefined as multisystemic because of the frequent involvement of other organs. It is now defined as IgG4-related disease (Bledsoe et al., 2018), and concurrent keratoconjunctivitis sicca, sialoadenitis, biliary tract disease, and glomerulonephritis are common. Early work in English Cocker Spaniels also shows IgG4-positive plasma cells in the pancreas and kidney (Watson et al., 2012). The disease in humans responds well to steroid therapy, including a reduction in insulin requirements in some diabetics. This is clearly differentiated from the proposed autoimmunity in young German Shepherd Dogs with pancreatic acinar atrophy (PAA), which is acinar-centered and does not result in DM (see later). There are not yet any controlled trials evaluating the use of immunosuppressive drugs in English Cocker Spaniels with chronic pancreatitis, but there is now enough circumstantial evidence to justify their use in this particular breed, and the author has had anecdotal success with both prednisolone and cyclosporine therapy in affected dogs. The decision to start immunosuppressive therapy is based on clinical severity including the presence of recurrent bouts of pancreatitis and/or renal involvement with marked proteinuria nonresponsive to conventional therapies. As in humans, less severely affected cases can be treated symptomatically and with "watchful waiting" (Bledsoe et al., 2018). However, the clinician should note that many cases of chronic pancreatitis in dogs are not autoimmune; most terriers in Britain, for example, have a different histopathologic and clinical picture of disease that does not appear to be autoimmune. Confirmation of autoimmune disease requires histologic confirmation, which is rarely available. In the absence of pancreatic histopathology, presence of autoimmune disease in other organs (for example, keratoconjunctivitis sicca and glomerulonephritis) is highly suggestive and justifies the use of immunosuppressives. The use of immunosuppressives in dogs that are not Cocker Spaniels with isolated chronic pancreatitis is not recommended.

Clinical Features

Dogs with chronic pancreatitis, regardless of the cause, usually present with mild intermittent gastrointestinal signs. Typically, they have bouts of anorexia, occasional vomiting, mild hematochezia, and obvious postprandial pain, which often go on for months to years before a veterinarian is consulted. The trigger for finally seeking veterinary attention is often an acute-on-chronic bout or the development of DM or EPI. The main differential diagnoses in the low-grade cases are inflammatory bowel disease and primary gastrointestinal motility disorders. Dogs may become more playful and less picky with their food when they are switched to a low-fat diet, which suggests that they previously had postprandial pain. Chronic epigastric pain is a hallmark of the human disease and is sometimes severe enough to lead to opiate addiction or surgery, so it should not be overlooked or underestimated in small animal patients. In more severe, acute-on-chronic cases, the dogs are clinically indistinguishable from those with classic acute pancreatitis (see earlier), with severe vomiting, dehydration, shock, and potential MOF. The first clinically severe bout tends to come at the end of a long subclinical phase (often years) of quietly progressive and extensive pancreatic destruction in dogs. It is important for clinicians to be aware of this because these dogs are at much higher risk for developing exocrine and/or endocrine dysfunction than those with acute pancreatitis; in addition, they usually already have protein-calorie malnutrition at presentation, which makes their management even more challenging. It is also relatively common for dogs with chronic pancreatitis to present first with signs of DM and a concurrent acute-on-chronic bout of pancreatitis resulting in a ketoacidotic crisis. In some dogs there are no obvious clinical signs until the development of EPI, DM, or both. The development of EPI in a middle-aged to older dog of a breed not typical for PAA has to increase the index of suspicion for underlying chronic pancreatitis. The development of EPI or DM in a dog or cat with chronic pancreatitis requires the loss of approximately 90% of exocrine or endocrine tissue function, respectively, which implies considerable tissue destruction and end-stage disease.

In cats the clinical signs of chronic pancreatitis are usually mild and nonspecific. This is not surprising considering that cats display mild clinical signs, even in association with acute necrotizing pancreatitis. One study showed that the clinical signs of histologically confirmed chronic nonsuppurative pancreatitis in cats were indistinguishable from those of acute necrotizing pancreatitis (Ferreri et al., 2003). However, chronic pancreatitis in cats is significantly more often associated with concurrent disease than acute pancreatitis, particularly inflammatory bowel disease, cholangiohepatitis, hepatic lipidosis, and/or renal disease. The clinical signs of these concurrent diseases may predominate, further confusing diagnosis. Nevertheless, some cats will eventually develop end-stage disease, with resultant EPI and/or DM.

Chronic pancreatitis is the most common cause of extrahepatic biliary obstruction in dogs (see Chapters 33 and 36), and dogs and cats with acute-on-chronic pancreatitis frequently develop jaundice.

Diagnosis

Noninvasive diagnosis

In the absence of a biopsy, which is the gold standard, the clinician must rely on a combination of clinical history, ultrasonography, and clinical pathology. The findings on diagnostic imaging and clinical pathology are similar to those outlined earlier (see "Acute Pancreatitis" and Tables 34.2 and 34.3). However, changes tend to be less marked in dogs and cats with chronic pancreatitis, and the diagnostic sensitivity of all tests is lower. Ultrasonography has a lower sensitivity in cats and dogs with chronic disease because there is less edema than in those with acute disease. A variety of ultrasonographic changes may be seen in patients with chronic pancreatitis, including a normal pancreas, mass lesion, mixed hyperechoic and hypoechoic appearance to the pancreas, and sometimes an appearance resembling that of typical acute pancreatitis, with a hypoechoic pancreas and a bright surrounding mesentery (Watson et al., 2011; see Fig. 37.5). In addition, in patients with chronic disease, adhesions to the gut may be apparent, and the anatomy of the pancreatic and duodenal relationship may be changed by these adhesions. Some patients, particularly English Cocker Spaniels, have large mass-like lesions associated with fibrosis and inflammation; some have tortuous and dilated, irregular ducts; and many patients have completely normal pancreatic ultrasonographic findings in spite of severe disease.

Similarly, clinical pathology can be helpful, but the results may also be normal. Increases in pancreatic enzyme levels are most likely to be seen during an acute-on-chronic bout than during a quiescent phase of disease, similar to the waxing and waning increases in liver enzyme levels in patients with ongoing chronic hepatitis. Again, similar to the situation in hepatic cirrhosis, in end-stage chronic pancreatitis there may not be enough pancreatic tissue left to cause increases in enzyme levels, even in acute flare-ups. On the other hand, occasionally the serum TLI level can temporarily increase into or above the normal range in dogs with EPI as a result of end-stage chronic pancreatitis, confusing the diagnosis of EPI in these dogs. cPLI appears to have the highest sensitivity for the diagnosis of canine chronic pancreatitis, but even this has a lower sensitivity than in acute disease. The diagnostic sensitivity of feline PLI for chronic pancreatitis in cats is unknown.

It is important to measure serum vitamin B_{12} concentrations in dogs and cats with chronic pancreatitis. The gradual development of EPI, often combined with concurrent ileal disease, particularly in cats, predisposes to cobalamin deficiency (see later, "Exocrine Pancreatic Insufficiency"). If the serum vitamin B_{12} concentration is low, cobalamin should be supplemented parenterally (0.02 mg/kg, administered intramuscularly or subcutaneously every 2 weeks in dogs and cats until the serum concentration is normalized). Oral

cobalamin may also be effective: see section on treatment of exocrine pancreatic insufficiency for doses.

Biopsy

The diagnosis of chronic pancreatitis can be difficult in dogs and cats, and these difficulties in diagnosis likely result in underrecognition of the disease. Establishing a definitive diagnosis relies on obtaining a pancreatic biopsy. However, this will not be indicated in most cases until there is an effective treatment, because a biopsy is a relatively invasive procedure; the results do not alter treatment or outcome, except perhaps in English Cocker Spaniels. However, with the potential for more specific therapies, routine biopsy may be indicated in the future. In humans the preferred method is needle biopsy via transendoscopic ultrasonographic guidance. Transendoscopic ultrasonography is expensive and of limited availability in veterinary medicine, so in dogs and cats surgical or laparoscopic biopsies remain the most applicable. Cytology of ultrasonography-guided transcutaneous FNA of the pancreas may help differentiate neoplasia or dysplasia from inflammation, but veterinary experience in this area is limited. If the clinician is performing a laparotomy to obtain other biopsies, it makes perfect sense to obtain a pancreatic biopsy at that time as well. Pancreatitis is not a risk, provided the pancreas is handled gently and the blood supply is not disrupted. However, the biopsy should be small and from the tip of a lobe; this might therefore miss the area of disease, which is usually patchy, particularly early on, and can also be centered on large ducts. Unfortunately, even biopsy has its limitations.

Treatment and Prognosis

Dogs and cats with chronic intermittent pancreatitis may have intermittent bouts of mild gastrointestinal signs and anorexia, and often the owner's primary concern is that the pet has missed a meal. These animals can be managed at home, as long as anorexia is not long-lasting, and the owner should be reassured that a short period of self-induced starvation is not harmful.

As for patients with acute pancreatitis, treatment is largely symptomatic. Dogs and cats with acute flare-ups require the same intensive treatment as cats and dogs with classic acute pancreatitis and have the same risk of mortality (see earlier). The difference from isolated acute pancreatitis is that if the animal recovers from the acute bout, it is likely to remain with considerable exocrine and/or endocrine functional impairment. In the milder cases, symptomatic treatment can make a real difference in the animal's quality of life. Changing to a low-fat diet (e.g., Hill's i/d Low Fat, Royal Canin Digestive Low Fat, or Eukanuba Intestinal) may often reduce postprandial pain and acute flare-ups. Owners often underestimate the effects of fatty treats, which can precipitate a recurrence in susceptible individuals. Some animals need analgesia, intermittently or continuously (see "Acute Pancreatitis" and Table 37.4). According to anecdotal reports, short courses of metronidazole (10 mg/kg PO q12h) seem to help some patients, particularly Cavalier King Charles Spaniels after acute bouts, presumably because they develop secondary bacterial overgrowth as a result of a stagnant loop phenomenon in the adjacent duodenum. The serum vitamin B_{12} concentration should be measured regularly, and cobalamin should be supplemented parenterally as necessary (0.02 mg/kg IM every 24 weeks until serum concentration normalizes). Oral cobalamin may also be effective: see section on treatment of exocrine pancreatic insufficiency for doses. The treatment of suspected autoimmune pancreatitis in English Cocker Spaniels is detailed in an earlier section.

The treatment of extrahepatic biliary tract obstruction associated with acute-on-chronic disease should be as given in the acute pancreatitis section, and most patients can be managed medically. In patients with end-stage disease, exocrine and/or endocrine deficiency may develop. Dogs and cats with EPI and/or DM are managed with the administration of enzymes (see later) and insulin as necessary in the usual way (see Chapter 49). Most do surprisingly well over the long term.

EXOCRINE PANCREATIC INSUFFICIENCY

EPI is a functional diagnosis that results from a lack of pancreatic enzymes. As such, unlike pancreatitis, it is diagnosed on the basis of clinical signs and pancreatic function test results and not primarily by the results of pancreatic histopathology. However, finding a marked reduction in pancreatic acinar mass on histology is supportive of a diagnosis of EPI. The pancreas is the only significant source of lipase, so fat maldigestion with fatty feces (steatorrhea) and weight loss are the predominant signs of EPI.

Pathogenesis

PAA is believed to be the predominant cause of EPI in dogs, but studies have shown that end-stage chronic pancreatitis is also important (Fig. 37.8; Batchelor et al., 2007a; Watson et al., 2010). PAA has only been definitively reported once in cats (Thompson et al., 2009); end-stage pancreatitis is believed to be the most common cause of feline EPI (Fig. 37.9), although reports in cats as young as 3 months of age suggest other congenital or acquired causes in this species (Xenoulis et al., 2016). The raccoon pancreatic fluke *Eurytrema procyonis* has also been reported to cause end-stage fibrosis and EPI in cats in the eastern United States. The development of clinical EPI requires approximately a 90% reduction in lipase production and thus extensive loss of pancreatic acini. It is therefore extremely unlikely to occur after a single severe bout of pancreatitis but tends to result from chronic ongoing disease. However, the chronic disease may be largely subclinical or only present as occasional clinical acute-on-chronic episodes, so the degree of underlying pancreatic damage may be underestimated.

PAA is particularly recognized in young German Shepherd Dogs (see Fig. 37.8, *A*), in which an autosomal mode of inheritance has been suggested, although a recent study refutes this and suggests that the inheritance is more complex (Westermarck et al., 2010). PAA has also been described in Rough Collies, suspected in English Setters, and sporadically



FIG 37.8
(A) Physical appearance of a 2-year-old male German Shepherd Dog with exocrine pancreatic insufficiency (EPI). **(B)** An 11-year-old neutered female English Springer Spaniel with EPI caused by end-stage chronic pancreatitis. This dog also had diabetes mellitus (DM) but was still losing weight in spite of good control of the DM. **(C)** EPI had not initially been suspected, but once it was diagnosed and treated with enzyme supplements, the dog returned to normal weight and coat condition within 6 months. (**A,** Courtesy Dr. William E. Hornbuckle, Cornell University, College of Veterinary Medicine, Ithaca, NY; **B** from Watson PJ: Exocrine pancreatic insufficiency as an end stage of pancreatitis in four dogs, *J Small Anim Pract* 44:306, 2003.)

reported in other breeds. A large study of EPI in Britain reported that young Chow Chows were overrepresented (Batchelor et al., 2007a). The pathogenesis was unknown, but the juvenile onset suggested PAA or perhaps a congenital defect in this breed.

Histologic studies in German Shepherd Dogs suggest that PAA is an autoimmune disease directed against the acini (Wiberg et al., 2000). Therefore the islets are spared, and dogs with PAA are not typically diabetic. However, affected dogs do not respond to immunosuppressive therapy. Most dogs develop the disease in young adulthood, but some German Shepherd Dogs remain subclinical for a prolonged period and present only late in life.

There has been one published study of EPI in young Greyhounds in the United States (Brenner et al., 2009). These dogs differ from the German Shepherd Dogs in that they also have endocrine tissue loss and DM, and some dogs are affected at a very young age (as young as 4 weeks). The cause of the Greyhound disease is unknown.

In contrast, many dogs with end-stage chronic pancreatitis also develop DM before or after EPI as a result of concurrent islet cell destruction (Watson, 2003; Watson et al., 2010). The situation is similar in cats with end-stage chronic pancreatitis. There is no breed relationship in cats, but dogs with EPI as a result of end-stage chronic pancreatitis tend to be middle-aged to older medium- or small-breed dogs, particularly Cavalier King Charles Spaniels, English Cocker Spaniels, and Collies (see Fig. 37.7). Interestingly, although Boxers in Britain were reported to have a high prevalence of chronic pancreatitis in one study, they rarely develop EPI and have also been reported to be significantly underrepresented among dogs with DM. This suggests that, in this breed, their chronic pancreatitis does not progress to end-stage disease. Underrepresented breeds in a large study of EPI were Golden



FIG 37.9
Middle-aged Persian cat with end-stage chronic pancreatitis and exocrine pancreatic insufficiency. Note matting of the coat with feces and poor body condition.

Retrievers, Labrador Retrievers, Rottweilers, and Weimaraners (Batchelor et al., 2007a). Finding compatible clinical signs in these breeds should first trigger a search for other possible causes, such as chronic infection or inflammatory bowel disease.

Cats with EPI are typically middle aged, with a median age of 7.7 years reported in the largest published study (range 3 months to 18.8 years) (Xenoulis et al., 2016). Domestic short-haired cats are most commonly affected, but it has also been reported in a variety of pedigree cats.

Other causes of EPI in dogs and cats are pancreatic tumors, hyperacidity of the duodenum inactivating lipase, and isolated enzyme deficiency, particularly lipase. These are all rare causes. Patients with pancreatic tumors usually present for other reasons, but tumors can result in EPI caused by a combination of compression of pancreatic ducts by the mass, destruction of acinar tissue, and associated pancreatitis.

Early studies suggested that up to 70% of dogs with EPI have concurrent small intestinal bacterial overgrowth (SIBO). Although SIBO as a definition has been replaced now with the term *antibiotic-responsive enteropathy*, the concept of a small intestinal dysbiosis due to unabsorbed nutrients in EPI remains. This may contribute to clinical signs and should be considered when treating an affected dog. Bacteria deconjugate bile salts, thus decreasing fat emulsification and therefore fat digestion. Bacteria also break down the undigested fat to hydroxy fatty acids. These and deconjugated bile salts irritate the colonic mucosa and may cause large intestinal diarrhea by stimulating secretion. Dogs with EPI therefore tend to present with signs of both small and large bowel diarrhea.

A high proportion of dogs, particularly those with low body condition scores, also have reduced duodenal enzyme activity, which may be caused by the effects of malnutrition on the gut and possibly the loss of the trophic influence of pancreatic secretions. Cobalamin deficiency is common in dogs and cats with EPI and seems to be a negative prognostic indicator in dogs if untreated (Batchelor et al., 2007b). Cobalamin is absorbed from the distal ileum via a carrier-mediated process that requires it to bind to IF. The latter is produced entirely by the pancreas in cats and mainly by the pancreas in dogs, although the canine stomach can also produce a small amount. Therefore most cats with EPI are expected to be vitamin B_{12}–deficient, whereas most but not all of dogs with EPI have hypocobalaminemia. In one large study of dogs with EPI, 82% of dogs had low serum cobalamin concentrations (Batchelor et al., 2007b). In the largest study of EPI in cats, 77% of cases had serum cobalamin below the reference range, and serum feline TLI concentrations were significantly lower in the cats with low cobalamin, suggesting more severe and chronic disease than in the cats with normal concentrations (Xenoulis et al., 2016). In cats with end-stage pancreatitis, the hypocobalaminemia is compounded by the high prevalence of concurrent inflammatory bowel disease, which often decreases the ileal absorption of vitamin B_{12}. Cobalamin deficiency causes villous atrophy and reduced gastrointestinal function, weight loss, and diarrhea in cats; therefore it is important not only to document hypocobalaminemia but also to treat it as discussed in the treatment section below.

Clinical Features

Most dogs and cats with EPI present because of chronic diarrhea and emaciation in conjunction with a ravenous appetite (see Fig. 37.8). The diarrhea tends to be fatty (steatorrhea) because of prominent fat maldigestion but is variable from day to day and among individuals. Sometimes diarrhea is not a prominent feature because digestion is interrupted so early in the process that the osmotic effect of molecules is relatively small. Affected dogs and cats also often have chronic seborrheic skin disease resulting from deficiency of essential fatty acids and cachexia, and some patients present to a dermatology clinic for this reason. If EPI is caused by chronic pancreatitis, the diagnosis may be complicated by concurrent ongoing pancreatitis that may cause intermittent anorexia and vomiting. Animals with end-stage chronic pancreatitis may also develop DM before or months to years after the development of EPI.

Concurrent diseases are common in dogs with EPI, related or unrelated to the pancreatic deficiency. In one study in dogs, concurrent gastrointestinal, skeletal, and skin conditions were common (Batchelor et al., 2007b). Cats with pancreatitis often have concurrent cholangitis and/or inflammatory bowel disease and some also have hepatic lipidosis; it is often difficult to differentiate the clinical signs of these conditions because they are so similar.

Diagnosis

ROUTINE CLINICAL PATHOLOGY

CBC and serum biochemistry profile results are often normal in dogs and cats with EPI. In very cachectic animals there may be subtle nonspecific changes consistent with malnutrition, negative nitrogen balance, and breakdown of body muscle, such as low albumin and globulin concentrations, mildly increased liver enzyme levels, low cholesterol and triglyceride concentrations, and lymphopenia.

Finding marked hypoproteinemia or more severe changes on the CBC and biochemistry profiles in an animal with EPI should trigger a search for another concurrent disease. Cats and dogs with end-stage pancreatitis may present with more severe secondary clinicopathologic changes (see earlier). A high percentage of these patients with end-stage pancreatitis (up to 50%) also have concurrent DM, so they have clinicopathologic changes typical of DM (see Chapter 49).

PANCREATIC ENZYMES

The diagnosis of EPI in dogs and cats relies on demonstrating reduced pancreatic enzyme output. The most sensitive and specific way of doing this is by measuring reduced circulating enzyme activity.

Measurement of decreased TLI in the blood has a high sensitivity and specificity for the diagnosis of EPI in dogs and cats, and is currently the single test of choice for diagnosis in small animals. It is important to measure it on a fasting sample because the release of pancreatic enzymes associated with feeding can raise the activity in the serum. It is not necessary to stop exogenous pancreatic enzyme supplementation before measuring TLI, because exogenous enzymes should not be absorbed from the gut into the circulation; even if they are, the test is an immunoassay that does not cross-react with the trypsin or trypsinogen of other species in the supplement. However, there are some problems in interpreting the results, as shown in Box 37.3.

Fecal tests for EPI are rarely used because of their low sensitivity and specificity compared with serum tests. Measurement of fecal elastase may have some usefulness in dogs with EPI as a result of chronic pancreatitis or duct blockage, in which TLI results may be misleading. More details are found in Chapter 34.



BOX 37.3

Interpretation of Trypsin-Like Immunoreactivity (TLI) Results in the Diagnosis of Canine Exocrine Pancreatic Insufficiency

- A low serum TLI level (<2.5 µg/L in dogs) in a dog with compatible clinical signs, particularly in a high-risk breed, is diagnostic of EPI.
  - A repeat blood sample to confirm diagnosis in a few weeks to months is recommended in cats and in older dogs that are not German Shepherd Dogs. Occasionally, a single TLI level may be low in a dog with pancreatitis as a result of a temporary reduction in enzyme production.
- A low serum TLI level (<2.5 µg/L in dogs) with no compatible clinical signs (i.e., no weight loss or diarrhea) is not diagnostic of EPI but should be repeated.
  - A dog with a persistently low TLI level but no steatorrhea or weight loss should be considered to have subclinical EPI and should not be treated but monitored for any evidence of clinical disease. A TLI stimulation test may provide more information about the status of the animal but is rarely performed (Wiberg et al., 1999). Subclinical EPI has been reported in a small number of German Shepherd Dogs with PAA (Wiberg et al., 1999) but has not yet been reported in cats. It is uncommon.
- A TLI level in the gray area (2.5–5.0 µg/L in dogs) is not diagnostic of EPI and should be repeated in a few weeks to months.
  - In some dogs (45% in one study: Wiberg et al., 1999), the TLI level will return to the normal range. In other dogs (about 10%), the TLI level will decrease to the level diagnostic of EPI and in some it may remain in the gray area.
  - In an older dog that is not a German Shepherd Dog, TLI levels may fluctuate, as described below, and samples should be repeated when there is no clinically acute flare-up.
- A normal TLI level in a German Shepherd Dog rules out EPI resulting from PAA, and a search should be made for another cause of the presenting clinical signs.
- A single normal or high TLI level in an older, non–German Shepherd Dog with suspicious clinical signs does not rule out EPI. TLI levels can transiently and intermittently increase into or above the normal range in dogs with EPI secondary to chronic end-stage pancreatitis if it is measured during a bout of inflammation. This is understandable because EPI reduces the TLI level but pancreatitis elevates it, so the two conditions occurring concurrently interfere with interpretation of the test result. This is likely to be true in cats as well, although it has not been well documented. Therefore in any animal with suspected EPI secondary to chronic pancreatitis, TLI level measurements should be repeated, preferably when the animal is showing no clinical signs of pancreatitis. Alternatively, a test for enzyme activity in the gut such as a fecal elastase test could be used in these animals. If clinical signs are suggestive of EPI in a dog or cat with chronic pancreatitis, a trial of enzyme supplementation is indicated even with a normal TLI.

EPI, Exocrine pancreatic insufficiency; *PAA,* pancreatic acinar atrophy.

OTHER DIAGNOSTIC TESTS

It is also advisable to measure the serum cobalamin concentration in animals with EPI because it is often decreased because of a deficiency of pancreatic IF, as noted earlier. If the serum vitamin B_{12} concentration is low, it should be supplemented either parenterally or enterally as detailed in the treatment section.

Serum folate concentrations are high in about one-third of dogs with EPI. This may indicate dysbiosis or SIBO, although the sensitivity and specificity of high serum folate concentration for the diagnosis of SIBO are poor. The definition and diagnosis of SIBO is problematic; if a newly diagnosed dog with EPI fails to respond to enzyme and cobalamin supplementation and other comorbidities have been ruled out, a trial antibiotic therapy for putative SIBO would be indicated. The importance of SIBO and the role of antibiotic treatment in cats with EPI are unknown. Occasionally, in dogs and cats with EPI, the serum folate concentration may be low; this can suggest dietary deficiency or concurrent inflammatory or infiltrative disease in the jejunum, or potentially metabolism by bacteria, which is also reported. Unlike cobalamin, there is no clear evidence that folate should be supplemented in dogs when its level is low.

Dogs with EPI have reduced gut immunity and are thus likely to be more susceptible to GI pathogens. A fecal culture would be indicated in any dog failing to respond to standard therapy, particularly if it had a history of being fed raw diet or raw pancreas.

Treatment

DRUGS

All dogs and cats with clinical EPI require enzyme supplementation for the rest of their lives. In most cases, this is provided as a powder or in the form of a capsule, which is opened and then sprinkled on the food. A recent study confirmed the efficacy of one enteric-coated canine enzyme preparation (Mas et al., 2012). Fresh raw pancreas, which can be frozen in aliquots, may be used as an alternative and can be effective, but there is also the potential for acquiring gastrointestinal infections (e.g., *Salmonella* and *Campylobacter* spp.). The dose of enzymes is initially as recommended by the manufacturer and then titrated to the individual. A large proportion of enzyme activity is lost in the acid pH of the stomach (up to 83% of lipase activity and 65% of trypsin activity). To overcome this, the dosage of enzymes given is increased or an H_2 blocker is administered concurrently to increase the gastric pH. Preincubating enzymes with the food is not indicated because they require the alkaline environment of the small intestine to work properly. Reports suggest that the dosage of enzyme replacement may be reduced over the long term between 6% and 58% but not stopped completely, perhaps because of resolution of the secondary bacterial overgrowth and the effects of chronic malnutrition and cobalamin deficiency on enterocytes and brush border enzymes.

As noted, dogs and cats with hypocobalaminemia require vitamin B_{12} supplementation. This may be by parenteral injections (0.02 mg/kg IM every 2–4 weeks until the serum concentration normalizes) or orally. Recent studies have demonstrated the efficacy of oral cobalamin even in dogs and cats with EPI and a lack of IF (Toresson et al., 2017; 2018). Cyanocobalamin tablets are given at a dose of 0.25 mg once a day for cats and dogs 1 to 10 kg; 0.5 mg once a day for dogs of body weight of >10 to 20 kg; and 1 mg once a day for dogs body weight >20 kg. Efficacy of treatment is monitored with regular measurement of serum cobalamin concentration.

Dogs and cats with EPI failing to respond to standard therapy should also have a fecal culture as previously described and any pathogens treated. Concurrent SIBO may also be suspected in these cases and may respond to courses of appropriate antibiotics (e.g., oxytetracycline, tylosin, metronidazole). It is advisable to administer antibiotics in affected dogs only as necessary if they fail to respond to enzyme and cobalamin therapy.

It is relatively common for German Shepherd Dogs with PAA to have concurrent inflammatory bowel disease, and this must also be addressed. Animals with EPI as a result of chronic pancreatitis may require insulin therapy for concurrent DM and other treatment for acute flare-ups, including analgesics (see earlier).

DIET

Disruption of fat digestion is the most important feature of EPI. A low-fat food has therefore been traditionally recommended, but it may not contain enough calories to feed a large-breed dog (e.g., German Shepherd Dog) effectively. Fat usually contributes a significant proportion of daily energy intake because it is more energy-dense than carbohydrates. In large-breed dogs with EPI and cachexia, weight gain may be difficult to achieve with a low-fat diet. There is no convincing evidence in the literature that long-term feeding of a low-fat diet improves outcome in dogs with PAA, although there is some evidence that it may result in faster resolution of clinical signs. However, high-fat diets, such as proprietary renal diets, should obviously be avoided. We therefore recommend that dogs with PAA be fed a normal to moderately fat-restricted, highly digestible diet, with reasonable calorie density. The diet should also be low in fiber because fiber impairs the activity of pancreatic enzymes, and soluble fiber may actually absorb pancreatic enzymes. Fiber may also reduce small intestinal absorption and activity of brush border enzymes. The proprietary veterinary diets marketed for gastrointestinal disease in dogs (e.g., Hill's i/d, Royal Canin Gastrointestinal diet, Eukanuba Intestinal or Dermatosis FP) fulfill these requirements and are recommended, at least for initial stabilization. In the long term, after the gut wall recovers, these dogs can be maintained on a normal fat level in most cases and can often return to their normal diet. In some individuals with PAA, extra calories can be added to the diet between meals in the form of medium-chain

triglycerides, such as coconut oil. They should not be used in cats and should not be given in overly high doses in dogs because of the risk of osmotic diarrhea. The recommended daily amount is ¼ to 4 teaspoons in dogs in divided doses. Medium-chain triglycerides also cannot carry fat-soluble vitamins, may cause vomiting in some dogs, and are contraindicated in dogs with liver disease because they may worsen encephalopathy.

In dogs with EPI as a result of chronic pancreatitis, dietary advice is slightly different. Many of these dogs benefit from long-term feeding of a low-fat diet, which seems to reduce postprandial pain and acute flare-ups of disease (Hill's i/d Low Fat, Royal Canin Digestive Low Fat, or Eukanuba Intestinal). Therefore proprietary low-fat diets would be preferred for these patients. The use of medium-chain triglycerides is not recommended for dogs with chronic pancreatitis, but fortunately these are often small-breed dogs with less cachexia than German Shepherd Dogs with PAA.

It is best to feed two or more meals a day, each with enzymes added. Owners often do not realize the importance of adding enzymes to all the meals, so this should be stressed and the dog should not be allowed to scavenge. This is often difficult because they are polyphagic, but scavenging, especially of fatty foods, causes recurrence of diarrhea and sets back recovery.

Cats with EPI are often best managed on a hypoallergenic intestinal type diet (e.g., Hill's d/d, Eukanuba Dermatosis LB, Royal Canin limited ingredient diets) because there is a high incidence of concurrent inflammatory bowel disease in cats. If they are also diabetic, most cases should still be fed an intestinal diet because proprietary feline diabetes diets (e.g., Hill's m/d, Royal Canin diabetic diet, Purina DM) are anecdotally associated with postprandial pain in cats with underlying chronic pancreatitis. The feline diabetic diets are most indicated in insulin resistant (type 2) diabetes in cats and not end-stage chronic pancreatitis.

Prognosis

The prognosis for EPI is good because the disease can be successfully treated in most dogs. However, a surprising number of dogs (19% in one study) are euthanized within the first year of treatment because of poor response to therapy (Batchelor et al., 2007b). The same study showed that the median survival time of dogs that responded to treatment was very good (>5 years). This underlines the importance of scheduling regular follow-up appointments, particularly in the initial stages of therapy, to evaluate progress and change management as necessary, and to address all concurrent morbidities as described in the previous treatment section. Prognosis for dogs and cats with EPI as a result of end-stage chronic pancreatitis is surprisingly good in most cases, even if it is complicated by concurrent DM, with survival times of several years in most cases.

EXOCRINE PANCREATIC NEOPLASIA

Neoplasms of the exocrine pancreas are uncommon in cats and dogs. Pancreatic adenocarcinomas have a very aggressive biologic behavior and have usually disseminated widely by the time of diagnosis. They are often subclinical until they have metastasized but can result in single or repeat bouts of pancreatitis and/or EPI. Some pancreatic tumors have been associated with paraneoplastic syndromes such as sterile panniculitis in dogs, alopecia with shiny skin in cats, and hypercalcemia. Chronic pancreatitis is a risk factor for the development of pancreatic adenocarcinomas in humans; this may also be true in dogs because the published reports of these tumors in dogs show a predominance of Cocker and Cavalier King Charles Spaniels.

Pancreatic adenomas are rare in small animals but have been reported in cats. Nodular hyperplasia of the exocrine pancreas is also common in older dogs and cats. This usually presents as multiple small masses, whereas pancreatic tumors are usually single, but histopathology or cytology is necessary to definitively differentiate hyperplasia from neoplasia. Dogs and cats with acute and chronic pancreatitis sometimes present with a large pancreatic mass as a result of fat necrosis and/or associated fibrosis, and it is important not to confuse these with neoplasia. Again, histopathology is required to differentiate these conditions. Ultrasonography-guided FNA cytology has been suggested as a useful means of differentiating inflammatory and neoplastic lesions of the pancreas (see Chapter 34).

Pancreatic tumors are not associated with any specific clinicopathologic changes and may cause no changes in enzyme levels at all. Alternatively, they can result in recurrent bouts of pancreatitis, with typical associated blood changes, and EPI can develop. In some cases biliary tract obstruction may occur, with associated jaundice and marked elevations in liver enzyme levels. Occasionally, pancreatic tumors have been reported to be associated with marked hyperlipasemia.

The prognosis in dogs and cats with pancreatic adenocarcinoma is very poor. The tumors are extremely aggressive, poorly sensitive to chemotherapy or radiotherapy, and usually have disseminated widely by the time of diagnosis.

Neuroendocrine tumors such as insulinomas and gastrinomas appear to be more common than pancreatic adenocarcinomas in dogs and tend to be seen in different breeds, predominantly large breeds (Watson et al., 2007). These are tumors of the endocrine pancreas that produce clinical signs related to the secretion of hormones and are therefore outside the scope of this chapter.

PANCREATIC ABSCESSES, CYSTS, AND PSEUDOCYSTS

Pancreatic abscesses, cysts, and pseudocysts are uncommonly reported in dogs and cats and are usually a complication or sequelae of pancreatitis. Pancreatic cysts may be congenital (e.g., as part of the polycystic renal disease in Persian cats) or

associated with cystic neoplasia (e.g., cystadenocarcinoma), but the most common are pseudocysts secondary to pancreatitis. A pancreatic pseudocyst is a collection of fluid containing pancreatic enzymes and debris in a nonepithelialized sac. Pseudocysts have been recognized in association with pancreatitis in cats and dogs, although they appear to be rare, and microscopic acinar cysts have been found frequently in feline chronic pancreatitis. Pseudocysts are not associated with any distinct clinicopathologic findings other than those associated with the underlying pancreatitis. Analysis of fluid obtained from a pseudocyst by FNA generally shows a modified transudate. Amylase and lipase levels can be measured in the pseudocyst fluid. In humans the enzyme levels are higher in pseudocysts associated with pancreatitis than in those associated with cystic carcinomas, but the value of this measurement in small animals is unknown. Cytology can differentiate a pseudocyst from a true abscess because a pseudocyst contains amorphous debris, some neutrophils and macrophages, and, rarely, small numbers of reactive fibroblasts, whereas an abscess contains many degenerative neutrophils and variable numbers of pancreatic acinar cells, which may appear very atypical as a result of inflammation.

A true pancreatic abscess is a collection of septic exudate that results from secondary infection of necrotic pancreatic tissue or a pancreatic pseudocyst. They are associated with a poor prognosis but fortunately are rare in dogs and cats.

Treatment of pancreatic pseudocysts can be surgical or medical. Medical treatment by ultrasonography-guided cyst aspiration has had a reasonable success rate. Pancreatic abscesses should be treated surgically with omentalization or open peritoneal drainage. Both carry a high mortality rate, but one study suggested that omentalization may be preferable (Johnson et al., 2006).

Suggested Readings

Abbo, et al. Pharmacokinetics of buprenorphine following intravenous and oral transmucosal administration in dogs. *Vet Ther*. 2008;9:83.

Abdallah AA, et al. Biliary tract obstruction in chronic pancreatitis. *HPB (Oxford)*. 2007;9:421.

Al-Omran M, et al. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Syst Rev*. 2010;(1):CD002837.

Batchelor DJ, et al. Breed associations for canine exocrine pancreatic insufficiency. *J Vet Intern Med*. 2007a;21:207.

Batchelor DJ, et al. Prognostic factors in canine exocrine pancreatic insufficiency: prolonged survival is likely if clinical remission is achieved. *J Vet Intern Med*. 2007b;21:54.

Besselink MG, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371:651.

Bishop MA, et al. Evaluation of the cationic trypsinogen gene for potential mutations in miniature schnauzers with pancreatitis. *Can J Vet Res*. 2004;68:315.

Bishop MA, et al. Identification of variants of the SPINK1 gene and their association with pancreatitis in Miniature Schnauzers. *Am J Vet Res*. 2010;71:527.

Bledsoe, et al. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. *APMIS*. 2018;126:469.

Bostrom BM, et al. Chronic pancreatitis in dogs: a retrospective study of clinical, clinicopathological, and histopathological findings in 61 cases. *Vet J*. 2013;195:73.

Brenner K, et al. Juvenile pancreatic atrophy in Greyhounds: 12 cases (1995-2000). *J Vet Intern Med*. 2009;23:67.

Chandler ML, et al. A pilot study of protein sparing in healthy dogs using peripheral parenteral nutrition. *Res Vet Sci*. 2000;69:47.

De Cock HE, et al. Prevalence and histopathologic characteristics of pancreatitis in cats. *Vet Pathol*. 2007;44:39.

Etemad B, et al. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology*. 2001;120:682.

Fass J, et al. Effects of intravenous ketamine on gastrointestinal motility in the dog. *Intensive Care Med*. 1995;7:584.

Ferreri JA, et al. Clinical differentiation of acute necrotizing from chronic non-suppurative pancreatitis in cats: 63 cases (1996-2001). *J Am Vet Med Assoc*. 2003;223:469.

Furrow E, et al. High prevalence of the c.74A>C SPINK1 variant in Miniature and Standard Schnauzers. *J Vet Intern Med*. 2012;26:1295.

Gerhardt A, et al. Comparison of the sensitivity of different diagnostic tests for pancreatitis in cats. *J Vet Intern Med*. 2001;15:329.

Guija de Arespacochaga A, et al. Comparison of lipase activity in peritoneal fluid of dogs with different pathologies—a complementary diagnostic tool in acute pancreatitis? *J Vet Med A Physiol Pathol Clin Med*. 2006;53:119.

Hess RS, et al. Clinical, clinicopathological, radiographic and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995). *J Am Vet Med Assoc*. 1998;213:665.

Hess RS, et al. Evaluation of risk factors for fatal acute pancreatitis in dogs. *J Am Vet Med Assoc*. 1999;214:46.

Hill RC, et al. Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat: a retrospective study of 40 cases (1976-1989). *J Vet Intern Med*. 1993;7:25.

Jennings M, et al. Successful treatment of feline pancreatitis using an endoscopically placed gastrojejunostomy tube. *J Am Anim Hosp Assoc*. 2001;37:145.

Johnson MD, et al. Treatment for pancreatic abscesses via omentalization with abdominal closure versus open peritoneal drainage in dogs: 15 cases (1994-2004). *J Am Vet Med Assoc*. 2006;228:397.

Kimmel SE, et al. Incidence and prognostic value of low plasma ionised calcium concentration in cats with acute pancreatitis: 46 cases (1996-1998). *J Am Vet Med Assoc*. 2001;219:1105.

Kook PH, et al. Feasibility and safety of endoscopic ultrasound-guided fine needle aspiration of the pancreas in dogs. *J Vet Intern Med*. 2012;26:513.

Mansfield CS, et al. A pilot study to assess tolerability of early enteral nutrition via esophagostomy tube feeding in dogs with severe acute pancreatitis. *J Vet Intern Med*. 2011;25:419.

Mansfield CS, et al. Review of feline pancreatitis. Part 2: clinical signs, diagnosis and treatment. *J Feline Med Surg*. 2001;3:125.

Mansfield CS, et al. Trypsinogen activation peptide in the diagnosis of canine pancreatitis. *J Vet Intern Med*. 2000;14:346.

Mansfield, et al. Development of a clinical severity index for dogs with acute pancreatitis. *J Am Vet Med Assoc*. 2008;233:936.

Mas A, et al. A blinded randomised controlled trial to determine the effect of enteric coating on enzyme treatment for canine exocrine pancreatic efficiency. *BMC Vet Res*. 2012;8:127.

Mohr AJ, et al. Effect of early enteral nutrition on intestinal permeability, intestinal protein loss, and outcome in dogs with severe parvoviral enteritis. *J Vet Intern Med*. 2003;17:791.

Newman S, et al. Localization of pancreatic inflammation and necrosis in dogs. *J Vet Intern Med*. 2004;18:488.

Pápa K, et al. Occurrence, clinical features and outcome of canine pancreatitis (80 cases). *Acta Vet Hung*. 2011;59:37.
Pearce CB, et al. A double-blind, randomised, controlled trial to study the effects of an enteral feed supplemented with glutamine, arginine, and omega-3 fatty acid in predicted acute severe pancreatitis. *JOP*. 2006;7:361.
Quan H, et al. A meta-analysis of enteral nutrition and total parenteral nutrition in patients with acute pancreatitis. *Gastroenterol Res Pract*. 2011. article ID 698248.
Robertson SA, et al. Systemic uptake of buprenorphine by cats after oral mucosal administration. *Vet Rec*. 2003;152:675.
Ruaux CG, et al. A severity score for spontaneous canine acute pancreatitis. *Aust Vet J*. 1998;76:804.
Ruaux CG. Pathophysiology of organ failure in severe acute pancreatitis in dogs. *Compend Cont Educ Small Anim Vet*. 2000;22:531.
Sato, et al. Assesment of severity and changes in C-reactive protein concentration and various biomarkers in dogs with pancreatitis. *J Vet Med Sci*. 2017;79:35.
Schaer M. A clinicopathological survey of acute pancreatitis in 30 dogs and 5 cats. *J Am Anim Hosp Assoc*. 1979;15:681.
Spadafora, et al. Naturally occurring mutations in the canine CFTR gene. *Physiol Genomics*. 2010;43:480.
Spillmann T, et al. An immunoassay for canine pancreatic elastase 1 as an indicator of exocrine pancreatic insufficiency in dogs. *J Vet Diagn Invest*. 2001;13:468.
Spillmann T, et al. Canine pancreatic elastase in dogs with clinical exocrine pancreatic insufficiency, normal dogs and dogs with chronic enteropathies. *Eur J Comp Gastroenterol*. 2000;5:1.
Spillmann T, et al. Endoscopic retrograde cholangiopancreatography in dogs with chronic gastrointestinal problems. *Vet Radiol Ultrasound*. 2005;46:293.
Spillmann T, et al. Evaluation of serum values of pancreatic enzymes after endoscopic retrograde pancreatography in dogs. *Am J Vet Res*. 2004;65:616.
Steiner JM, et al. Serum canine lipase immunoreactivity in dogs with exocrine pancreatic insufficiency. *J Vet Intern Med*. 2001;15:274.
Swift NC, et al. Evaluation of serum feline trypsin-like immunoreactivity for diagnosis of pancreatitis in cats. *J Am Vet Med Assoc*. 2000;217:37.
Thompson, et al. Feline exocrine pancreatic insufficiency: 16 cases (1992-2007). *J Feline Med Surg*. 2009;12:935.
Toresson, et al. Comparison of efficacy of oral and parenteral cobalamin supplementation in normalising low cobalamin concentrations in dogs: a randomised controlled study. *Vet J*. 2018;232:27.
Toresson, et al. Oral cobalamin supplementation in cats with hypocobalaminaemia: a retrospective study. *J Feline Med Surg*. 2017;12:1302.
Watson PJ, et al. Characterization of chronic pancreatitis in cocker spaniels. *J Vet Intern Med*. 2011;25:797.
Watson PJ, et al. Chronic pancreatitis in the English Cocker Spaniel shows a predominance of IgG4$^+$ plasma cells in sections of pancreas and kidney. Presented at the American College of Veterinary Internal Medicine Forum, New Orleans, May 30-June 2, 2012.
Watson PJ, et al. Observational study of 14 cases of chronic pancreatitis in dogs. *Vet Rec*. 2010;167:968.
Watson PJ, et al. Prevalence and breed distribution of chronic pancreatitis at post-mortem examination in first opinion dogs. *J Small Anim Pract*. 2007;48:609.
Watson PJ. Exocrine pancreatic insufficiency as an end stage of pancreatitis in four dogs. *J Small Anim Pract*. 2003;44:306.
Weiss DJ, et al. Relationship between inflammatory hepatic disease and inflammatory bowel disease, pancreatitis and nephritis in cats. *J Am Vet Med Assoc*. 1996;206:1114.
Westermarck E, et al. Exocrine pancreatic insufficiency in dogs. *Vet Clin North Am Small Anim Pract*. 2003;33:1165.
Westermarck E, et al. Heritability of exocrine pancreatic insufficiency in German Shepherd dogs. *J Vet Intern Med*. 2010;24:450.
Wiberg ME, et al. Cellular and humoral immune responses in atrophic lymphocytic pancreatitis in German shepherd dogs and rough-coated collies. *Vet Immunol Immunopathol*. 2000;76:103.
Wiberg ME, et al. Serum trypsin-like immunoreactivity measurement for the diagnosis of subclinical exocrine pancreatic insufficiency. *J Vet Intern Med*. 1999;13:426.
Wiberg ME. Pancreatic acinar atrophy in German shepherd dogs and rough-coated collies: etiopathogenesis, diagnosis and treatment. A review. *Vet Q*. 2004;26:61.
Williams DA, Batt RM. Sensitivity and specificity of radioimmunoassay of serum trypsin-like immunoreactivity for the diagnosis of canine exocrine pancreatic insufficiency. *J Am Vet Med Assoc*. 1988;192:195.
Xenoulis, et al. Feline exocrine pancreatic insufficiency: a retrospective study of 150 cases. *J Vet Intern Med*. 2016;30(6):1790.



Drugs Used for Hepatobiliary and Pancreatic Disorders

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Analgesics		See Table 37.4
Antibacterials		
Amoxicillin, ampicillin	10-20 mg/kg PO, SC, IV, q8-12h, dogs and cats	Broad-spectrum bactericidal and therapeutic levels in liver and bile Biliary tract infections; control of gut bacteria in hepatic encephalopathy; control of systemic infection of gut origin Preferably used on basis of culture and sensitivity

Continued

Drugs Used for Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Cephalexin or cefazolin	10-20 mg/kg PO, SC, IV, q8-12h, dogs and cats	Very similar activity and spectrum to ampicillin—see ampicillin Helpful for patients with penicillin hypersensitivity; <10% show cross-reaction to cephalexin
Enrofloxacin (Baytril)	5 mg/kg SC, IV, PO, IM, q24h, dogs and cats	Bactericidal, particularly against gram-negative organisms; poor efficacy against anaerobes and streptococci; good tissue penetration Biliary tract infections, particularly with gram-negative organisms Also infectious complications of pancreatitis Preferably used on basis of culture and sensitivity and not as first line choice Should not be used in growing dogs (toxic to growing cartilage) Use only with care in cats—risk of retinal damage
Marbofloxacin (Zeniquin)	2 mg/kg SC, PO, IV, q24h, dogs and cats	Use as for enrofloxacin
Metronidazole	10 mg/kg PO or slowly IV, q12h, dogs and cats If significant hepatic functional impairment, reduce to 7.5 mg/kg q12h	Bactericidal particularly effective against anaerobes Often used in combination with ampicillin for biliary tract infections or to control gut bacteria in hepatic encephalopathy
Neomycin	20 mg/kg PO q6-8h or as retention enema, dogs and cats	Particularly used for acute hepatic encephalopathy Systemic absorption and oto- and nephrotoxicity can occur if there is concurrent GI ulceration, particularly in cats
Potentiated sulfonamides, (e.g., trimethoprim-sulfamethoxazole)	15 mg/kg of combined ingredients (trimethoprim + sulfonamide) PO q12h	Bactericidal, broad-spectrum, and probably drug of choice with infectious complications of pancreatitis Should not be used in liver disease if possible because hepatotoxic in susceptible individuals Should not be used in Doberman Pinschers because of reduced hepatic clearance Occasional adverse effects with concurrent immune-mediated diseases
Antiemetics		
Chlorpromazine	0.2-0.4 mg/kg SC q8h, dogs and cats	Indicated for vomiting associated with pancreatitis and some cases of hepatitis, but only if other antiemetics tried and ineffective because it is a phenothiazine sedative Effective antiemetic but also sedative, so ensure adequate hydration and avoid or use very low dose with encephalopathy and cardiovascular compromise
Metoclopramide	0.2-0.5 mg/kg PO, SC, q8h, or 1-2 mg/kg IV q24h as constant rate infusion	Indicated for vomiting associated with liver disease and some cases of pancreatitis; however, peripheral prokinetic effect may increase pain in pancreatitis Neurologic adverse effects occasionally seen Avoid in encephalopathy

Drugs Used for Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Maropitant (Cerenia)	Dogs > 8 wk—1 mg/kg SC q24h for up to 5 days, or 2 mg/kg orally q24h for up to 5 days Cats > 16 wk—1 mg/kg SC q24h for up to 5 days; not currently licensed for oral use in cats	Centrally acting antiemetic (NK1 receptor antagonist) Antiemetic of choice in canine pancreatitis, no obvious prokinetic effect Use with care in liver disease because metabolized in the liver, so do not use if significant liver dysfunction Not licensed for oral use cats
Ondansetron (Zofran)	Cats and dogs—0.5 mg/kg IV loading dose followed by 0.5 mg/kg/h infusion q6h or 0.5-1 mg/kg PO q12-24h	Refractory vomiting; may be contraindicated in pancreatitis because it has been reported to trigger vomiting in humans
Antiencephalopathic		
Lactulose	5-15 mL PO q8h (dogs) 0.25-1 mL PO q8h (cats) Can also be given as retention enema in acute encephalopathy	Hepatic encephalopathy with acquired or congenital portosystemic shunts Overdose produces diarrhea Titrate to effect (two or three soft bowel movements/day)
Antibiotics (e.g., ampicillin, metronidazole, neomycin)	See antibacterial section	
Propofol	Constant rate infusion; rate calculated by giving initial bolus to effect (usually ≈1 mg/kg) and timing duration of action; usually ≈0.1-0.2 mg/kg/min	Drug of choice for seizures because of liver disease, hepatic encephalopathy Should not be used in pancreatitis because it is a lipid vehicle
Phenobarbital	5-10 mg/kg PO q24h preoperatively followed by 3-5 mg/kg q12h postoperatively for 3 wk	Can be used prophylactically before and immediately after surgery to reduce risk of postoperative seizures after ligation of PSS, but anecdotal evidence of effectiveness
Levetiracetam (Keppra)	Dogs—20 mg/kg PO q8 for minimum of 24 hours before surgery for portosystemic shunt. Doses of 30 or 60 mg/kg IV have been reported in status epilepticus in dogs	Efficacy for preventing hepatic encephalopathy only reported with pretreatment before surgery for portosystemic shunts Drug appears most effective short term Efficacy of longer term oral treatment not demonstrated
Antiinflammatory-Antifibrotic		
(Note spironolactone also has putative antifibrotic effect—see diuretic section)		
Prednisolone (prednisone)	Antiinflammatory dose—0.5 mg/kg PO q24h Immunosuppressive dose—1-2 mg/kg PO q24h Taper at 0.5 mg/kg PO q24h or q48h	Antiinflammatory or immunosuppressive doses in lymphocytic cholangitis in cats; immunosuppressive doses in suspected autoimmune chronic hepatitis in dogs (see text), and in suspected immune-mediated pancreatitis in English Cocker Spaniels (see text) Avoid in suppurative cholangitis Avoid in portal hypertension or animals with ascites (potential GI ulceration) Avoid use of dexamethasone—very ulcerogenic

Continued



Drugs Used for Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Antioxidants		
S-adenosylmethionine (SAM-e) (Denosyl)	Dogs—20 mg/kg (or more) PO q24h Cats—20 mg/kg or 200-400 mg total daily	Indicated for any liver disease, but particularly hepatic lipidosis in cats and toxic hepatitis and diseases causing biliary stasis in dogs and cats Tablets must be given whole on empty stomach for effective absorption
Sylmarin (silymarin, silibin)	50-200 mg/kg PO q24h, for dogs	Antioxidant derived from milk thistle Likely safe, but efficacy unknown as very limited studies on which to base dose advice for dogs; studies were in toxic hepatitis
Vitamin E (tocopherol)	400 IU/day for medium-sized dogs (titrate accordingly for other sizes); 5-25 IU/kg PO daily, dogs and cats	Indications as for SAM-e but including any chronic hepatitis in dogs
Zinc (see copper-chelating agents) and ursodeoxycholic acid (see choleretic); also has antioxidant activities		
Antidotes		
N-acetylcysteine	Cats and dogs—140 mg/kg IV or PO as loading dose; then continued at 70 mg/kg q6h for total of seven treatments or for up to 5 days	Antidote for acetaminophen toxicity that binds toxic metabolite and increases glucuronidation process Can cause nausea and vomiting when given orally Foul taste makes oral dosing difficult without nasogastric tube
Cimetidine	Dogs—5-10 mg/kg IV, IM, PO, q6-8h Cats—2.5-5 mg/kg IV, IM, PO, q8-12h	Slows oxidative hepatic drug metabolism by binding to microsomal cytochrome P-450, so useful additional antidote for acetaminophen toxicity in dogs and cats
Antioxidants (e.g., S-adenosylmethionine) and vitamins E and C also supportive for oxidant toxins such as acetaminophen	See sections on antioxidants and vitamins	
Antiulcer Treatment		
Ranitidine (Zantac)	2 mg/kg PO or slowly IV q12h, dogs and cats	Acid secretory inhibitor of choice in liver disease May not be necessary if gastric pH is high Cimetidine should be avoided because of action on cytochrome P-450 enzymes, except as antidote (see earlier)
Sucralfate (Carafate)	Dogs—1 g/30 kg PO q6h Cats—250 mg/cat PO q8-12h	Gastric ulceration associated with liver or pancreatic disease
Copper-Chelating Agents		
Penicillamine	Dogs only—10-15 mg/kg PO q12h	Copper chelator of choice for copper storage disease; takes months to remove copper from liver Give on an empty stomach; vomiting common Immune-mediated, renal, and skin disease possible

Drugs Used for Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
2,3,2-tetramine tetrahydrochloride (2,3,2–T) and 2,2,2-tetramine tetrahydrochloride	Dogs only—10-15 mg/kg PO q12h	Copper chelator for copper storage disease in dogs More rapid effect than penicillamine so may be more useful in acute disease 2,3,2-Tetramine produces greater copper loss but not available as a drug Isolated case reports of their use in dogs but no extensive trials Toxicity data unclear except that prolonged use may lead to clinical signs resulting from low copper levels
Zinc acetate or sulfate	1-20 mg/kg/day of elemental zinc for dogs 7 mg/kg/day of elemental zinc for cats	Indicated in copper storage disease to reduce copper absorption Also antioxidant, antifibrotic, increases ammonia detoxification, so may be helpful in any chronic hepatitis or hepatic encephalopathy Monitor blood levels every 1-2 wk and keep below 200-300 µg/dL to avoid toxicity (iron deficiency and hemolysis) Main side effect is vomiting—give 1 hour before food to minimize this
Choleretic		
Ursodeoxycholic acid (Ursodiol)	4-15 mg/kg/day split into two doses 12 hours apart (dogs); 15 mg/kg PO once daily (cats)	Choleretic, also moderates bile acid pool to be less toxic Antiinflammatory, antioxidant Indicated for conditions associated with biliary stasis but without complete bile duct obstruction Contraindicated with obstruction in case of gallbladder rupture
Diuretic		
Spironolactone	2-4 mg/kg day PO in two or three divided doses, dogs and cats	Diuretic of choice in ascites of liver disease (see Chapter 39) Gradual onset of action over 2-3 days May be combined with furosemide for more marked diuresis
Furosemide	2 mg/kg PO q8-12h, dogs and cats	Use as additional diuretic if necessary in ascites of liver disease Always use concurrent spironolactone to avoid compensatory increase aldosterone action with further water retention and hypokalemia
Treatment Modalities for Coagulopathies		
Fresh-frozen plasma	Dogs and cats—starting dose of 10 mL/kg; dose of plasma titrated based on results of OSPT and APTT	Replenish depleted clotting factors in severe acute or chronic liver disease, particularly if prolonged OSPT and/or APTT and no response to vitamin K treatment alone
Vitamin K_1 (phytomenadione) (Konakion)	0.5-2 mg/kg, SC or IM, 12 hours before biopsy and then q12h for 3 days, mainly in cats	Treatment of coagulopathy associated with liver disease, particularly if concurrent biliary stasis and/or gut disease reducing vitamin K absorption Treatment of coagulopathy before liver biopsy, particularly in cats. No evidence of efficacy in dogs

Continued

Drugs Used for Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Vitamins		
Vitamin B_{12} (cyanocobalamin)	Dogs and cats—0.02 mg/kg IM, SC every 2-4 wk until serum concentration normalizes or oral doing cyanocobalamin tablets: 0.25 mg once a day cats and dogs 1-10 kg; 0.5 mg once a day dogs >10-20; 1 mg once a day dogs body weight >20 kg.	Treatment of vitamin B_{12} deficiency, particularly associated with EPI and lack of pancreatic intrinsic factor
Vitamin K_1 (phytomenadione)	See treatment of coagulopathy section	
Vitamin E	See antioxidant section	
Vitamin C (ascorbic acid)	Cats and dogs oxidant toxins—30-40 mg/kg SC q6h for seven treatments	Indicated only as supportive treatment for oxidant toxins affecting the liver (e.g., acetaminophen) Not indicated in other cases of hepatitis or copper storage disease because increases absorption and hepatic buildup of metals

APPT, Activated partial thromboplastin time; *EPI,* exocrine pancreatic insufficiency; *GI,* gastrointestinal; *IM,* intramuscular; *IV,* intravenous; *NK1,* neurokinin 1; *OSPT,* one-stage prothrombin time; *PO,* by mouth; *PSS,* portosystemic shunt; *SC,* subcutaneous.

PART FIVE ▪ Urinary Tract Disorders

Stephen P. DiBartola and Jodi L. Westropp

CHAPTER 38

Clinical Manifestations of Urinary Disorders



Azotemia refers to an increased concentration of nonprotein nitrogenous compounds in blood, usually urea and creatinine. Prerenal azotemia is a consequence of decreased renal perfusion (e.g., severe dehydration, heart failure); postrenal azotemia results from interference with excretion of urine from the body (e.g., obstruction, uroabdomen). Primary renal azotemia is caused by parenchymal renal disease. The term *renal failure* refers to the clinical syndrome that occurs when the kidneys are no longer able to maintain their regulatory, excretory, and endocrine functions, resulting in retention of nitrogenous solutes and derangements of fluid, electrolyte, and acid–base balance. Renal failure occurs when 75% of more of the nephron population is nonfunctional. Uremia refers to the constellation of clinical signs and biochemical abnormalities associated with a critical loss of functional nephrons. It includes the extrarenal manifestations of renal failure (e.g., uremic gastroenteritis, hyperparathyroidism). The term *renal disease* refers to the presence of morphologic or functional lesions in one or both kidneys, regardless of extent.

CLINICAL APPROACH

Try to answer the following questions:

1. Is renal disease present?
2. Is the disease glomerular, tubular, interstitial, or a combination?
3. What is the extent of the renal disease?
4. Is the disease acute or chronic? Reversible or irreversible? Progressive or nonprogressive?
5. What is the current status of the patient's renal function?
6. Can the disease be treated?
7. Which nonurinary complicating factors are present and require treatment (e.g., infection, electrolyte and acid–base disturbances, hypertension, dehydration, obstruction)?
8. What is the prognosis?

The diagnosis of renal disease begins with a careful evaluation of the history and physical examination findings.

History

Take a complete history, including signalment (age, breed, sex, presenting complaint, husbandry, and review of body systems). The history of the presenting complaint should include information about onset (acute or gradual), progression (improving, unchanging, or worsening), and response to previous therapy. Information about husbandry includes the animal's immediate environment (indoor or outdoor), use (pet, breeding, show, or working animal), geographic origin and travel history, exposure to other animals, vaccination status, diet, and information about previous trauma, illness, or surgery.

Questions relating to the urinary tract include those about changes in water intake and the frequency and volume of urination. Ask about pollakiuria, dysuria, or hematuria. Be careful to distinguish dysuria and pollakiuria from polyuria and to differentiate polyuria from urinary incontinence. The distinction between pollakiuria and polyuria is important because polyuria may be a sign of upper urinary tract disease, whereas pollakiuria and dysuria usually are indicative of lower urinary tract disease. Nocturia may be an early sign of polyuria but can also occur as a result of dysuria. Polydipsia usually is more readily detected by owners than is polyuria. Describe amounts in quantitative terms familiar to the owner, such as cups (≈250 mL/cup) or quarts (≈1 L/quart). Question the owner about exposure of the animal to potential nephrotoxins such as ethylene glycol in antifreeze, chicken jerky treats (dogs), Easter lilies (cats only), aminoglycosides, and nonsteroidal antiinflammatory drugs.

Physical Examination

Perform a complete physical examination, including fundic and rectal examinations. Pay close attention to hydration status and to the presence of ascites or subcutaneous edema

that may accompany nephrotic syndrome (e.g., glomerular disease). Examine the oral cavity for ulcers, tongue tip necrosis, and pallor of the mucous membranes. Note retinal edema, detachment, hemorrhage, or vascular tortuosity during the fundic examination. Occasionally severe hypertension secondary to renal disease will result in acute onset of blindness caused by retinal detachment. Young growing animals with renal failure may develop marked fibrous osteodystrophy characterized by enlargement and deformity of the maxilla and mandible (so-called rubber jaw), but this is rare in older dogs with renal failure.

Both kidneys can be palpated in most cats and the left kidney in some dogs. Kidneys should be evaluated for size, shape, consistency, pain, and location. Unless empty, the bladder can be palpated in most dogs and cats. The bladder should be evaluated for degree of distention, pain, wall thickness, and presence of intramural (e.g., tumors) or intraluminal (e.g., calculi, clots) masses. In the absence of obstruction, a distended bladder in a dehydrated animal suggests abnormal renal function or the administration of drugs that impair urinary concentrating ability (e.g., glucocorticoids, diuretics). Evaluate the prostate gland and pelvic urethra during the rectal examination. Exteriorize and examine the penis, and palpate the testes. Perform a vaginal examination to evaluate for abnormal discharge, masses, and appearance of the urethral orifice.

PRESENTING PROBLEMS

HEMATURIA

Hematuria can be caused by any disease that compromises the urogenital mucosa and results in bleeding. Thus it may be associated with diseases of the urinary tract (i.e., kidneys, ureters, bladder, urethra) or genital tract (i.e., prostate, penis, prepuce, uterus, vagina, vestibule). Hematuria may be classified as macroscopic (i.e., visible to the naked eye) or microscopic (i.e., identified only as increased numbers of red blood cells in the urine sediment). Macroscopic hematuria results in a red, pink, or brown coloration of the urine. Centrifugation of the urine sample readily allows differentiation of pigmenturia (e.g., hemoglobinuria, myoglobinuria) from hematuria (i.e., a pellet of red cells with clear yellow supernatant; Fig. 38.1). Disorders associated with hematuria include urinary tract infection, neoplasia, urolithiasis, trauma, coagulopathies, vascular anomalies (e.g., renal telangiectasia in Welsh Corgi dogs), and idiopathic renal hematuria (Box 38.1). Cystocentesis is commonly associated with microscopic hematuria, and a voided sample should always be obtained to evaluate for this possibility when abnormal numbers of red blood cells (e.g., >three/high-power field) are observed in the sediment of a urine sample collected by cystocentesis. Occasionally microscopic hematuria caused by cystocentesis is interpreted as evidence of ongoing feline

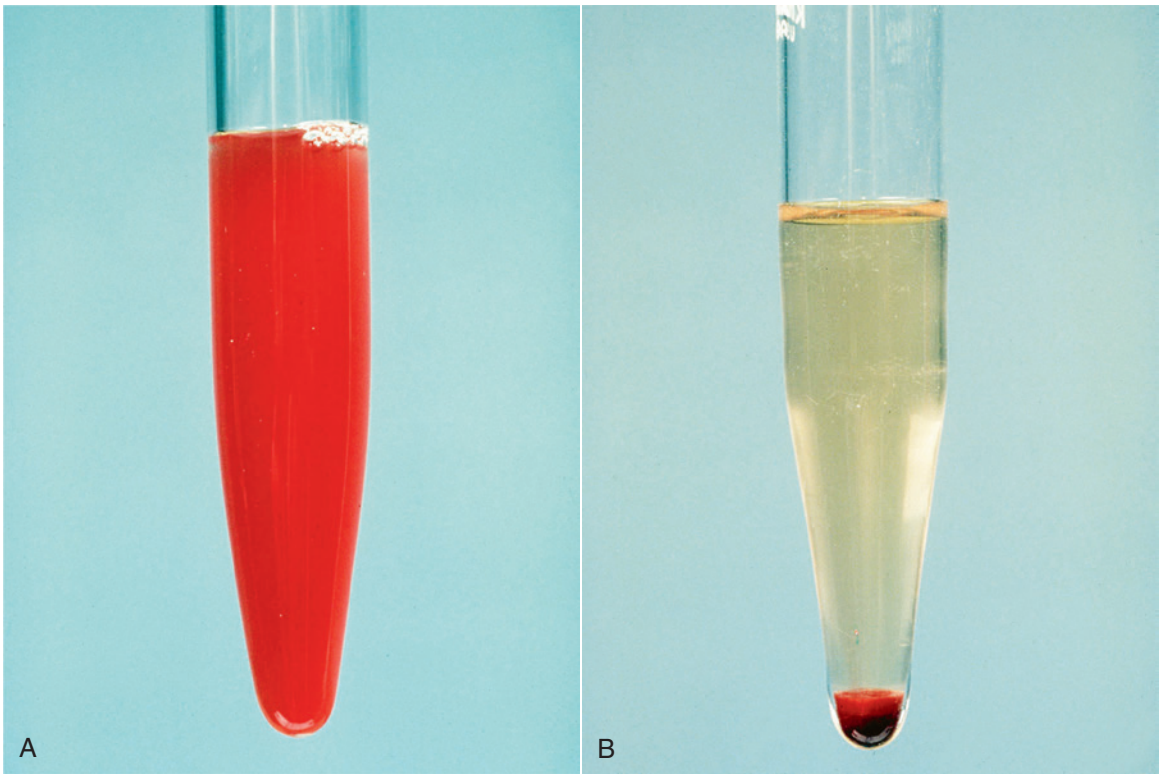


FIG 38.1
(A) Unspun urine sample from a dog with hematuria. Without centrifugation, one cannot differentiate pigmenturia (e.g., hemoglobinuria) from hematuria (i.e., red cells). **(B)** Red blood cell pellet after centrifugation of a urine sample from a dog with hematuria.

BOX 38.1

Causes of Hematuria

Urinary Tract Origin (Kidneys, Ureters, Bladder, Urethra)

- Trauma
  - Traumatic collection (e.g., catheterization, cystocentesis)
  - Renal biopsy
  - Blunt trauma (e.g., automobile accident)
- Urolithiasis
- Neoplasia
- Inflammatory disease
  - Urinary tract infection
  - Feline idiopathic cystitis, urethritis (idiopathic feline lower urinary tract disease)
  - Chemically induced inflammation (e.g., cyclophosphamide-induced cystitis)
  - Polypoid cystitis
  - Proliferative urethritis (granulomatous urethritis)
- Parasites
  - Dioctophyma renale
  - Capillaria plica
- Coagulopathy
  - Intoxication by vitamin K antagonists
  - Coagulation factor deficiencies
  - Disseminated intravascular coagulation
  - Thrombocytopenia
- Renal infarction
- Renal pelvic hematoma
- Vascular malformation
  - Renal telangiectasia (Welsh Corgi)
  - Idiopathic renal hematuria
- Polycystic kidney disease

Genital Tract Contamination (E.G., Prostate, Prepuce, Vagina)

- Estrus
- Subinvolution of placental sites
- Inflammatory, neoplastic, and traumatic lesions of the genital tract

idiopathic cystitis in a cat with a previous history of the disease. This erroneous conclusion (and ongoing diagnostic evaluation) can sometimes be avoided by simply comparing the results of a voided urine sample with those observed in the sample obtained by cystocentesis.

During the history, it is crucial to determine whether dysuria (see later) is associated with hematuria. If present, signs of dysuria (e.g., pollakiuria, stranguria) suggest involvement of the lower urinary tract (i.e., bladder, urethra), whereas painless hematuria suggests upper urinary tract involvement. If hematuria is present, ask the owner about its timing. Blood at the beginning of urination may indicate a disease process in the urethra or genital tract. Blood at the end of urination or throughout urination may signify a problem in the bladder or upper urinary tract (kidneys or ureters). Hematuria is more common in dogs with urinary bladder neoplasia than in dogs with renal neoplasia. Often, dogs with renal neoplasia present with nonspecific signs, such as weight loss and poor appetite. When hematuria is associated with coagulopathies, other signs such as epistaxis, melena, bruising, and prolonged bleeding from venipuncture sites are also likely to be present.

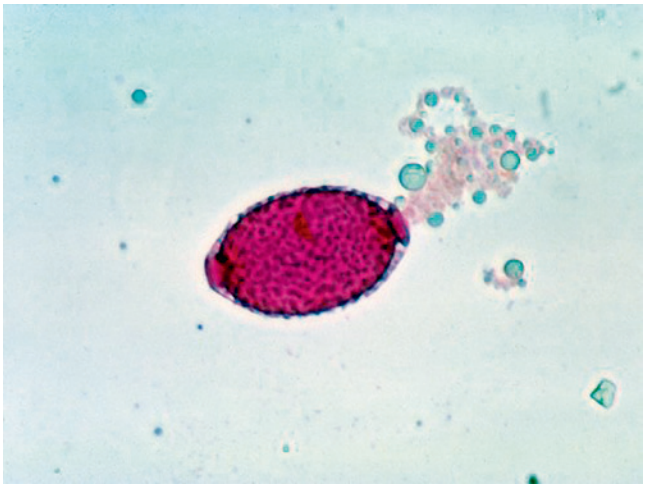


FIG 38.2
Capillaria plica ovum in the urine sediment of a cat (100×).

The first step in the diagnostic evaluation of an animal with hematuria is assessment of a properly collected urine sample by urinalysis and urine culture to rule out bacterial urinary tract infection. The presence of increased numbers of white blood cells in the urine sediment (i.e., pyuria) indicates an inflammatory process and increases the suspicion of bacterial urinary tract infection. Identification of hematuria in a voided urine sample but not in a sample collected by cystocentesis suggests the urethra or genital tract as the source of bleeding. Abnormal transitional epithelial cells observed in urine sediment stained with Wright-Giemsa increases the suspicion of transitional cell carcinoma. However, this diagnosis should always be based on histopathologic findings in tissue biopsy samples collected during urethrocystoscopy or by a catheter-assisted (aspiration) approach because irritation and inflammation can result in dysplastic changes in epithelial cells observed on routine cytologic evaluation. Anemia associated with blood loss is uncommon in patients with hematuria and is mainly seen in dogs with benign renal hematuria (see later). Hematuria is not a common presentation for patients with coagulopathies, but if the cause of hematuria remains obscure after routine clinical diagnostic evaluation, which includes urinalysis, complete blood count, serum biochemical profile, and diagnostic imaging studies, coagulation tests and a platelet count may be indicated. Ova are observed in the urine sediment of animals with urinary tract parasites (Fig. 38.2). Plain abdominal radiographs are useful to identify radiopaque calculi (e.g., struvite, oxalate). A double-contrast cystogram, positive contrast urethrogram, or excretory urogram may be necessary to identify radiolucent calculi and investigate

other potential causes of hematuria (e.g., blood clots in the kidney or bladder). Abdominal ultrasonography is useful to identify soft tissue lesions such as neoplasia and polypoid cystitis.

Idiopathic Renal Hematuria

The urinary bleeding in this disorder originates in the kidney, but its cause is obscure. Renal hemorrhage usually is unilateral, but occasionally it may be bilateral. Large-breed dogs (e.g., Weimaraners, Boxers, Labrador Retrievers) of both sexes often are affected. Most are younger than 5 years at presentation, and approximately one-third of reported cases have been in immature dogs (<1 year).

The owner typically reports severe macroscopic hematuria that does not appear to cause any discomfort to the dog (i.e., no dysuria), and hematuria typically occurs throughout urination. Blood clots also may be observed in the urine. Bleeding may occur for days or weeks and then disappear for months, only to return at a later time. There is no history of trauma, and no abnormalities are detected on physical examination.

The regenerative anemia may be acute (e.g., macrocytosis, polychromasia, reticulocytosis) or chronic, with evidence of iron deficiency (e.g., microcytosis, hypochromasia). Serum creatinine and blood urea nitrogen (BUN) concentrations are normal, urine specific gravity (USG) shows moderately concentrated urine, coagulation tests and platelet count are normal, and urine culture is negative. Hydronephrosis and hydroureter, caused by obstructive blood clots, may be observed on the affected side by diagnostic imaging studies. Filling defects caused by blood clots also sometimes can be observed in the bladder. In female dogs, cystoscopy allows identification of the affected side by observation of normal urine flowing from one ureteral opening as compared with blood coming from the contralateral ureteral opening (Fig. 38.3 and Video 38.1).

Nephrectomy should be considered if bleeding is documented to be unilateral and has been intractable, with the development of severe anemia. Nephrectomy resolves hematuria in dogs with unilateral renal hemorrhage, but some dogs have been reported to develop hemorrhage from the contralateral kidney at some point after nephrectomy. Thus the decision to perform nephrectomy should be weighed carefully. Some affected dogs have intermittent periods of hemorrhage interspersed with long asymptomatic time periods. If there is no anemia or anemia is mild, then observation of the patient over time with monitoring of hematocrit may be preferable to nephrectomy. Recently, endoscopically guided sclerotherapy using solutions containing povidone iodine, silver nitrate, or both has been used as a renal-sparing technique to successfully control renal hemorrhage in dogs with idiopathic renal hematuria.

DYSURIA

Dysuria refers to painful or difficult urination and typically is manifested as pollakiuria (excessively frequent passage of small volumes of urine) and stranguria (straining to urinate because of spasm of the bladder and urethra). It usually is associated with disorders of the lower urinary tract, especially cystitis, urethritis, cystic calculi, bladder neoplasia, and obstruction of the urethra by calculi or neoplasia (Box 38.2). Dysuria can also be associated with neoplastic and inflammatory diseases of the genital tract (e.g., prostate gland, vagina). Frequent licking at the genital area often is observed in dogs and cats with dysuric disorders. Dogs with perineal hernias will sometimes present for dysuria.

During history taking, it is important to clarify what the owner actually is observing. Many owners cannot readily differentiate a dog or cat that is straining to urinate from one that is straining to defecate. Thus owners sometimes believe that their animal is constipated when in fact it is straining to urinate. Also, sometimes owners report that their dog is

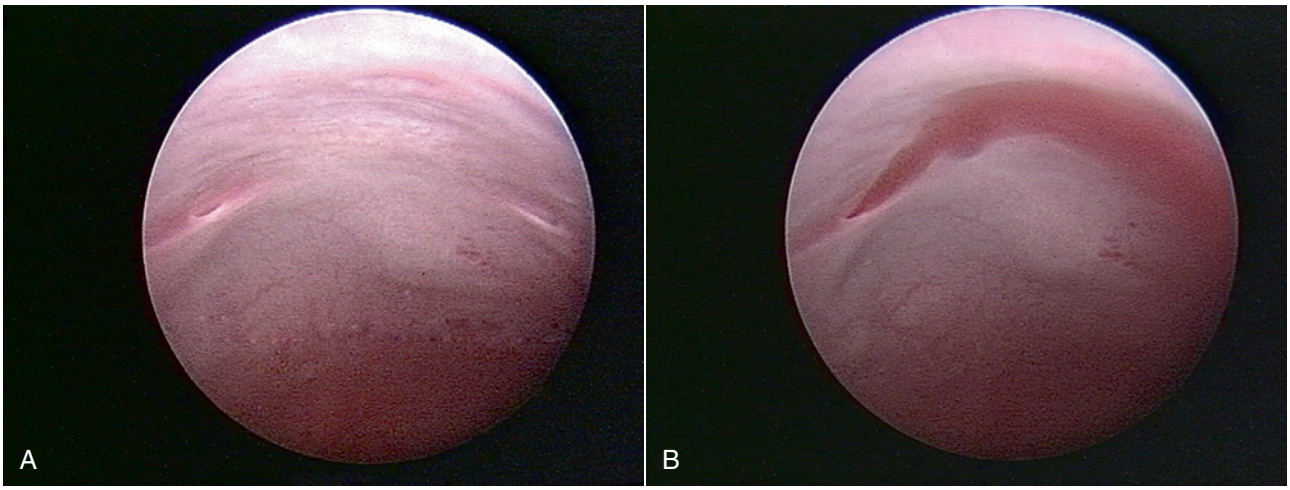


FIG 38.3
(A) Normal ureteral openings in the trigone region of the bladder of a normal dog on cystoscopy. **(B)** Blood coming from a ureteral opening in the trigone region of the bladder in a dog with idiopathic hematuria.

BOX 38.2

Causes of Dysuria

- Inflammatory disease
  - Urinary tract infection
  - Feline idiopathic cystitis, urethritis (idiopathic feline lower urinary tract disease)
  - Chemically induced inflammation (e.g., cyclophosphamide-induced cystitis)
  - Polypoid cystitis
  - Proliferative urethritis (granulomatous urethritis)
- Urolithiasis
  - Cystic calculi
  - Urethral calculi
- Neoplasia
  - Transitional cell carcinoma of bladder or urethra
  - Prostatic neoplasia
  - Vaginal neoplasia
- Trauma
  - Bladder or urethral rupture
  - Urethral stricture (previous trauma or surgery)
- Neurogenic disorder
  - Reflex dyssynergia
- Other
  - Perineal hernia

incontinent because they find urine in inappropriate locations in the house. Although incontinent dogs often leave wet spots where they have been lying down, dogs with polyuria and polydipsia (PU-PD) urinate voluntarily but in inappropriate locations and at inappropriate times because they are not allowed outside frequently enough to accommodate their large volume of urine production. A careful history is therefore very important for understanding the problem.

Dogs and cats with dysuria assume the normal posture for urination but spend an inordinate amount of time attempting to urinate, often passing only small volumes of urine. They shift position, get up, move to another location, and posture repeatedly. Even with an empty bladder, mucosal irritation results in repeated unsuccessful attempts to urinate. Cats with urethral obstruction sometimes adopt a distressed yowling vocalization during attempts to urinate. It is important in this clinical situation to evaluate the animal for the presence of urethral obstruction. Complete urethral obstruction is readily identified during abdominal palpation by the presence of a large, turgid, painful bladder, whereas a small, painful bladder suggests cystitis without obstruction. Caution should be taken to avoid excessive pressure when palpating a bladder that is suspected to be obstructed.

Observing the animal urinate can be valuable for identifying the problem as dysuria. Attempting to pass a urinary catheter allows the clinician to determine quickly whether the urethra is patent or obstructed. Masses and calculi are most easily detected by palpation when the bladder is empty or only partially full. The presence of many small cystic calculi generates a crepitant sensation on palpation, whereas a single large calculus can be difficult to differentiate from a tumor or large blood clot. Rectal palpation should be performed in all dysuric patients, both male and female. Not only is rectal examination important to evaluate the prostate gland in males, but it allows the identification of urethral tumors and proliferative urethritis in female dogs. The perineum should be inspected for perineal hernia, and the penis should be extruded completely to look for lesions such as transmissible venereal tumor in male dogs.

POLYURIA AND POLYDIPSIA

Normal water intake in dogs may be as high as 60 to 90 mL/kg/day; maximal normal water intake in cats is 45 mL/kg/day. Polyuria and polydipsia typically are reported simultaneously and, with the exception of dogs with psychogenic polydipsia (PPD; see later), polydipsia usually occurs in response to polyuria. The presence of polydipsia can be documented by having the owner measure the animal's water intake at home, but this is more practical in dogs than in cats. Normal water intake is more variable than urine output because of variation in several factors, including ambient temperature and respiratory evaporative loss of water, exercise level, water content of food, fecal water content, age, and physiologic state (e.g., pregnancy, lactation). Normal urine production in dogs and cats is 26 to 44 mL/kg/day.

Polyuria and polydipsia can be caused by several disorders, notably diseases of the kidney and endocrine system. In many cases, the pathophysiology of PU-PD is multifactorial (Table 38.1). The history should always include information about drugs that the animal may have been given that could contribute to PU-PD, especially corticosteroids (administered by any route, including topically) and diuretics. Pollakiuria must be differentiated from polyuria because some owners erroneously conclude that because an animal is urinating more frequently, it must be producing more urine. Animals with polyuria may have increased frequency of urination, but each urination consists of a large volume and there is no evidence of stranguria. Nocturia often accompanies polyuria and sometimes is the first sign detected by the dog's owner.

Routine urinalysis, including determination of the USG, is the logical starting point for the diagnostic evaluation of an animal with PU-PD. The USG of dogs can vary widely throughout the day, but the highest USG (usually >1.035–1.040) typically is found in the morning, before the dog eats and drinks. USG varies less throughout the day in cats, and cats typically have moderately concentrated urine when eating dry food (usually ≥1.035). USG values of 1.050 to 1.076 and 1.047 to 1.087 occur in normal dogs and cats, respectively, deprived of water until signs of dehydration have developed. Generally, a USG of 1.040 or higher is expected in sick dogs or cats that are dehydrated. Finding a relatively high USG (>1.025) would cast doubt about the accuracy of the history in an animal presented for evaluation of PU-PD. If the USG at presentation is in the hyposthenuric (<1.007) or isosthenuric (1.007–1.014) range, a minimum database of a complete blood count, serum biochemistry

TABLE 38.1

Causes of Polyuria and Polydipsia Seen in Small Animal Practice

DISEASE	MECHANISM OF POLYURIA AND POLYDIPSIA	CONFIRMATORY TESTS
Chronic renal disease (S)*	Osmotic diuresis in remnant nephrons Disruption of medullary architecture by structural disease	ECC, CBC Biochemistry profile Urinalysis Radiography Abdominal ultrasonography Iohexol clearance
Hyperadrenocorticism (W)*	Defective ADH release and action Psychogenic	LDDST Plasma ACTH concentration Abdominal ultrasonography
Diabetes mellitus (S)*	Osmotic diuresis caused by glucosuria	Blood glucose concentration Urinalysis
Hyperthyroidism (W)*	Increased medullary blood flow, MSW Psychogenic Hypercalciuria	Thyroxine Technetium scan
Pyometra (W)	*Escherichia coli* endotoxin Immune complex glomerulonephritis	History Physical examination, CBC, abdominal radiography
Postobstructive diuresis (S)	Elimination of retained solutes Defective response to ADH Defective sodium reabsorption	History Physical examination Urinalysis
Hypercalcemia (W)	Defective ADH action Increased medullary blood flow Impaired NaCl transport in loop of Henle Hypercalcemic nephropathy Direct stimulation of thirst center	Serum calcium concentration
Liver disease (W)	Decreased urea synthesis with loss of medullary solute Decreased metabolism of endogenous hormones (e.g., cortisol, aldosterone) Psychogenic (hepatic encephalopathy) Hypokalemia	Liver enzyme levels Serum bile acids Blood ammonia Liver biopsy
Pyelonephritis (W)	*E. coli* endotoxin Increased renal blood flow MSW Renal parenchymal damage	Urinalysis Urine culture CBC Excretory urography Abdominal ultrasonography
Hypoadrenocorticism (W)	Renal sodium loss with MSW	Serum sodium and potassium concentrations ACTH stimulation
Hypokalemia (W)	Defective ADH action Increased medullary blood flow and loss of medullary solute	Serum potassium concentration
Diuretic phase of oliguric ARF (S)	Elimination of retained solutes Defective sodium reabsorption	History CBC Biochemistry profile Urinalysis Abdominal ultrasonography Renal biopsy
Partial urinary tract obstruction (S)	Redistribution of renal blood flow Defective sodium reabsorption Renal parenchymal damage	History Physical examination

TABLE 38.1

Causes of Polyuria and Polydipsia Seen in Small Animal Practice—cont'd

DISEASE	MECHANISM OF POLYURIA AND POLYDIPSIA	CONFIRMATORY TESTS
Drugs (W)	Various mechanisms, depending on drug	History
Salt administration (S)	Osmotic diuresis caused by excess sodium administered	History
Excessive parenteral fluid administration (W) (polyuria only)	Water diuresis caused by excess water administered	History
Central diabetes insipidus (CDI) (W)	Congenital lack of ADH (rare) Acquired lack of ADH (idiopathic, tumor, trauma)	Water deprivation test Exogenous ADH test ADH assay
Nephrogenic diabetes insipidus (NDI) (W)	Congenital lack of renal response to ADH (very rare) Acquired lack of renal response to ADH	Water deprivation test Exogenous ADH test ADH assay ECC
Psychogenic polydipsia (PP) (W)	Neurobehavioral disorder (anxiety?) Increased renal blood flow MSW	Water deprivation test Exogenous ADH test Behavioral history
Renal glucosuria (S)	Solute diuresis caused by glucosuria	Blood glucose concentration Urinalysis
Primary hypoparathyroidism (W)	Unknown (psychogenic?)	Serum calcium, phosphorus PTH concentrations
Acromegaly (W, S)	Insulin antagonism Glucose intolerance Diabetes mellitus in affected cats	Computed tomography or magnetic resonance imaging Insulin-like growth factor I assay
Polycythemia (W)	Unknown (increased blood viscosity?)	CBC
Multiple myeloma (W)	Unknown (increased blood viscosity?)	Serum protein electrophoresis
Renal MSW (W)	Depletion of medullary interstitial solute (urea, sodium, potassium)	Gradual water deprivation (3-5 days) Hickey-Hare test

*Most common causes of polyuria and polydipsia.
ACTH, Adrenocorticotropic hormone; *ADH,* antidiuretic hormone; *ARF,* acute renal failure; *CBC,* complete blood count; *ECC,* endogenous creatinine clearance; *LDDST,* low-dose dexamethasone suppression test; *MSW,* medullary washout of solute; *PTH,* parathyroid hormone; *S,* solute diuresis; *W,* water diuresis.
From DiBartola SP: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Elsevier.

profile, and serum thyroxine concentration (in cats) should be obtained. Often this information will shed light on the cause of the PU-PD. USG tends to be lowest (i.e., 1.001–1.007) in conditions such as PPD, central diabetes insipidus, and nephrogenic diabetes insipidus. If the USG is higher than 1.014 and the animal seems otherwise healthy, it is reasonable to have the owner quantify water consumption at home before proceeding with the diagnostic evaluation. The water deprivation test (see Chapter 42) should be considered in animals that have normal blood test results after the initial diagnostic evaluation of PU-PD. If the USG is in the isosthenuric range and the cause of the PU-PD is not apparent, abdominal ultrasonography to evaluate renal architecture is indicated. Measurement of serum symmetric dimethylarginine (SDMA) concentration or estimation of glomerular filtration rate by endogenous creatinine clearance or iohexol clearance also is valuable to eliminate nonazotemic chronic renal disease (i.e., <75% loss of renal mass) as a contributing factor (see Chapter 42).

Psychogenic Polydipsia

PPD is an uncommon disorder that usually occurs in large-breed dogs (e.g., German Shepherds, Doberman Pinschers). It is rare to nonexistent in cats. Owners of affected dogs may report that the dog has a nervous disposition or experienced some stressful event before the onset of polydipsia. In some cases, the owner has unknowingly reinforced the water drinking behavior in some way. Some dogs with PPD dramatically decrease their water consumption during hospitalization, which facilitates diagnosis. Dogs with PPD typically

have extremely hyposthenuric urine (i.e., USG = 1.001–1.003). Although not consistently present, mild hyponatremia in a dog with marked hyposthenuria is suggestive of PPD. Dogs with PPD of recent onset often have a normal response to abrupt water deprivation testing, but those with long-standing PPD develop renal medullary washout of solute because the release of vasopressin from the pituitary gland is suppressed by plasma hypo-osmolality. Vasopressin normally facilitates urea reabsorption in the inner medulla of the kidney and helps maintain medullary hypertonicity. Gradual water deprivation testing allows time for restoration of the renal medullary solute gradient and is the preferred diagnostic test in dogs with PPD. Treatment of PPD is accomplished by gradual water restriction into the normal range over several days.

RENOMEGALY

Renomegaly refers to enlargement of the kidney. It may be unilateral or bilateral, and bilateral enlargement may be symmetric or asymmetric. Renomegaly may be acute or chronic in onset. In most animals with renomegaly, onset is insidious. Acute renomegaly is uncommon and when it occurs (e.g., acute obstruction of a kidney by a nephrolith), the presentation is that of acute abdomen (i.e., abdominal pain, reluctance to move, vomiting). Chronic renomegaly typically is moderate or severe but occasionally can be mild. For example, mild enlargement may occur in some dogs with renal amyloidosis and in some cases of acute renal failure (e.g., leptospirosis) because of renal swelling. The renal capsule, however, limits the extent of acute swelling that can occur. Unilateral renal enlargement can occur because of compensatory hypertrophy in animals with a solitary kidney or with severe end-stage disease in the contralateral kidney.

Normally, feline kidneys are 3.5 to 4.5 cm in length and can be readily palpated in cooperative cats. The size of canine kidneys varies according to body size, and generally kidneys are more difficult to palpate in dogs than in cats. Occasionally the left kidney can be palpated in a cooperative dog. Renal length and volume in dogs is correlated with body weight. For example, dogs up to about 15 kg in weight are expected to have kidneys 3 to 5.5 cm in length, whereas dogs in the 30- to 45-kg range are expected to have kidneys 7 to 8 cm in length. A rule of thumb that has been used for many years is based on the ratio of the length of the kidney as observed on plain abdominal radiographs to the length of the second lumbar vertebra (L2). On plain abdominal radiographs, this ratio is 2.5-3.0-to-1 in cats and 2.5-3.5-to-1 in dogs.

Disorders that cause renomegaly include polycystic kidney disease, neoplasia, and obstruction. Renomegaly can occur in dogs and cats, but it is more common in cats. Polycystic kidney disease is inherited as an autosomal dominant trait in Bull Terriers and Persian cats (autosomal dominant polycystic kidney disease [ADPKD]). It is caused by a mutation in exon 29 of the polycystin-1 gene in Persian cats, and prevalence in the breed approaches 30%. Many young Persian cats with ADPKD are asymptomatic, and renomegaly is recognized as an incidental finding. The kidneys of cats with ADPKD become progressively enlarged and irregular over time as the cysts increase in number and size. Renal failure usually does not develop until 7 or 8 years of age. Currently, ultrasonography is the clinical test of choice for identifying ADPKD in affected cats. In one study, renal ultrasonography had a sensitivity of 75% when performed at 4 months of age and a sensitivity of 91% when performed at 9 months of age for the diagnosis of ADPKD. Primary and metastatic renal tumors can cause renomegaly, and lymphosarcoma often is responsible, especially in cats. Renal lymphoma is usually bilateral in cats and often is associated with the alimentary form of the disease. Occasionally renal involvement may be extensive enough to cause renal failure. The diagnosis of renal lymphosarcoma often can be made by cytologic evaluation of a fine-needle aspirate of the kidney that identifies a monomorphic population of immature lymphocytes. Renal obstruction by a nephrolith or ureterolith, or inadvertent ligation of a ureter during ovariohysterectomy, can result in hydronephrosis and renomegaly. Uncommonly, ureteral fibrosis, secondary to previous ureterolith removal or idiopathic in nature, can result in hydronephrosis. Blunt abdominal trauma can cause subcapsular hemorrhage and renomegaly, but the renal capsule usually limits the extent of enlargement. Bacterial infection can result in a renal abscess or pyonephrosis. The noneffusive form of feline infectious peritonitis often affects the kidneys, liver, mesenteric lymph nodes, central nervous system, and eyes. Renal involvement occurs in many affected cats, and they may have enlarged, irregular kidneys on abdominal palpation.

Perinephric Pseudocysts

Although not a renal disease, perinephric pseudocysts can easily be confused with renomegaly on routine abdominal palpation. Perinephric pseudocysts are fluid-filled fibrous sacs that surround the kidney but are not lined by epithelium—hence the term *pseudocyst.* They are idiopathic in origin but often occur in association with chronic kidney disease (CKD) in older (>10 years) cats of both sexes and any breed. Most cats with perinephric pseudocysts have at least mild CKD. Occasionally small kidneys and CKD are diagnosed before the development of perinephric pseudocysts. The presenting complaints may be related to underlying CKD (e.g., PU-PD, anorexia, and weight loss), but usually abdominal distention is the only abnormality detected by the owner. Perinephric pseudocysts may be unilateral or bilateral. Renal ultrasonography is the diagnostic test of choice and demonstrates an accumulation of anechoic fluid between the capsule and renal parenchyma of one or both kidneys (Fig. 38.4). Definitive treatment involves surgical resection of the pseudocyst capsule. The kidney should not be removed in cats with unilateral perinephric pseudocysts because progression of renal disease in the remnant kidney can be accelerated dramatically, and renal failure may worsen rapidly (Fig. 38.5). Recently, a laparoscopic approach has been used for fenestration or subtotal resection of perinephric pseudocyst capsules. Ultimately, the prognosis of

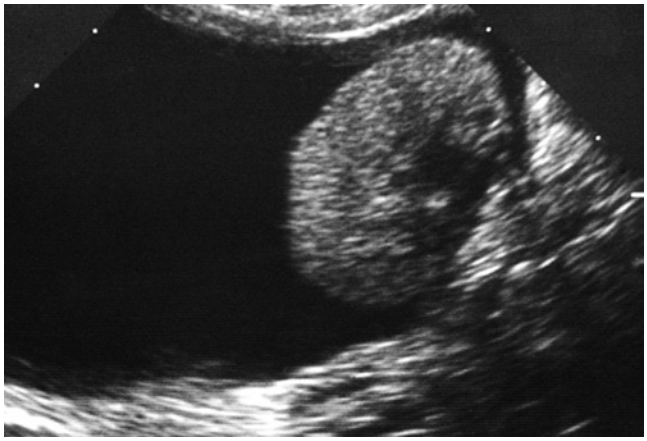


FIG 38.4
Ultrasonographic appearance of a perinephric pseudocyst in a cat. *Left,* Anechoic fluid within the cyst *(black area). Right,* The echogenic structure represents the kidney itself.

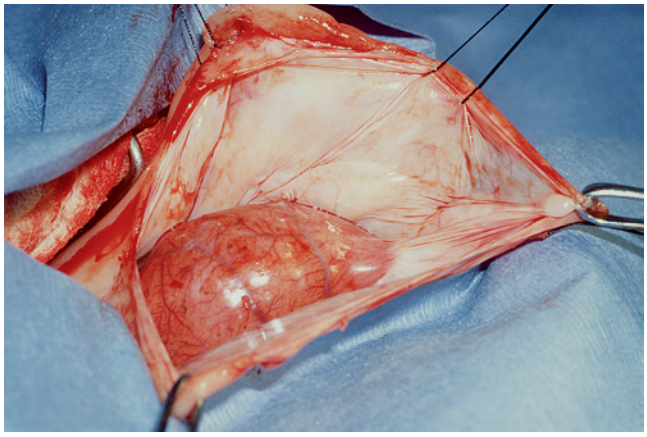


FIG 38.5
Appearance of kidney in a cat with a perinephric pseudocyst after surgically opening the pseudocyst capsule.

cats with perinephric pseudocysts is related primarily to the extent of underlying CKD at the time of diagnosis. Rarely, a perinephric pseudocyst can occur in conjunction with transitional cell carcinoma.

Suggested Readings

Berent AC, et al. Endoscopic-guided sclerotherapy for renal-sparing treatment of idiopathic renal hematuria in dogs: 6 cases (2010-2012). *J Am Vet Med Assoc*. 2013;242:1556.

Chew DJ. Approach to polyuria and polydipsia. In: Chew D, Di Bartola S, Schenck P, eds. *Canine and feline nephrology and urology*. 2nd ed. St Louis: Elsevier Saunders; 2011:465–486.

Di Bartola SP. Miscellaneous syndromes. In: Chew D, DiBartola S, Schenck P, eds. *Canine and feline nephrology and urology*. 2nd ed. St Louis: Elsevier Saunders; 2011:487–507.

Forrester SD. Diagnostic approach to hematuria in dogs and cats. *Vet Clin North America Small Animal Pract*. 2004;34:849.

Helps CR, et al. Detection of the single-nucleotide polymorphism causing feline autosomal dominant polycystic kidney disease in Persians from the UK using a novel real-time PCR assay. *Mol Cell Probes*. 2007;21:31.

Watson ADJ. Dysuria and haematuria. In: Elliott J, Grauer GF, eds. *BSAVA manual of canine and feline nephrology and urology*. Gloucester, England: British Small Animal Veterinary Association; 2007.

CHAPTER 39

Diagnostic Tests for the Urinary System



GLOMERULAR FUNCTION

Evaluation of glomerular function is an essential part of the diagnostic approach to patients with suspected renal disease because the glomerular filtration rate (GFR) is directly related to functional renal mass. Serum creatinine (SCr) and blood urea nitrogen (BUN) concentrations are commonly used screening tests; symmetric dimethylarginine (SDMA) and creatinine clearance are useful for patients with suspected renal disease who have normal BUN and SCr. Plasma clearance of radioisotopes and renal scintigraphy are advanced techniques that may be used to determine GFR and obtain information about individual kidney function but do not require urine collection. Iohexol clearance provides an estimate of the GFR without the need of urine samples, radioisotopes, or specialized equipment. Evaluation of urinary protein excretion allows for the assessment of the patient for glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis).

BLOOD UREA NITROGEN

Urea is synthesized in the liver via the ornithine cycle from ammonia derived from amino acid catabolism. Amino acids used in the production of urea arise from the catabolism of exogenous (i.e., dietary) and endogenous proteins. Renal excretion of urea occurs by glomerular filtration, and BUN concentrations are inversely proportional to the GFR. Urea is subject to passive reabsorption in the tubules, which occurs to a greater extent at slower tubular flow rates during dehydration and volume depletion. Thus urea clearance is not a reliable estimate of the GFR and, in the face of volume depletion, decreased urea clearance may occur without a decrease in GFR.

The production and excretion of urea do not proceed at a constant rate. Urea production and excretion increase after a high-protein meal, and an 8- to 12-hour fast is recommended before measuring BUN concentrations to avoid the effect of feeding on urea production. Gastrointestinal bleeding can increase BUN concentrations because blood represents an endogenous protein load. Clinical conditions characterized by increased catabolism (e.g., starvation, infection, fever) also can increase BUN concentrations slightly. Some drugs may increase BUN concentrations by increasing tissue catabolism (e.g., glucocorticoids, azathioprine) or decreasing protein synthesis (e.g., tetracyclines), but these effects are usually minimal. Conversely, BUN concentrations can be decreased by low-protein diets, anabolic steroids, severe hepatic insufficiency, or portosystemic shunting. These nonrenal variables limit the usefulness of BUN as an indicator of the GFR. Normal BUN concentrations are 8 to 25 mg/dL in the dog and 15 to 35 mg/dL in the cat. Reagent test strips (Azostix, Bayer, Elkhart, Ind) can be used to estimate BUN levels in whole blood samples from dogs and cats, with relatively high sensitivity and specificity.

SERUM CREATININE

Creatinine is a nonenzymatic breakdown product of phosphocreatine in muscle; the daily production of creatinine in the body is determined largely by the muscle mass of the individual. Young animals have lower serum concentrations, whereas males and well-muscled individuals have higher concentrations. SCr concentration is not affected appreciably by diet. Creatinine is not metabolized and is excreted by the kidneys almost entirely by glomerular filtration. Its rate of excretion is relatively constant in the steady state, and SCr varies inversely with the GFR. Thus determination of creatinine clearance provides an estimate of the GFR.

Creatinine is measured by the alkaline picrate reaction, which is not entirely specific for creatinine and measures another group of substances collectively known as noncreatinine chromagens. These substances are found in plasma, in which they may constitute up to 50% of the measured creatinine at normal serum concentrations but normally do not appear in urine. As SCr increases because of the progression of renal disease and decreasing GFR, the amount of noncreatinine chromagens is unchanged and contributes progressively less to the total measured SCr. Normal SCr in the dog and cat are 0.3 to 1.3 mg/dL and 0.8 to 1.8 mg/dL, respectively. Greyhounds have slightly higher SCr than non-Greyhounds; this difference is attributable to increased muscle mass and not to any decrease in the GFR. Relatively wide reference intervals and assay imprecision can result in

considerable interassay variation in SCr concentration measurements. As a consequence, comparing an individual animal's fasting SCr concentration to previous results from the same animal over time (so-called trending) rather than to a laboratory reference range can improve the clinician's ability to identify progressive kidney disease and establish a prognosis.

The relationship of BUN or SCr to the GFR is a rectangular hyperbola. The slope of the curve is small when the GFR is mildly or moderately decreased but large when the GFR is severely decreased (Fig. 39.1). Thus large changes in the GFR early in the course of renal disease cause small increases in BUN or SCr, which may be difficult to appreciate clinically, whereas small changes in the GFR in advanced renal disease cause large changes in the BUN or SCr. The inverse relationship between SCr and the GFR is valid only in the steady state.

When nonrenal variables have been eliminated from consideration, an increase in BUN or SCr above normal implies that at least 75% of the nephrons are not functioning (see Fig. 39.1). Neither the cause nor the reversibility of this malfunction can be predicted from the magnitude of the BUN or SCr. The magnitude of the BUN or SCr cannot be used to predict whether azotemia is prerenal, primary renal, or postrenal in origin and cannot be used to distinguish between acute and chronic, reversible and irreversible, or progressive and nonprogressive processes. The BUN-to-creatinine ratio in prerenal and postrenal azotemia may be increased as a result of increased tubular reabsorption of urea at lower tubular flow rates or easier absorption of urea than creatinine across the peritoneal membranes in animals with uroabdomen. A decrease in the BUN-to-creatinine ratio often follows fluid therapy and reflects decreased tubular reabsorption of urea rather than an increased GFR.

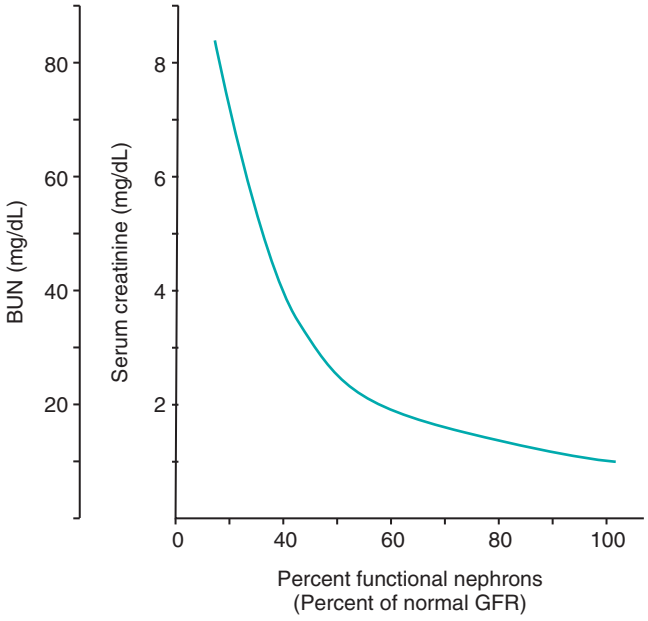


FIG 39.1
Relationship of blood urea nitrogen (BUN) or SCr to percentage of functional nephrons. *GFR,* Glomerular filtration rate.

SYMMETRIC DIMETHYLARGININE

SDMA is a low-molecular-weight (113 Da) by-product of posttranslational methylation of arginine residues in proteins. More than 90% of SDMA is removed from the body by filtration in the kidneys, and therefore its serum concentration can be used as an indicator of GFR. The serum concentration of SDMA is highly correlated with inulin clearance (the gold standard for GFR determination) as well as with SCr in humans, dogs, and cats. Its serum concentration increased above the upper limit of the reference range when GFR decreased by 40% from median normal GFR in cats with chronic kidney disease (CKD). In this study, it had 100% sensitivity, 100% negative predictive value, 91% specificity, and 86% positive predictive value. In longitudinal studies of animals with CKD, it increased a median of 17 months before SCr in cats and mean of almost 10 months before SCr in dogs. It is not highly protein-bound, is produced at a relatively constant rate in the body, and is not affected by nonrenal factors. Especially important, and unlike SCr, SDMA is not affected by lean body mass and thus is a more reliable indicator of GFR in animals with decreased muscle mass, in which SCr can be falsely low. Normal serum SDMA concentrations are < 14 μg/dL in adult dogs and cats and < 16 μg/dL in puppies and kittens.

CYSTATIN C

Cystatin C is a small polypeptide protease inhibitor that is freely filtered by the glomeruli and meets many of the criteria for an endogenous marker of GFR. Serum cystatin C concentration in cats is not affected by age, breed, or sex, and food does not have to be withheld before testing. In dogs, plasma cystatin C concentration may be affected by age and body weight, and it decreases markedly 1 hour after feeding, only returning to normal 12 hours later. In some studies, serum cystatin C concentrations could not reliably differentiate dogs and cats with low, borderline, or normal GFR. In one study, serum cystatin C concentrations were not different between hyperthyroid cats that became azotemic after treatment and those that remained non-azotemic, did not increase with establishment of euthyroidism, and could not differentiate nonhyperthyroid CKD cats from healthy geriatric cats. Based on the results of these studies, serum cystatin C concentration does not appear to be a clinically useful indicator of GFR in dogs and cats.

FIBROBLAST GROWTH FACTOR-23

Fibroblast growth factor-23 (FGF-23) is a phosphate regulatory hormone (i.e., a phosphatonin) produced by osteocytes and osteoblasts in response to hyperphosphatemia and increased serum calcitriol concentration. It inhibits 1-α-hydroxylase in the kidney (thus decreasing calcitriol production), downregulates sodium-phosphate co-transport in the proximal tubules (thus increasing urinary phosphate excretion), and decreases parathyroid hormone secretion by

the parathyroid glands. Its concentration has been shown to increase from baseline in cats that developed azotemia over a 1-year time period as compared with cats that remained non-azotemic, and survival of cats with CKD has been negatively correlated with serum FGF-23 concentrations. Serum FGF-23 concentration decreases from baseline in cats with stable azotemic CKD fed a decreased protein diet.

N-ACETYL-β-D-GLUCOSAMINIDASE AND γ-GLUTAMYL TRANSFERASE

N-acetyl-β-D-glucosaminidase (NAG) is located in the cytoplasm (in lysosomes) and γ-glutamyl transferase (GGT) in the luminal brush border of proximal tubular cells. Their large molecular size precludes glomerular filtration, and increased urinary concentration of these enzymes indicates tubular cell injury. Their clinical utility lies in the early detection of renal tubular injury in patients with acute kidney injury (AKI). For example, twofold to threefold increases in urinary NAG-to-creatinine or GGT-to-creatinine ratios have been observed in models of aminoglycoside nephrotoxicity. Pyelonephritis can result in increased urinary NAG-to-creatinine ratio, but it does not seem to be affected by lower urinary tract infection. Thus additional studies are warranted to determine if urinary NAG-to-creatinine ratio can help differentiate upper from lower urinary tract infection.

KIDNEY INJURY MOLECULE-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein expressed on the luminal surface of proximal tubular cells that is thought to function in cell-to-cell or cell-to-matrix adhesion. It is expressed at low to nondetectable levels in the normal kidney, but it is markedly upregulated 24 to 48 hours after ischemic or toxic injury to the proximal tubules and shed in urine. KIM-1 likely plays a role in tubular repair because tubular cells that survive ischemic damage express KIM-1 and develop a phagocytic phenotype that allows them to internalize apoptotic cells and clear tubular debris. In cats, it was not detected in normal renal tissue but was identified in the kidneys and urine of cats with kidney injury.

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN

Neutrophil gelatinase-associated lipocalin (NGAL) is a small glycoprotein expressed on neutrophils as well as many types of epithelial cells including renal proximal epithelial cells, the loop of Henle, and collecting ducts. Its siderophore-chelating properties allow it to interfere with iron accumulation by bacteria. NGAL is upregulated in response to inflammatory signals that occur with proximal tubular cell injury. It is not kidney-specific, however, and also can be increased in the urine of dogs with pyuria caused by lower urinary tract infection. A canine-specific NGAL ELISA has been validated in dogs, and serum and urine NGAL concentrations as well as urine NGAL-to-creatinine ratios (UNCR) have been reported in normal dogs and those with AKI, CKD, and lower urinary tract disorders. NGAL seems to be a sensitive and specific biomarker for AKI, and the urine NGAL-to-creatinine ratio may facilitate early detection of AKI in high-risk clinical situations such as renal ischemia associated with general anesthesia, heatstroke, and nephrotoxin exposure. The UNCR recently was evaluated in healthy dogs and those with non-azotemic (IRIS stage I) and azotemic (IRIS stage II-V) AKI, CKD, and lower urinary tract disorders. Dogs with non-azotemic and azotemic AKI had the highest UNCR, followed by those with CKD and lower urinary tract disorders. Among the dogs with AKI, there was no significant difference between survivors and nonsurvivors.

CREATININE CLEARANCE

The renal clearance of a substance is the volume (V) of plasma (P) that would have to be filtered by the glomeruli per minute to account for the amount of that substance appearing in the urine per minute. The renal clearance of a substance that is neither reabsorbed nor secreted by the tubules is equal to the GFR. For such a substance in a steady state, the amount filtered equals the amount excreted, so the $GFR \times P_x = U_x \times V$. Dividing both sides of the equation by P_x gives the familiar clearance formula (U_xV/P_x), which in this case is equal to the GFR.

Creatinine is produced endogenously and excreted by the body largely by glomerular filtration. Its clearance can be used to estimate the GFR in the steady state. Numerous studies in the dog and cat have shown that endogenous creatinine clearance in these species is 2 to 5 mL/min/kg. Values for glomerular function tests in the dog and cat are presented in Table 39.1.

In chronic progressive renal disease, the urinary concentrating ability is impaired after two-thirds of the nephron population has become nonfunctional, whereas azotemia typically does not develop until 75% of the nephrons have become nonfunctional. Thus the main reason to determine endogenous creatinine clearance is the clinical suspicion of renal disease in a patient with polyuria and polydipsia but normal BUN and SCr. The only requirements for the determination of endogenous creatinine clearance are an accurately timed collection of urine (preferably, 12 or 24 hours) and determination of the patient's body weight and serum and urine creatinine concentrations. Failure to collect all urine produced will erroneously decrease the calculated clearance value.

To eliminate inaccuracy caused by noncreatinine chromagens, some investigators have advocated the use of exogenous creatinine clearance. In this procedure, creatinine is administered subcutaneously or intravenously to increase the SCr approximately 10-fold and decrease the relative effect of noncreatinine chromagens. Exogenous creatinine clearance exceeds endogenous creatinine clearance and closely approximates inulin clearance in the dog. The creatinine-to-inulin clearance ratio is not affected by sex, dietary protein, or duration of time after renal ablation. Endogenous creatinine clearance is a reliable estimate of the GFR only when methodology specific for creatinine is used.

TABLE 39.1

Normal Values for Tests of Renal Function in Dogs and Cats

TEST	DOG	CAT
Blood urea nitrogen concentration (mg/dL)	8-25	15-35
Serum creatinine concentration (mg/dL)	0.3-1.3	0.8-1.8
Serum symmetric dimethylarginine (µg/dL)	<14	<14
Serum cystatin C concentration (mg/dL)	0.5-1.5	0.5-1.5
Plasma fibroblast growth factor-23 (pg/mL)	211-499	56-700
Endogenous creatinine clearance (mL/min/kg)	2-5	2-5
Exogenous creatinine clearance (mL/min/kg)	3-5	2-4
Iohexol clearance (mL/min/kg)	1.7-4.1	1.3-4.2
24-hour urine protein excretion (mg/kg/day)	<20	<20
U_{Pr}/U_{Cr}	<0.5	<0.4
Urine NGAL-to-creatinine ratio (pg/mg)	40-3660	NA

In cats, exogenous creatinine clearance may be slightly lower than inulin clearance.

SINGLE-INJECTION METHODS FOR ESTIMATION OF GLOMERULAR FILTRATION RATE

Single-injection plasma clearance methods using inulin, iohexol, or creatinine have been used in dogs and cats with normal or decreased renal mass to estimate the GFR. Using these methods, the plasma clearance of a substance that is not bound to plasma proteins and is excreted only by the GFR (e.g., inulin, iohexol, creatinine) is calculated as the quotient of the administered dose divided by the area under the plasma concentration versus time curve. This technique has the advantage of not requiring collection of urine, but its accuracy depends on the pharmacokinetic model used to calculate the area under the curve and timing and number of samples used to make the calculation.

IOHEXOL CLEARANCE

Iohexol is an iodinated, water-soluble, nonionic, low-osmolar contrast agent that can be used to estimate the GFR in humans and domestic animals. It is nontoxic, confined to the extracellular space, not metabolized, experiences negligible binding to plasma proteins, and almost 100% of an injected dose can be recovered in the urine within 24 hours of injection.

Determination of iohexol clearance allows estimation of the GFR with a limited number of plasma samples and without the need for urine collection. Other advantages include the stability of iodine in plasma, which allows samples to be shipped to remote laboratories, no radioactivity, relatively easy measurement, and wide availability. Iohexol has not been reported to be toxic in dogs and cats, and the only disadvantage is the relatively large injection volume required in large dogs when the usual dosage of 300 mg iodine/kg body weight is used.

The clearance of iohexol is calculated as the dose administered divided by the area under the plasma disappearance curve. The elimination of iohexol can be described by a two-compartment model with initial disappearance from plasma (30–60 minutes) followed by disappearance from interstitial fluid (6–8 hours). For clinical use, a two-sample method with plasma samples collected at 5 and 120 minutes in dogs and at 20 and 180 minutes in cats can be used.

Normal values for iohexol clearance vary, depending on the pharmacokinetic model used to calculate clearance and laboratory method used to measure iohexol in plasma. Results should be normalized to body weight or body surface area. Normal values are 1.7 to 4.1 mL/min/kg or 44 to 96 mL/min/m^2 in dogs and 1.3 to 4.2 mL/min/kg or 22 to 65 mL/min/m^2 in cats.

RADIOISOTOPES

Radioisotopes (e.g., ^{125}I- or ^{131}I-iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid [EDTA], ^{99m}Tc-diethylenetriaminepentaacetic acid [DTPA]) also have been used to estimate the GFR in dogs and cats using plasma clearance and dynamic renal scintigraphy. The plasma clearance approach has the same advantages and limitations as described for iohexol or exogenously administered creatinine, but procedures using radioisotopes require technical expertise and equipment available primarily at referral institutions. The percentage of an injected dose of ^{99m}Tc-DTPA extracted by the kidneys over a finite time period correlates well with inulin clearance, the gold standard for estimation of the GFR. A major advantage of dynamic renal scintigraphy is that it provides information about individual kidney function, but this method correlates less well with inulin clearance than does the plasma clearance method in dogs with renal disease.

URINE PROTEIN-TO-CREATININE RATIO

In animals with persistent proteinuria on routine urinalysis, the severity of proteinuria may be assessed by measuring 24-hour urine protein excretion or determining a urine protein–to–urine creatinine ratio (U_{Pr}/U_{Cr}) on a spot urine sample. Normal values for 24-hour urine protein excretion in dogs and cats are less than 20 mg/kg/day. Dogs with primary glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis) often have markedly increased 24-hour urine protein excretion, and those with amyloidosis generally have the highest 24-hour urine protein excretion. Determination of U_{Pr}/U_{Cr} eliminates the necessity of a 24-hour

urine collection, and the U_{Pr}/U_{Cr} has been shown to be highly correlated with 24-hour urine protein excretion in dogs and cats. Its utility lies in the fact that whereas both urine creatinine and protein concentrations are affected by total urine solute concentration, their ratio is not. According to International Renal Interest Society (IRIS) guidelines, dogs with $U_{Pr}/U_{Cr} < 0.2$ are considered nonproteinuric, those with U_{Pr}/U_{Cr} 0.2–0.5 are considered borderline proteinuric, and those with $U_{Pr}/U_{Cr} > 0.5$ are considered proteinuric. In cats the guidelines are < 0.2 (nonproteinuric), 0.2–0.4 (borderline proteinuric) and > 0.4 (proteinuric).

In general, U_{Pr}/U_{Cr} results are not affected by differences in sex, method of urine collection, fasted versus fed states, or by time of day of collection. Urine samples collected at home may have somewhat lower U_{Pr}/U_{Cr} than samples collected in the hospital. The U_{Pr}/U_{Cr} should be determined within 2 to 4 hours of sample collection because values may increase after 12 hours at room temperature. Pyuria and marked blood contamination of urine samples have the potential to affect the U_{Pr}/U_{Cr}. Consequently, the urine protein concentration should be evaluated in conjunction with urinary sediment findings, and ideally the U_{Pr}/U_{Cr} should be evaluated only if the patient does not have pyuria. In a recent study, 25% of apparently healthy geriatric dogs had U_{Pr}/U_{Cr} results in the borderline proteinuric or proteinuric range as defined by IRIS guidelines. A high degree of overlap is found between dogs with glomerulonephritis and those with amyloidosis with regard to their 24-hour urine protein excretion and U_{Pr}/U_{Cr}. Thus renal biopsy remains the only reliable way to differentiate these two diseases. Values for 24-hour urine protein excretion and U_{Pr}/U_{Cr} are presented in Table 39.1.

MICROALBUMINURIA

In humans, microalbuminuria is defined as excretion of 30 to 300 mg/day of albumin in urine, and its presence may be an early indicator of vascular endothelial damage. Microalbuminuria is an established risk factor for progression of renal disease in human patients with diabetes mellitus and may be predictive of progressive renal disease in those with essential hypertension. Microalbuminuria in dogs and cats has been defined as a urine albumin concentration of 1 to 30 mg/dL, and urine albumin concentrations in this range can be detected by antigen capture enzyme-linked immunoassay. Microalbuminuria can be detected in 15% to 20% of otherwise healthy dogs and cats, and its prevalence increases with increasing age (e.g., approximately 7% in dogs < 3 years but 49% in dogs ≥ 12 years). Its prevalence in a hospital population of dogs was 36%. The effect of pyuria on microalbuminuria is variable. Many urine samples of dogs with pyuria have a negligible urine albumin concentration (<1 mg/dL) and a normal U_{Pr}/U_{Cr} ratio (<0.4). The addition of blood to canine urine samples does not result in a urine albumin concentration more than 1 mg/dL until the urine is grossly pink or red and more than 250 red blood cells (RBCs)/high-power field (hpf) are observed in the urine sediment. U_{Pr}/U_{Cr} ratios generally do not exceed 0.4 with the addition of RBCs to canine urine. Semiquantitative tests for microalbuminuria have relatively high specificity (92% in dogs, 82% in cats) but low sensitivity (37% in dogs, 43% in cats) for differentiating healthy animals from those with systemic diseases. It remains to be determined whether seemingly normal dogs and cats with microalbuminuria are at increased risk for the development of progressive renal disease. Sequential monitoring of animals with documented microalbuminuria probably is warranted until its prognostic value in otherwise normal animals can be determined.

BLADDER TUMOR ANTIGEN TEST

The first-generation bladder tumor antigen (BTA) test is a qualitative latex agglutination dip strip test run on voided urine that detects a glycoprotein antigen complex associated with bladder neoplasia. The BTA test has high sensitivity but low specificity for the detection of transitional cell carcinoma in dogs. False positives occur in urine samples with marked proteinuria or glucosuria and in those with pyuria or hematuria. The high sensitivity of the test and its less reliable performance in the presence of pyuria and hematuria suggest that its most appropriate use would be as a routine screening test to rule out transitional cell carcinoma in geriatric dogs. Second- and third-generation BTA and other tests that use monoclonal antibodies against human bladder tumor antigens give false-negative results in dogs and should not be used.

TUBULAR FUNCTION

The kidney is an organ of water conservation. Depending on the needs of the animal, the kidney can produce urine that is highly concentrated or very dilute. Normal urinary concentrating ability is dependent on the ability of hypothalamic osmoreceptors to respond to changes in plasma osmolality, release of antidiuretic hormone (ADH) from the neurohypophysis, and response of the distal nephron to ADH. In addition, medullary hypertonicity must be generated and maintained by the countercurrent multiplier and exchanger systems of the kidney, and an adequate number of functional nephrons must be present to generate the appropriate response to ADH. Laboratory tests of tubular function are summarized in Table 39.2.

URINE SPECIFIC GRAVITY AND OSMOLALITY

Total urine solute concentration is measured by urine specific gravity (USG) or urine osmolality (U_{Osm}). Urine osmolality depends only on the number of osmotically active particles, regardless of their size. USG is defined as the weight of a solution compared with an equal volume of distilled water. It is dependent on the number and molecular weight of the solute particles but has the advantage of requiring only simple, inexpensive equipment for measurement.

Normally, urine is composed of solutes of relatively low molecular weight (e.g., urea, electrolytes), and a roughly

TABLE 39.2

Normal Values for Tests of Renal Tubular Function in Dogs and Cats

TEST	DOG	CAT
Random urine specific gravity	1.001-1.070	1.001-1.080
Urine specific gravity after 5% dehydration	1.050-1.076	1.047-1.087
Urine osmolality after 5% dehydration (mOsm/kg)	1787-2791	1581-2984
Urine-to-plasma osmolality ratio after 5% dehydration	5.7 : 1-8.9 : 1	Not available
Fractional Electrolyte Excretion (%)		
Sodium	<1	<1
Potassium	<20	<24
Chloride	<1	<1.3
Phosphate	<39	<73

linear relationship exists between urine osmolality and specific gravity. The range of urine osmolality corresponding to a given USG value, however, may be relatively wide. If the urine contains appreciable amounts of larger molecular weight solutes, such as glucose, mannitol, or radiographic contrast agents, these substances will have a proportionally greater effect on specific gravity than on osmolality.

The term *isosthenuria* (USG, 1.007–1.015; U_{Osm}, 300 mOsm/kg) refers to urine of the same total solute concentration as unaltered glomerular filtrate. The term *hyposthenuria* refers to urine of a lower total solute concentration than glomerular filtrate (USG < 1.007, U_{Osm} < 300 mOsm/kg). Although rarely used clinically, the term *hypersthenuria* (baruria) refers to urine of a higher total solute concentration than glomerular filtrate (USG > 1.015, U_{Osm} > 300 mOsm/kg). The normal range of total urine solute concentration for dogs and cats is wide (USG, 1.001–1.080). Samples obtained in the morning have higher USG values than those obtained in the evening, and urine concentration decreases with age, but there is no effect of sex on USG. Normal young puppies have a lower USG than do older dogs.

WATER DEPRIVATION TEST

The water deprivation test is a useful test of tubular function and is indicated for the evaluation of animals with confirmed polydipsia and polyuria, the cause of which remains undetermined after initial diagnostic evaluation. It usually is performed in animals with hyposthenuria (USG < 1.007) suspected to have central or nephrogenic diabetes insipidus or psychogenic polydipsia. An animal that is dehydrated but has dilute urine has already failed the test and should not be subjected to water deprivation. In such an animal, failure to concentrate urine likely is caused by structural damage, renal dysfunction, or administration of drugs that interfere with urinary concentrating ability (e.g., glucocorticoids, diuretics). The water deprivation test also is contraindicated in animals that are azotemic. It should be performed with extreme caution in animals with severe polyuria because they may rapidly become dehydrated during water deprivation if they have a defective urinary concentrating ability.

At the beginning of the water deprivation test, the bladder must be emptied and baseline data collected—body weight, hematocrit, plasma proteins, skin turgor, serum osmolality, urine osmolality, and USG. Water is then withheld and these parameters monitored every 2 to 4 hours. Urine and serum osmolalities are the best tests to follow, but osmolality results are often not immediately available to the clinician. Thus USG and body weight assume the greatest importance for decision making during performance of the test. An increase in the total plasma protein concentration is a relatively reliable indicator of progressive dehydration, but increases in hematocrit and changes in skin turgor are not reliable. SCr and BUN concentrations should not increase during a properly conducted water deprivation test.

Maximal stimulation of ADH release will be present after loss of 5% of body weight. The test is concluded when the patient demonstrates adequate concentrating ability or becomes dehydrated, as evidenced by loss of 5% or more of its original body weight. Use the same scale each time when weighing the animal, and empty the bladder at each evaluation.

The time required for dehydration to develop during water deprivation varies. Dehydration usually becomes evident within 48 hours in normal dogs and cats but, rarely, a longer period of time may be required. Dogs with diabetes insipidus and psychogenic polydipsia usually become dehydrated after a much shorter period of water deprivation (<12 hours). By the time dehydration is evident, USG usually exceeds 1.045 in normal dogs and cats. Failure to achieve maximal urinary solute concentration does not localize the level of the malfunction, and a structural or functional defect may be present anywhere along the hypothalamic-pituitary-renal axis. Furthermore, animals with medullary solute washout may have impaired concentrating ability, regardless of the underlying cause of polyuria and polydipsia.

If there has been less than a 5% increase in urine osmolality or less than a 10% change in USG for three consecutive determinations, or if the animal has lost 5% or more of its original weight, 0.2 to 0.4 U/kg aqueous vasopressin (Pitressin), up to a total dose of 5 U, or 5 µg desmopressin (DDAVP) may be given subcutaneously and parameters of urinary concentrating ability monitored 2 to 4 hours after ADH injection. Any additional increase in urine osmolality after the administration of ADH should not exceed 5% to 10% in normal dogs and cats.

GRADUAL WATER DEPRIVATION

Gradual water deprivation can be used to eliminate diagnostic confusion caused by medullary solute washout. The owner can be instructed to restrict water consumption to 60 mL/lb/day 72 hours before, 45 mL/lb/day 48 hours before, and 30 mL/lb/day 24 hours before the scheduled water deprivation test. In dogs with psychogenic polydipsia, this will promote the endogenous release of ADH, increased permeability of the inner medullary collecting ducts to urea, and restoration of the normal gradient of medullary hypertonicity. An alternate approach is to instruct the owner to decrease water consumption by approximately 10%/day over a 3- to 5-day period (but not < 30 mL/lb/day). Gradual water deprivation should only be used in animals that are otherwise healthy on initial clinical evaluation, and the owner should provide dry food ad lib and weigh the dog daily to monitor for loss of body weight. During the period of gradual water restriction, the water provided each day should be divided into several aliquots that can be given to the dog throughout the 24-hour time period to prevent the dog from drinking all of its daily allotment at once.

FRACTIONAL CLEARANCE OF ELECTROLYTES

The extent to which electrolytes appear in the urine is the net result of tubular reabsorption and secretion. The fractional clearance of electrolytes (FC_x) can be used to evaluate tubular function. Fractional clearance is defined as the ratio of the clearance of the electrolyte in question (U_xV/P_x) to that of creatinine ($U_{Cr}V/P_{Cr}$):

$$FC_x = (U_xV/P_x)/(U_{Cr}V/P_{Cr}) = (U_xP_{Cr})/(U_{Cr}P_x)$$

This ratio usually is multiplied by 100 and the fractional clearance value expressed as a percentage. The advantage of this measurement is that a timed urine collection is not necessary. In normal animals, the fractional clearances of all electrolytes are much less than 1.0 (100%), implying net conservation, but values are higher for potassium and phosphorus than for sodium and chloride. Unfortunately, fractional excretion values calculated from so-called spot urine samples are highly variable and do not correlate well with values calculated using 72-hour urine samples.

The fractional clearance of sodium may be useful in the differentiation of prerenal and primary renal azotemia. In animals with prerenal azotemia and volume depletion, sodium conservation should be avid and the fractional clearance of sodium very low (<1%). On the other hand, in animals with azotemia caused by primary parenchymal renal disease, the fractional clearance of sodium will be higher than normal (>1%). Normal values for urinary fractional clearance of electrolytes are summarized in Table 39.2.

URINALYSIS

Urine for urinalysis may be collected by voiding (midstream sample), catheterization, or cystocentesis. Cystocentesis is preferred because it prevents contamination of the sample by the urethra or genital tract, it is simple to perform when the bladder is palpable, there is negligible risk of introducing infection, and it is well tolerated by both dogs and cats. In animals presented for the evaluation of hematuria, however, it may be helpful first to evaluate a sample collected by voiding because other methods of urine collection may add RBCs to the sample as a result of trauma.

When performing the urinalysis, fresh urine should be examined whenever possible. Refrigerated urine should be warmed to room temperature before performing the urinalysis. Note how the sample was collected because this may influence interpretation. Urinalysis is divided into three parts—physical properties, chemical properties, and sediment evaluation.

PHYSICAL PROPERTIES OF URINE

Appearance

Normal urine is yellow because of the presence of urochrome pigment. Very concentrated urine may be deep amber in color, whereas very dilute urine may be almost colorless. A red or reddish-brown color usually is caused by RBCs, hemoglobin, or myoglobin, whereas a yellow-brown to yellow-green color may be caused by bilirubin; urine containing bilirubin appears concentrated. Normal urine usually is clear. Cloudy urine often contains increased cellular elements, crystals, or mucus. The most common abnormal odor is ammoniacal and is caused by the release of ammonia by urease-producing bacteria.

Specific Gravity

USG is a reflection of the total solute concentration of urine, and the amount of any substance in urine must be interpreted in light of the specific gravity. For example, 4+ protein in 1.010 urine represents more severe proteinuria than 4+ protein in 1.045 urine. Refractometry is the best technique for estimation of USG in general practice. Dip strip methods to estimate USG are unreliable in dogs and should not be used. USG should be determined before any treatment because fluids, diuretics, or glucocorticoids may alter the specific gravity.

CHEMICAL PROPERTIES OF URINE

pH

Urine pH varies with diet and acid–base balance. Normal urine pH of dogs and cats is 5.0 to 7.5. Causes of acidic urine pH include meat protein–based diet, administration of acidifying agents, metabolic acidosis, respiratory acidosis, paradoxic aciduria in metabolic alkalosis, and protein catabolic states. Causes of alkaline urine pH include urinary tract infection (UTI) by urease-positive bacteria, plant protein-based diet, urine allowed to stand exposed to air at room temperature, postprandial alkaline tide, administration of alkalinizing agents, metabolic alkalosis, respiratory alkalosis, and distal renal tubular acidosis. Dip strip methods to

estimate urine pH show moderate to poor agreement with pH meters, and the latter should be used when accurate pH measurements are necessary.

Protein

Randomly obtained urine samples from normal dogs contain small amounts of protein (up to 50 mg/dL). Commonly used dip strip methods for protein determination are much more sensitive to albumin than to globulin. For the evaluation of proteinuria, it is critical to localize the origin of the protein loss by history, physical examination, and critical evaluation of the urine sediment. Persistent, moderate to heavy proteinuria in the absence of urine sediment abnormalities is highly suggestive of glomerular disease (e.g., glomerulonephritis, glomerular amyloidosis). If the sediment is active and proteinuria is mild to moderate, consider inflammatory renal disease or disease of the lower urinary or genital tract.

Glucose

Glucose in the glomerular filtrate is almost completely resorbed in the proximal tubules and is not normally present in the urine of dogs and cats. Glucose will appear in the urine (glucosuria) if the blood glucose concentration exceeds the renal threshold (approximately 180 mg/dL in the dog and 300 mg/dL in the cat). Most dip strip kits are a colorimetric test based on an enzymatic reaction (glucose oxidase) specific for glucose. Causes of glucosuria include diabetes mellitus, stress or excitement in cats, administration of glucose-containing fluids, and renal tubular diseases, such as primary renal glucosuria and Fanconi syndrome. Glucosuria also may be observed occasionally in dogs and cats with chronic renal disease, with tubular injury caused by nephrotoxins, and in some dogs with familial renal disease.

Ketones

β-hydroxybutyrate, acetoacetate, and acetone are ketones, the products of exaggerated and incomplete oxidation of fatty acids. They are not normally present in the urine of dogs and cats. The nitroprusside reagent present in dip strip tests reacts with acetone and acetoacetate, but is much more reactive with acetoacetate. It does not react with β-hydroxybutyrate. Causes of ketonuria include diabetic ketoacidosis, starvation or prolonged fasting, glycogen storage disease, low-carbohydrate diet, persistent fever, and persistent hypoglycemia. Ketonuria occurs more readily in young animals and, of the causes listed, diabetic ketoacidosis is the most important cause in adult dogs and cats.

Occult Blood

Dip strip tests for blood are very sensitive but do not differentiate among erythrocytes, hemoglobin, and myoglobin. The test is more sensitive to hemoglobin than to intact erythrocytes; the former causes a diffuse color change, whereas the latter causes spotting of the reagent pad. A positive test must be interpreted in light of the urine sediment findings (i.e., presence or absence of RBCs). Free hemoglobin, secondary to hemolysis, is the most common abnormal pigment found in urine. Potential causes of hemolysis include immune-mediated hemolytic anemia, disseminated intravascular coagulation, postcaval syndrome, splenic torsion, and heat stroke. Myoglobinuria is less common but may occur if severe rhabdomyolysis (e.g., status epilepticus, crushing injury) occurs. For proper interpretation, the occult blood reaction must be considered together with the urine sediment findings (e.g., hematuria). Myoglobinuria can be distinguished from hemoglobinuria by ammonium sulfate precipitation or urine protein electrophoresis.

Bilirubin

Bilirubin is derived from the breakdown of heme by the reticuloendothelial system. It is transported to the liver, where it is conjugated with glucuronide and excreted in the bile. Only direct-reacting or conjugated bilirubin appears in the urine. The canine kidney can degrade hemoglobin to bilirubin, and the renal threshold for bilirubin is low in dogs. Thus in dogs with liver disease, bilirubin may be detected in the urine before its serum concentration is increased. It is relatively common to find small amounts of bilirubin in concentrated urine samples from normal dogs, especially males. Bilirubin is absent from normal feline urine. The causes of bilirubinuria are hemolysis (e.g., immune-mediated hemolytic anemia), liver disease, extrahepatic biliary obstruction, fever, and starvation.

Leukocyte Esterase Reaction

Indoxyl released by esterases from intact or lysed leukocytes reacts with a diazonium salt and is detected as a blue color reaction after oxidation by atmospheric oxygen. This test is specific for pyuria in canine urine samples but has low sensitivity (many false-negative results). In cats the leukocyte esterase test is moderately sensitive but not specific (many false-positive results) for the detection of pyuria.

URINARY SEDIMENT EXAMINATION

Depending on the criteria used for data analysis, as few as 3% or as many as 16% of dogs and cats with normal findings on physical and chemical evaluation of urine may have important urinary sediment abnormalities (e.g., pyuria, bacteriuria, microscopic hematuria). The sediment examination should be performed on fresh urine samples because casts and cellular elements degenerate rapidly at room temperature. Urine should be centrifuged at 1000 to 1500 rpm for 5 minutes and the sediment stained with Sedi-Stain (Becton Dickinson, Franklin Lakes, NJ) or examined unstained, depending on individual preference. When evaluating the urine sediment, keep the method of urine collection in mind because it will influence interpretation, and keep the USG in mind because it will influence the relative numbers of formed elements. The number of casts is recorded per low-power field (lpf) whereas numbers of RBCs, white blood cells, and epithelial cells are recorded per high-power field (hpf).

Red Blood Cells

Occasional RBCs are considered normal in the urine sediment. Normal values are: voided sample, 0 to 8/hpf; catheterized sample, 0 to 5/hpf; and, cystocentesis sample, 0 to 3/hpf. Excessive numbers of RBCs in urine is termed *hematuria* (Fig. 39.2) and may be microscopic or macroscopic. The causes of hematuria are summarized in Box 39.1.

White Blood Cells

Occasional white blood cells are considered normal in the urine sediment. Normal values are as follows: voided sample, 0 to 8/hpf; catheterized sample, 0 to 5/hpf; and cystocentesis sample, 0 to 3/hpf. An increased number of white blood cells in the urine sediment is termed *pyuria* (Fig. 39.3) and, in an appropriately collected urine sample, is indicative of inflammation somewhere in the urinary tract. The presence of white blood cells does not help localize the lesion unless white cell casts are present, indicating renal origin. UTI is the most common cause of pyuria, but it also can result from genital tract contamination in voided or catheterized samples (Box 39.2).

Epithelial Cells

Both squamous and transitional epithelial cells may be found in the urine sediment, but they are often of little diagnostic significance. Squamous cells are large polygonal cells with small round nuclei (Fig. 39.4). They are common in voided or catheterized samples because of urethral or vaginal contamination. Occasional squamous cells are normal and increased numbers may be present during estrus.

Transitional epithelial cells are variably sized cells derived from the urothelium from the renal pelvis to the urethra (Fig. 39.5). Although their size generally increases from the renal pelvis to the urethra, the finding of small transitional cells in the urine sediment does not have localizing value. Caudate cells are transitional cells with tapered ends thought to originate from the renal pelvis. Occasional transitional cells are normal, and increased numbers may be present if there is infection, irritation, or neoplasia of the urinary tract.

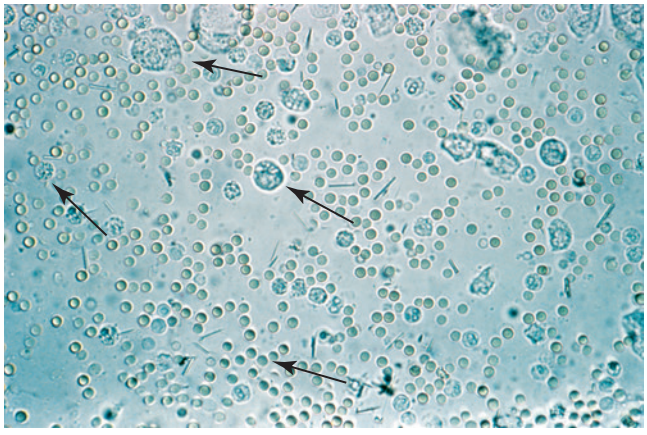


FIG 39.2
Photomicrograph of abnormal urine sediment. *Arrows, top* and *middle center,* indicate two different sizes of transitional epithelial cells; *arrow, middle left,* indicates a white blood cell; *arrow, bottom center,* indicates red blood cells (unstained, ×100).

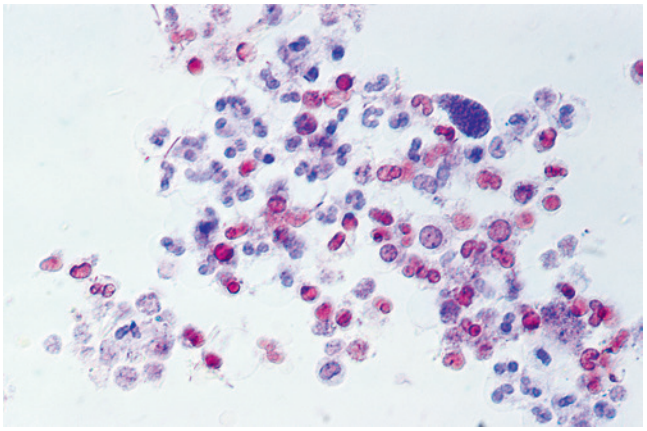


FIG 39.3
Photomicrograph of abnormal urine sediment showing large numbers of white blood cells (Sedi-Stain, ×100).

BOX 39.1

Causes of Hematuria in Dogs and Cats

Urinary tract origin (kidneys, ureters, bladder, urethra)
- Trauma
  - Traumatic collection (e.g., catheter, cystocentesis)
  - Renal biopsy
  - Blunt trauma (e.g., automobile accident)
- Urolithiasis
- Neoplasia (common in dogs with hemangiosarcoma)
- Inflammatory disease
  - Urinary tract infection
  - Idiopathic feline lower urinary tract disease
  - Chemically induced inflammation (e.g., cyclophosphamide-induced cystitis)
- Parasites
  - *Dioctophyma renale*
  - *Capillaria plica*
- Coagulopathy
  - Warfarin intoxication
  - Disseminated intravascular coagulation
  - Thrombocytopenia
- Renal infarction
- Renal pelvic hematoma
- Vascular malformation
  - Renal telangiectasia (Welsh Corgi)
  - Idiopathic renal hematuria

Genital tract contamination (prostate gland, prepuce, vagina)
- Estrus
- Inflammatory, neoplastic, and traumatic lesions of the genital tract

BOX 39.2

Causes of Pyuria in Dogs and Cats

Urinary tract origin (kidneys, ureters, bladder, urethra)
- Infectious
  - Urinary tract infection (e.g., pyelonephritis, cystitis, urethritis)
- Noninfectious
  - Urolithiasis
  - Neoplasia
  - Trauma
  - Chemically induced (e.g., cyclophosphamide)

Genital tract contamination (e.g., prostate gland, prepuce, vagina)

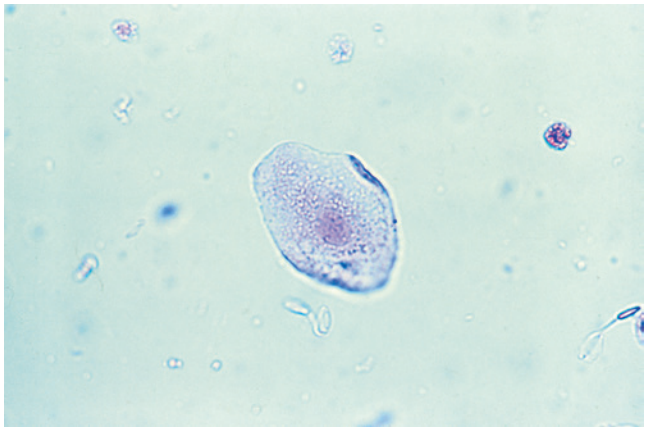


FIG 39.4
Photomicrograph of squamous epithelial cell in urine sediment (Sedi-Stain, ×400).

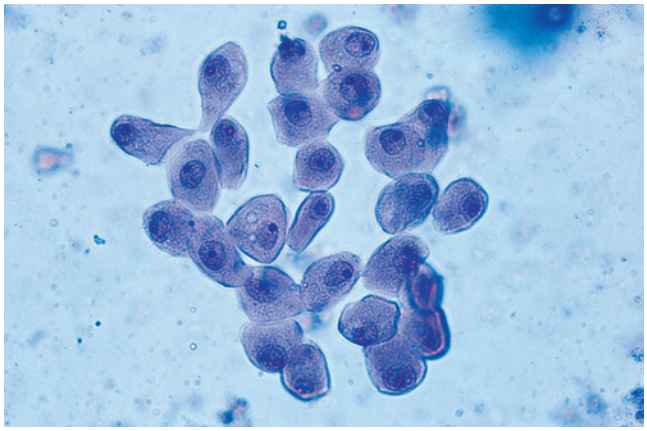


FIG 39.5
Photomicrograph of transitional epithelial cells in urine sediment (Sedi-Stain, ×100).

Renal cells are small epithelial cells from the renal tubules, but their renal origin can only be determined if they are observed in cellular casts. Neoplastic epithelial cells are best identified using conventional blood cell stains (e.g., Wright-Giemsa).

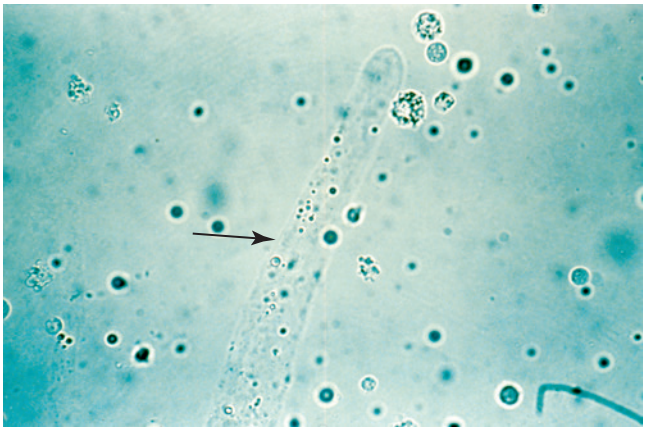


FIG 39.6
Photomicrograph of a hyaline cast in urine sediment *(arrow)* (unstained, ×400).

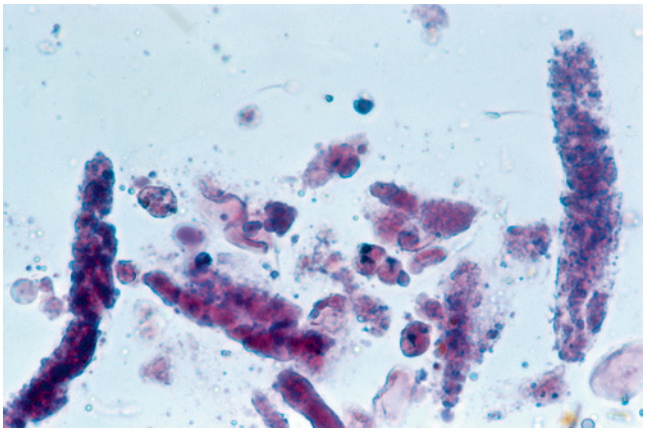


FIG 39.7
Photomicrograph showing coarsely granular casts in urine sediment (Sedi-Stain, ×400).

Casts

Casts are cylindric molds of the renal tubules composed of aggregated proteins or cells. They form in the ascending limb of the loop of Henle and distal tubule because of maximal acidity, highest solute concentration, and lowest flow rate in this area. The presence of casts in the urinary sediment indicates a disease process within the kidney itself and thus is of localizing value. Occasional hyaline and granular casts per low-power field are considered normal. No cellular casts should be observed in sediment from normal urine. Excretion of abnormal numbers of casts in the urine is termed *cylindruria*. The types of casts observed in the urine sediment are hyaline, granular, cellular, and waxy. Hyaline casts (Fig. 39.6) are pure protein precipitates (Tamm-Horsfall mucoprotein and albumin). They are difficult to see and dissolve rapidly in dilute or alkaline urine. Small numbers of hyaline casts may be observed in association with fever or exercise. They are commonly seen in renal diseases associated with proteinuria (e.g., glomerulonephritis, glomerular amyloidosis). Coarse (Fig. 39.7) and fine (Fig. 39.8) granular



FIG 39.8
Photomicrograph showing finely granular cast in urine sediment (Sedi-Stain, ×400).

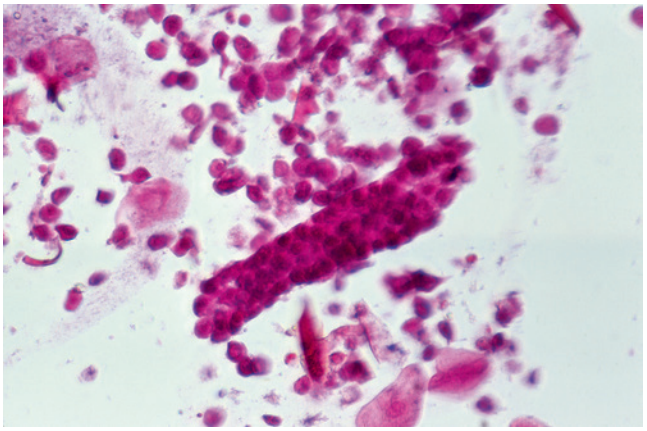


FIG 39.10
Photomicrograph showing an epithelial cell cast in urine sediment (Sedi-Stain, ×400).

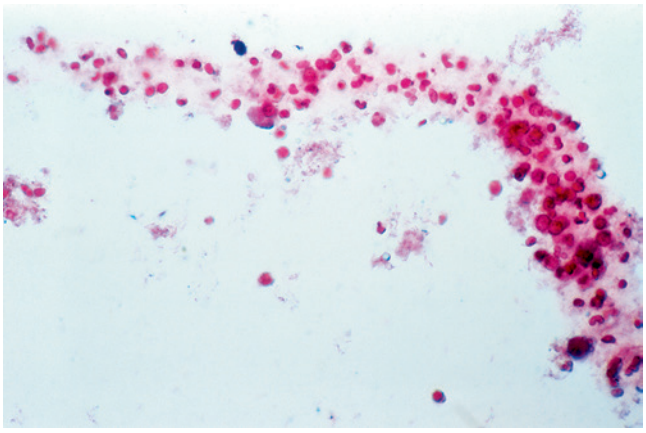


FIG 39.9
Photomicrograph showing a white blood cell cast in urine sediment (Sedi-Stain, ×400).

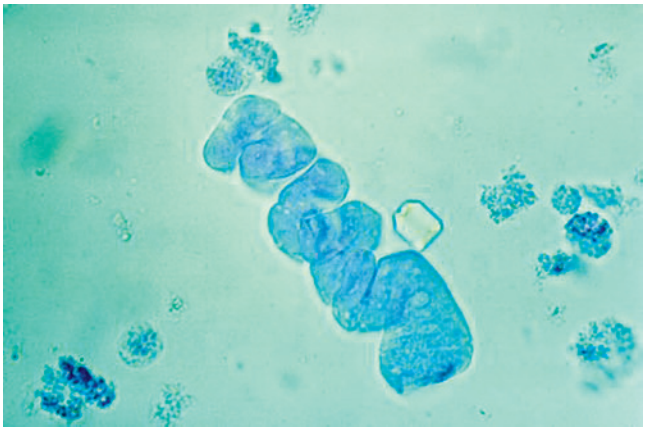


FIG 39.11
Photomicrograph showing a waxy cast in urine sediment (Sedi-Stain, ×400).

casts represent the degeneration of cells in other casts or precipitation of filtered plasma proteins and are suggestive of ischemic or nephrotoxic renal tubular injury. Fatty casts are a type of coarse granular cast containing lipid granules and may be seen in nephrotic syndrome or diabetes mellitus. Cellular casts include white cell or pus casts (suggestive of pyelonephritis; Fig. 39.9), red cell casts (fragile and rarely observed in dogs and cats), and renal epithelial cell casts (suggestive of acute tubular necrosis or pyelonephritis; Fig. 39.10). Waxy casts represent the final stage of degeneration of granular casts, are relatively stable, and suggest intrarenal stasis (Fig. 39.11). They often are very convoluted, with cracks and blunt ends.

Organisms

Normal bladder urine is sterile. The distal urethra and genital tract harbor bacteria, and voided or catheterized urine samples may be contaminated with bacteria from the distal urethra, genital tract, or skin. Contamination from the urethra in voided or catheterized specimens usually does not result in large enough numbers of bacteria to be visualized microscopically in the urine sediment. If allowed to incubate at room temperature, however, these contaminants may proliferate. To be readily apparent microscopically, there must be more than 10^4 rods/mL urine or more than 10^5 cocci/mL urine. Examination of modified Wright-Giemsa–stained urine sediment preparations improves light microscopic identification of bacteriuria. Large numbers of bacteria in urine collected by catheterization or cystocentesis suggest the presence of UTI (Fig. 39.12). Usually, there is accompanying pyuria. Particulate debris in the sediment may be confused with bacteria and cause false positive results. Also, the bottle of stain may be contaminated with bacteria. The microscopic absence of bacteria in the sediment does not rule out urinary tract infection. Yeast and fungal hyphae in the sediment usually are contaminants.

Crystals

The solubility of crystals is dependent on urine pH, temperature, and specific gravity. Crystals commonly are present in

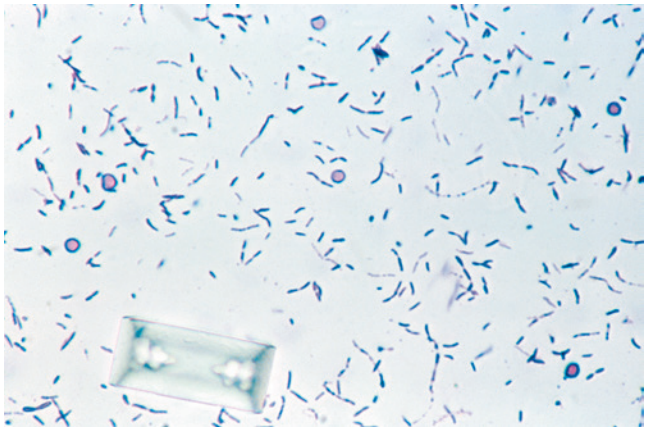


FIG 39.12
Photomicrograph showing numerous rod-shaped bacteria in urine sediment and a single struvite crystal *(lower left)*. Red blood cells also are present (Sedi-Stain, ×400).

TABLE 39.3

Conditions Associated With Crystalluria

CRYSTAL TYPE	ASSOCIATED CONDITIONS
Struvite	Normal Urinary tract infection with urease-positive bacteria Struvite urolithiasis Plant protein-based diet
Calcium oxalate	Normal Ethylene glycol intoxication Oxalate urolithiasis
Ammonium biurate	Breed-related (e.g., Dalmatian, English Bulldog) Urate urolithiasis Liver disease Portosystemic shunt
Cystine	Cystinuria
Bilirubin	Normal in concentrated urine from dogs (especially males); abnormal in feline urine Hemolytic disease Liver disease Posthepatic disease

urine of dogs and cats and often are of little diagnostic significance (Table 39.3). Struvite, amorphous phosphates, and oxalates are examples of crystals that may be found in normal urine samples. Prolonged storage of urine (24 versus 6 hours) and refrigeration can increase the number and size of crystals, especially calcium oxalate, observed in the urine sediment. Uric acid, calcium oxalate, and cystine typically are found in acidic urine, whereas struvite ($MgNH_4PO_4 \cdot 6H_2O$, so-called triple phosphate), calcium phosphate, calcium carbonate, amorphous phosphate, and ammonium biurate

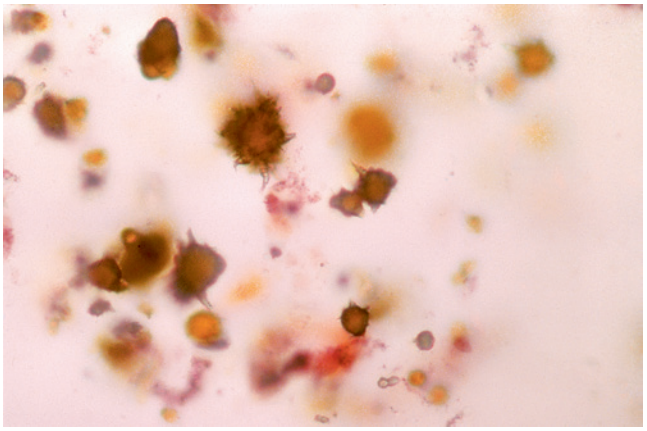


FIG 39.13
Photomicrograph of ammonium biurate crystals in urine sediment (Sedi-Stain, ×400).

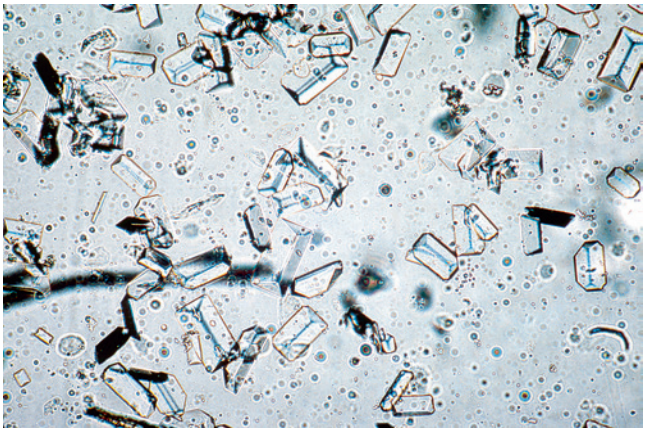


FIG 39.14
Photomicrograph showing numerous struvite crystals in urine sediment (unstained, ×400).

typically are found in alkaline urine. Characteristic crystals also may be found in the urine sediment of animals receiving certain drugs, especially sulfonamides. Bilirubin crystals may be found in concentrated samples of normal dog urine. Urates are commonly observed in the urine of Dalmatians and may be seen in the urine of animals with liver disease or portosystemic shunts (Fig. 39.13). Struvite crystals may be observed in the urine of cats with idiopathic lower urinary tract disease, in dogs and cats with struvite urolithiasis, and in the urine of normal animals (Fig. 39.14). In the presence of oliguric AKI, the presence of calcium oxalate crystals (Fig. 39.15) is highly suggestive of ethylene glycol intoxication. The presence of cystine crystals in urine of dogs and cats is abnormal and suggestive of cystinuria (Fig. 39.16).

Miscellaneous

Sperm are commonly found in urine samples from normal intact male dogs. Rarely, parasite ova of *Dioctophyma renale* or *Capillaria plica* or microfilaria of *Dirofilaria immitis* may be observed in the urine sediment. Refractile lipid droplets

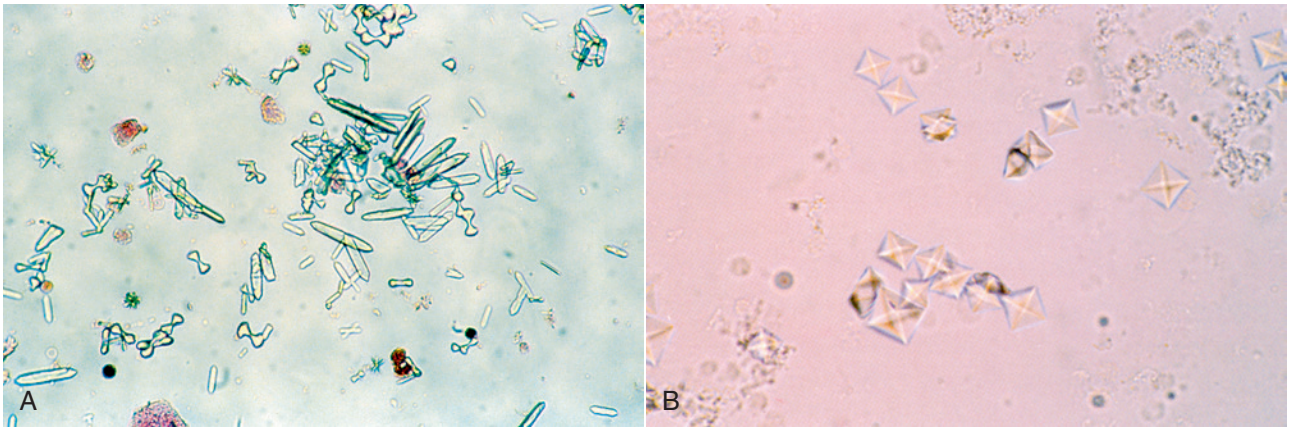


FIG 39.15
(A) Calcium oxalate monohydrate (unstained) and calcium oxalate dihydrate crystals **(B)** in urine sediment (Sedi-Stain, ×400).

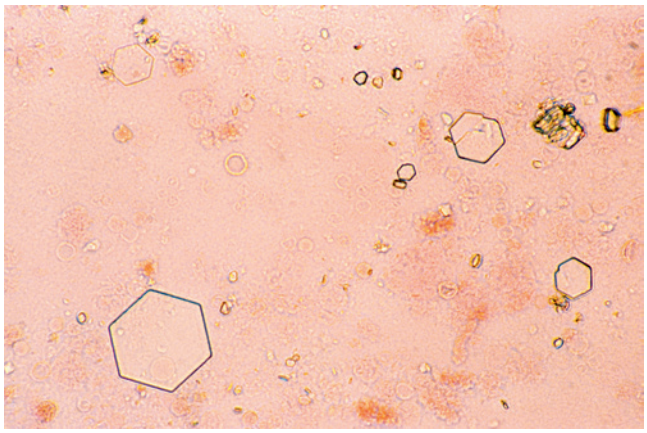


FIG 39.16
Photomicrograph showing cystine crystals in urine sediment (Sedi-Stain, ×400).

may occur in diabetes mellitus or nephrotic syndrome. They also may be observed in cats because of the degeneration of lipid-laden tubular cells.

MICROBIOLOGY

Clinical signs and urinalysis findings provide supportive evidence, but microbiology is required to diagnose UTI conclusively. The kidneys, ureters, bladder, and proximal urethra of normal dogs and cats are sterile, whereas a resident bacterial flora populates the distal urethra, prepuce, and vagina. UTI occurs when bacteria colonize areas of the urinary tract that normally are sterile. Aerobic gram-negative bacteria account for most UTIs in dogs and cats, and the remainder are caused by gram-positive organisms. *Escherichia coli* is the most common organism implicated in UTIs of dogs and cats. Other organisms isolated include *Proteus* spp., coagulase-positive staphylococci, and streptococci. *Pasturella multocida* occasionally is isolated from cats with UTIs. *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas aeruginosa* are observed less commonly in dogs and rarely in cats.

Results obtained by bacterial culture of urine are dependent on the method of urine collection. Voided urine has the greatest potential for bacterial contamination. Catheterization may inoculate the bladder with bacteria from the distal urethra, but urine collected by cystocentesis should be sterile in normal animals. Quantitative bacterial culture of urine allows determination of the number of bacterial colonies (colony-forming units [cfu]) that grow from 1 mL of urine (cfu/mL). Ideally urine should be submitted for culture within 30 minutes of collection. If this is not possible, the sample may be refrigerated for up to 24 hours without significant loss of bacterial growth.

Bacterial culture of midstream voided urine samples from normal dogs and cats often results in growth of $< 10^3$ to $\geq 10^5$ cfu/mL. Therefore culture of voided urine is not recommended for the evaluation of patients for UTI. If, however, no growth is obtained from a voided urine sample, UTI can be excluded as a diagnosis. Bacterial growth of $\geq 10^5$ cfu/mL may result from culture of urine obtained from catheterization in 20% of normal female dogs. Thus using $\geq 10^5$ cfu/mL as an indicator of UTI in female dogs will result in a substantial number of false-positive results. Also, the procedure of urethral catheterization itself may cause UTI in 20% of normal female dogs. Consequently, the collection of urine by cystocentesis is recommended for establishing a diagnosis of UTI in female dogs. Isolation of bacteria from urine collected by catheterization of male dogs is uncommon, and $\geq 10^4$ cfu/mL is recommended for establishing a diagnosis of UTI in urine samples collected by catheterization from male dogs. In male and female cats, growth of $\geq 10^3$ cfu/mL in samples collected by catheterization is considered compatible with UTI. Urine samples obtained by cystocentesis from normal dogs and cats should yield no growth because this procedure bypasses the normal bacterial flora of the urethra and genital tract. Consequently, results obtained by cystocentesis are the standard against which results obtained

using voided or catheterized samples are compared. Small numbers of organisms from the skin or environment occasionally contaminate samples obtained by cystocentesis, and growth of $< 10^3$ cfu/mL may be considered suggestive of contamination. Isolation of bacteria from urinary tissues obtained during surgery indicates UTI, regardless of number.

DIAGNOSTIC IMAGING

RADIOGRAPHY

Radiography provides precise information about renal size that frequently cannot be obtained from physical examination. To correct for variation in patient size and radiographic magnification, renal size is evaluated in reference to surrounding anatomic landmarks, usually the second lumbar vertebra (L2) on the ventrodorsal view. The left kidney normally is well–visualized in the dog, but the right kidney often cannot be seen as well, especially its cranial pole. In the dog, the left kidney (near vertebrae L2–L5) is located caudal to the right kidney (near vertebrae T13–L3). In the cat, the kidneys lie near vertebra L3, with the right kidney positioned slightly cranial to the left. Renal size in dogs and cats can be assessed radiographically and compared with the length of vertebra L2. On the ventrodorsal view, the kidney-to-L2 ratio is 2.5:1 to 3.5:1 in dogs and 2.4:1 to 3.0:1 in cats.

Excretory urography is performed by taking sequential abdominal radiographs after the intravenous (IV) administration of an iodinated organic compound. The contrast medium is filtered and excreted by the kidneys, and the quality of the study is partially dependent on the patient's GFR. Radiographs should be taken at appropriate intervals after injection (e.g., <1, 5, 20, and 40 minutes) to obtain maximal information about the renal parenchyma and collecting system. Excretory urography is useful for the evaluation of abnormalities in renal size, shape, or location, filling defects in the renal pelvis or ureters, certain congenital defects (e.g., unilateral agenesis), renomegaly, acute pyelonephritis, and rupture of the upper urinary tract. Excretory urography should not be performed in dehydrated patients or in those with known hypersensitivity to contrast media. Although excretory urography normally is a safe procedure, decreases in the GFR may persist for several days after IV administration of contrast agents to normal dogs, and AKI has been reported rarely in dogs after excretory urography.

ULTRASONOGRAPHY

Renal ultrasonography is a noninvasive imaging technique that does not depend on renal function, has no known adverse effects on the patient, and allows characterization of internal renal architecture. The major advantage of ultrasonography is the ability to discriminate among the renal capsule, cortex, medulla, pelvic diverticula, and renal sinus. Normally the kidney is less echogenic than the liver or spleen. Collagen and fat provide highly reflective acoustic interfaces and account for the observation that the renal capsule, diverticula, and sinus are the most echogenic structures in the kidney. The renal medulla normally is less echogenic than the renal cortex because of its higher water content and fewer acoustic interfaces. The hyperechogenicity of the renal cortex relative to the medulla varies among normal cats and has been attributed to variations in the amount of fat present in proximal tubular cells.

Renal length and volume, as determined by ultrasonography, are linearly related to body weight in dogs. In normal cats, renal length as determined by ultrasonography ranges from 3.0 to 4.3 cm. Measurements of renal size determined by excretory urography exceed those obtained by ultrasonography. This difference is caused by osmotic diuresis and radiographic magnification effects during excretory urography and by indistinct renal margins and inaccurate choice of scanning planes during ultrasonography. Ultrasonographic comparison of renal length to aortic luminal diameter (measured just caudal to the origin of the left renal artery in a longitudinal plane) and calculation of the kidney-to-aorta ratio can be used to assess renal size in dogs. Normal values for kidney-to-aorta ratio in dogs range from 5.5:1 to 9.1:1.

Renal ultrasonography is useful for differentiating solid from fluid-filled lesions and for determining the distribution of lesions within the kidney (i.e., focal, multifocal, or diffuse). A pattern of multiple anechoic cavitations is highly suggestive of polycystic kidney disease. Cysts are smooth, sharply demarcated, anechoic lesions that are characterized by "through transmission." The renal pelvis is dilated with anechoic fluid in hydronephrosis, and the kidney is surrounded by an accumulation of anechoic fluid in cats with perinephric pseudocysts. Organized hematomas, abscesses, and necrotic nodules result in a pattern of mixed echogenicity. Focal or diffuse lesions of mixed echogenicity that disrupt normal anatomy often are tumors. Poorly vascular tumors of a homogenous cell type (e.g., lymphoma) may produce hypoechoic lesions that occasionally may be misinterpreted as cysts. Diffuse parenchymal renal diseases characterized by cellular infiltration, with preservation of normal renal architecture (e.g., chronic tubulointerstitial nephritis), may produce diffuse hyperechogenicity, but occasionally are characterized by a normal ultrasonographic appearance. Consequently, normal renal ultrasonography does not eliminate the possibility of renal disease. Ultrasonography is the modality of choice to obtain fine-needle aspirates of renal or perirenal lesions. Ethylene glycol intoxication also causes renal hyperechogenicity. Renal hyperechogenicity in ethylene glycol intoxication is attributed to the deposition of calcium oxalate crystals in the kidneys.

Intrarenal resistance to blood flow may be assessed during duplex Doppler ultrasonography and evaluated by calculation of the resistive index (RI). Normal values for renal RI in normal nonsedated dogs are approximately 0.6. An upper limit of 0.7 has been suggested for RI in normal nonsedated cats. Higher than normal values for RI have been reported in dogs and cats with some renal diseases.

URODYNAMIC TESTING

URETHRAL PRESSURE PROFILE

Urodynamic testing can be useful in animals presented for evaluation of urinary incontinence, especially those refractory to standard treatment. The urethral pressure profile (UPP) evaluates pressure along the length of the urethra. This test is indicated for dogs with refractory urethral sphincter mechanism incompetence (USMI) or for dogs with USMI for which medications may cause potentially serious adverse effects. It usually is unnecessary in dogs that present for uncomplicated urinary incontinence suspected to be caused by USMI. A UPP also can be used to screen dogs with ectopic ureters before surgical or laser correction. The screening might suggest concurrent USMI and provide evidence that medication to treat this condition may be needed after ectopic ureter correction. Finally, UPP can be considered to evaluate dogs and cats with suspected functional urethral outflow tract obstruction.

Procedure

A UPP can be obtained on a male or female dog, and this test can be done on most cats. Urinary tract infections should be treated appropriately before performing urodynamic procedures.

All anesthetics will decrease urethral closure pressure to some extent, but performing this procedure without sedation can be challenging. If chemical restraint is necessary, a bolus of propofol (2–3 mg/kg IV) can be given to facilitate placement of the urinary catheter. Once the animal is sedated, a double- or triple-lumen catheter (of appropriate size) is inserted via the urethra to the level of the bladder trigone. The catheter is slowly withdrawn at a standard rate (0.5–1 mm/sec) while warm sterile water is infused at a rate of 2 mL/min. This procedure generates a pressure curve that can be visualized on the computer screen. From this curve, the maximal urethral closure pressure is determined, which is the maximal urethral pressure minus the resting bladder pressure. The UPP can be obtained in female cats, but catheters of appropriate size for male cats are not commercially available.

CYSTOMETROGRAPHY

Cystometrography (CMG) can be performed to evaluate detrusor function in dogs and cats. This study evaluates the detrusor reflex, bladder filling volume, and compliance. Referral for this procedure generally is indicated for dogs and cats with refractory USMI or those with persistent pollakiuria for which underlying causes, such as bacterial cystitis, urolithiasis, neoplasia, and polypoid cystitis, have been ruled out. CMG also can be used to evaluate dogs and cats with suspected detrusor atony. To perform this procedure, the patient is anesthetized with propofol and a catheter is inserted into the bladder. The catheter is connected to pressure transducers and the bladder is slowly filled with sterile warm water at a constant rate, calculated based on the animal's body size. The volume infused and intravesical pressure are monitored on the computer screen.

Procedure

As for the UPP, all drugs affect the detrusor reflex to some extent. Many drugs (e.g., inhalant anesthetics) can abolish the reflex and, ideally, the CMG should be done without sedation, but usually doing so is not practical. Intravenously administered propofol can be used for this procedure. Once the animal is sedated, a double-lumen urinary catheter is aseptically placed into the urinary bladder of the dog or cat. One of the ports is connected to the pressure transducer on the machine and the other is used for fluid administration. Sterile water is infused at a constant rate. The rate of fluid infusion is very important and should be calculated based on patient size. Pressures are measured as the bladder is filled with water, indicating the degree of compliance of the bladder. Resting bladder pressure, threshold pressure (the pressure at which the detrusor reflex occurs), and threshold volume (the volume at which the detrusor reflex occurs) are recorded. Bladder compliance then can be calculated.

URETHROCYSTOSCOPY

Urethrocystoscopy using a rigid cystoscope allows visual inspection of the mucosal surfaces of the vestibule, vagina, urethra, ureteral orifices, and bladder in female dogs and cats weighing > 3 kg. It is a valuable technique for the diagnosis of several lower urinary tract disorders, including ectopic ureter, urachal remnant, proliferative urethritis, polypoid cystitis, and transitional cell carcinoma of the bladder or urethra. It is the gold standard for the diagnosis of ectopic ureters in dogs and is valuable for identifying the termination sites of ectopic ureters. It allows a presumptive diagnosis of transitional cell carcinoma of the urethra or bladder and permits a biopsy to be performed in a minimally invasive manner. Female dogs with recurrent UTIs can be evaluated for predisposing anatomic abnormalities. The technique also is useful for the diagnosis of idiopathic renal hematuria in dogs and allows identification of the kidney responsible for hemorrhage by observing the discharge of bloody urine from the ureteral orifice on the affected side. Urethrocystoscopy also can be used to treat sphincter mechanism incompetence by submucosal injection of collagen in the urethra, to remove small cystic calculi in female dogs by voiding hydropulsion, and to perform lithotripsy.

RENAL BIOPSY

Renal biopsy allows the clinician to establish a histologic diagnosis and should be considered when the information obtained is likely to alter patient management. Examples of such situations include differentiation of protein-losing glomerular diseases, differentiation of AKI from CKD, determination of the status of tubular basement membranes in AKI,

and establishing the response of the patient to therapy or the progression of previously documented renal disease. Proteinuria is a common indication for renal biopsy in dogs and cats (Video 39.1).

Several techniques for renal biopsy are available; these include blind percutaneous, laparoscopic, keyhole, open, and ultrasonography-guided approaches. The choice of technique is dependent largely on the experience and technical skill of the operator, species to be biopsied, and size of sample required. The blind percutaneous technique works well in cats because their kidneys can be readily palpated and immobilized. Laparoscopy allows direct visualization of the kidney and detection of hemorrhage but requires special equipment and expertise. The keyhole approach occasionally is used in dogs but is useful only if the operator is experienced with the technique. Modifications of the keyhole technique and use of laparoscopy do not necessarily improve the quality of the biopsy specimen obtained or decrease the complication rate. If the operator is relatively inexperienced with renal biopsy or a larger sample is required, wedge biopsy via laparotomy is recommended. Advantages of this procedure include the ability to inspect the kidneys and other abdominal organs visually, choose the specific biopsy site, take an adequately sized sample, and observe the kidney for hemorrhage. Ultrasonography-guided techniques can be performed under sedation, allow specific regions of the kidney to be selected for biopsy, and allow for the evaluation of hemorrhage postbiopsy. Some techniques require general anesthesia to provide adequate patient restraint and analgesia, but needle biopsies of the kidney can be obtained from dogs and cats under ultrasound guidance using sedation. Occasionally, tissue architecture is less important (e.g., renal lymphosarcoma, feline infectious peritonitis), and aspiration of the kidney using a 23- or 25-gauge needle may provide useful material for cytology.

Before renal biopsy, an IV catheter should be placed and clotting ability evaluated (see Chapter 87). The patient's hematocrit and plasma protein concentration should be determined before biopsy but after adequate rehydration with parenteral fluids. Hematocrit and plasma protein concentration then may be monitored after biopsy to detect hemorrhage.

The most commonly used biopsy instruments consist of modifications of the Franklin-modified Vim Silverman needle and Tru-Cut biopsy needle. Spring-loaded biopsy units (e.g., Bard Biopty-Cut, Bard Biopsy Systems, Tempe, AZ) allow for the rapid and efficient retrieval of cores of renal tissue for histopathologic evaluation. Excessive penetration of the kidney with the outer cannula of the Franklin-modified Vim Silverman instrument should be avoided to prevent retrieval of an insufficient amount of renal cortex. Most biopsy needles have an outer cannula that advances 23 to 25 mm, and caution should be taken when directing the angle of the biopsy instrument to avoid the renal hilus and major vessels. Samples containing large amounts of medulla are more likely to contain large vessels and lead to infarction of renal tissue. Therefore it is recommended that the biopsy needle be directed along the long axis of the kidney, solely through cortical tissue. Because of the small size of the feline kidney, it is common to obtain relatively large amounts of medullary tissue, which has been associated with infarction and fibrosis.

After biopsy using the open approach or keyhole technique, the kidney should be digitally compressed for 5 minutes and, after release, the abdomen inspected for hemorrhage. The biopsy sample may be dislodged from the biopsy instrument using a stream of sterile saline from a syringe or, alternatively, the biopsy instrument may be immersed directly in fixative. For routine histopathology, the sample should be fixed in buffered 10% formalin for at least 3 to 4 hours. For immunofluorescence studies, the sample can be preserved in Michel's transport medium. Immunopathology studies also may be performed by a peroxidase-antiperoxidase method using formalin-fixed samples without the need for special preservation of the sample.

After renal biopsy, a brisk fluid diuresis should be initiated to prevent potential clot formation in the renal pelvis. The patient's hematocrit and plasma protein concentration should be monitored at appropriate intervals over the next 12 to 24 hours to detect serious hemorrhage.

The most common complication of renal biopsy is hemorrhage. Subcapsular hemorrhage may occur at the site of biopsy, and some patients experience microscopic hematuria during the first 48 hours after biopsy. Macroscopic hematuria is less common. In one study, severe hemorrhage occurred after renal biopsy in 10% of dogs and 17% of cats, but gross hematuria was uncommon (4% of dogs and 3% of cats). Severe hemorrhage into the peritoneal cavity should be treated aggressively by compression bandage of the abdomen, fresh whole blood transfusion, and exploratory surgery if necessary. Rarely, hydronephrosis may complicate renal biopsy. If the renal pelvis is penetrated by the biopsy needle, bleeding may occur and clot formation can lead to obstruction of the kidney and hydronephrosis. This complication should be considered if progressive renal enlargement is detected after renal biopsy. The risk of this complication is minimized by limiting the biopsy site to the renal cortex and instituting a fluid diuresis afterward.

Suggested Readings

Bland SK, et al. Characterization of kidney injury molecule-1 in cats. *J Vet Int Med*. 2014;28:1454.

DeLoor J, et al. Urinary biomarkers for acute kidney injury in dogs. *J Vet Int Med*. 2013;27:998.

Geddes RF, et al. Relationship between plasma fibroblast growth factor-23 concentration and survival time in cats with chronic kidney disease. *J Vet Int Med*. 2015;29:1494.

Ghys LFE, et al. Evaluation of cystatin C for the detection of chronic kidney disease in cats. *J Vet Int Med*. 2016;30:1074.

Hall JA, et al. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in cats with chronic kidney disease. *J Vet Int Med*. 1676;28:2014.

Hall JA, et al. Comparison of serum concentrations of symmetric dimethylarginine and creatinine as kidney function biomarkers in healthy geriatric cats fed reduced protein food enriched with

fish oil, L-carnitine, and medium-chain triglycerides. *Vet J*. 2014;202:588.

Hall JA, et al. Relationship between lean body mass and serum renal biomarkers in healthy dogs. *J Vet Int Med*. 2015;201:29.

Hall JA, et al. Serum concentrations of symmetric dimethylarginine and creatinine in dogs with naturally-occurring chronic kidney disease. *J Vet Int Med*. 2016;30:794.

Harjes LM, et al. Fibroblast growth factor-23 concentrations in dogs with chronic kidney disease. *J Vet Int Med*. 2017;31:784.

Hokamp JA, Nabity MB. Renal biomarkers in domestic species. *Vet Clin Pathol*. 2016;45:28.

Segev G, et al. Evaluation of neutrophil gelatinase-associated lipocalin as a marker of kidney injury in dogs. *J Vet Int Med*. 2013;27:1362.

Williams TL, et al. Serum cystatin C concentrations in cats with hyperthyroidism and chronic kidney disease. *J Vet Int Med*. 2016;30:1083.

CHAPTER 40

Glomerular Disease



Glomerular disease is an important cause of chronic kidney disease (CKD) in humans and has been increasingly recognized in veterinary medicine. Destruction of the glomerulus renders the remainder of the nephron nonfunctional, and progressive destruction of glomeruli can lead to decreased glomerular filtration rate, azotemia, and renal failure. Important glomerular diseases of dogs include glomerulonephritis (GN), glomerular amyloidosis, familial glomerular basement membrane (GBM) disorders, and glomerular sclerosis. GN is less common in cats, and amyloidosis in cats affects the renal medulla more severely than the glomeruli.

Marked, persistent proteinuria is the hallmark of primary glomerular disease. The term *nephrotic syndrome* traditionally has been used to describe patients with proteinuria, hypoalbuminemia, hypercholesterolemia, and edema or ascites. Many dogs and cats with glomerular disease, however, do not have clinically detectable ascites at presentation. In one study of dogs with glomerular disease, nephrotic syndrome was not associated with specific histopathologic diagnoses, but dogs with nephrotic syndrome had higher urine protein-to-creatinine (UPC) ratios and shorter survival times than dogs with nonnephrotic glomerular disease. Human patients excreting more than 3.5 g protein/1.73 m^2 body surface area/day (likely equivalent to 2 g/m^2 in dogs) in their urine or with UPC ratios > 2.0 to 3.5 are said to have nephrotic-range proteinuria.

NORMAL STRUCTURE

The glomerulus is a unique vascular structure consisting of a capillary bed between two arterioles (Fig. 40.1). The glomerular capillary wall is a size- and charge-selective barrier. It excludes macromolecules more than 35 Å in radius (serum albumin has a molecular radius of 36 Å) and, for any given size, negatively charged macromolecules experience greater restriction to filtration than neutral macromolecules.

The filtration barrier of the glomerulus consists of three layers, from the vascular space to the urinary space—the capillary endothelium, GBM, and interdigitating foot processes of the podocytes (Fig. 40.2). The fenestrated capillary endothelium is much more permeable to water and crystalloids than are systemic capillaries, and the negatively charged endothelial surface contributes to the charge selectivity of the glomerular barrier. The GBM contains type IV collagen, proteoglycans, laminin, fibronectin, and water. The proteoglycans are large, highly negatively charged molecules consisting of a protein backbone with polysaccharide (glycosaminoglycan) side chains. These proteoglycans are responsible for the charge selectivity of the basement membrane. Type IV collagen in the GBM forms a mesh and contributes to the size selectivity of the glomerular capillary wall. The visceral epithelial cells or podocytes cover the filtration barrier on the urinary side via primary and interdigitating secondary foot processes. The negatively charged cell surface of the podocyte foot processes contributes to their unique morphology and the charge selectivity of the glomerular barrier. The podocytes synthesize the GBM and may phagocytize macromolecules trapped in the filtration barrier.

The mesangial cells of the glomerulus provide structural support for the capillary loops (Fig. 40.3). They produce mesangial matrix, similar to the basement membrane in composition, and may clear filtration residues from the mesangial space by virtue of their phagocytic capacity. Their contractile elements can alter the amount of glomerular surface area available for filtration in response to mediators such as angiotensin II. The mesangium is an early site of deposition of immune complexes and amyloid fibrils, and mesangial cells can contribute to inflammation and progression of CKD by the release of eicosanoids, cytokines, and growth factors and by increased matrix production. Ultimately, these effects can lead to glomerular sclerosis.

The parietal epithelial cells line the urinary side of the glomerular capsule (Bowman's capsule) and are continuous with the visceral epithelial cells at the vascular pole of the glomerulus and with the proximal tubule at the urinary pole (see Fig. 40.1). The juxtaglomerular apparatus, at the vascular pole, consists of specialized smooth muscle cells of the afferent and efferent arterioles containing electron-dense renin granules, and the macula densa, a specialized segment of the distal tubule. The juxtaglomerular apparatus mediates tubuloglomerular feedback.

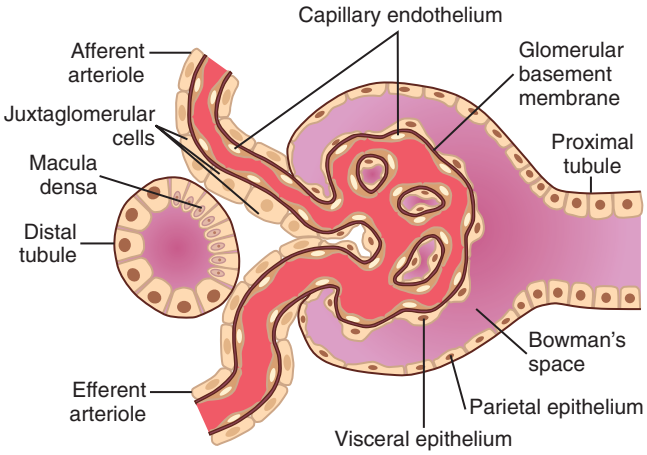


FIG 40.1
Schematic representation of normal glomerular morphology at the light microscopic level. (From Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology,* ed 2, St Louis, 2011, Elsevier Saunders.)

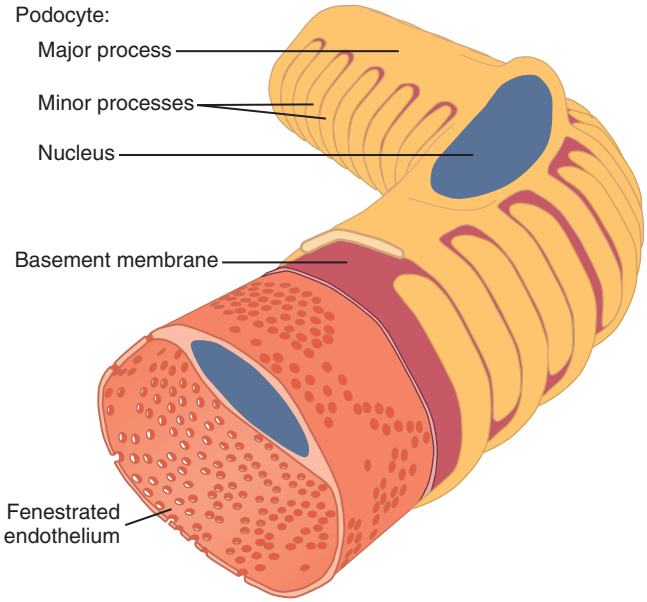


FIG 40.2
Schematic three-dimensional view of glomerulus demonstrating the scanning electron microscopic appearance of the glomerulus. The three layers of the glomerular capillary barrier are indicated in the cut-away section. (From Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology*, ed 2, St Louis, 2011, Elsevier Saunders.)

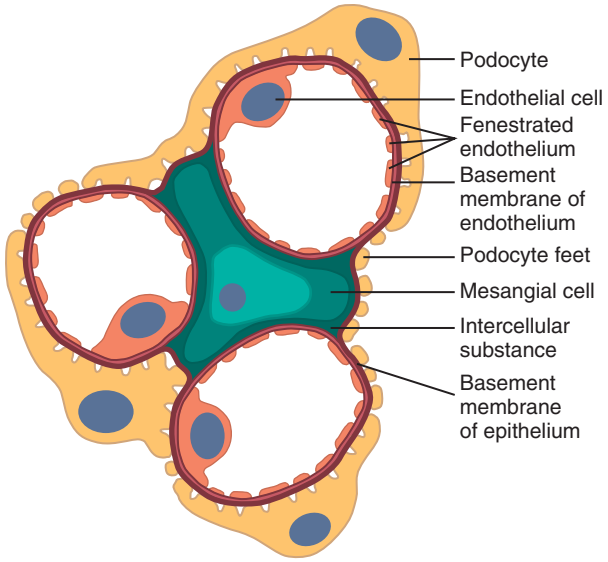


FIG 40.3
Schematic transverse section of glomerulus showing the location of mesangial cells. (From Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology,* ed 2, St Louis, 2011, Elsevier Saunders.)

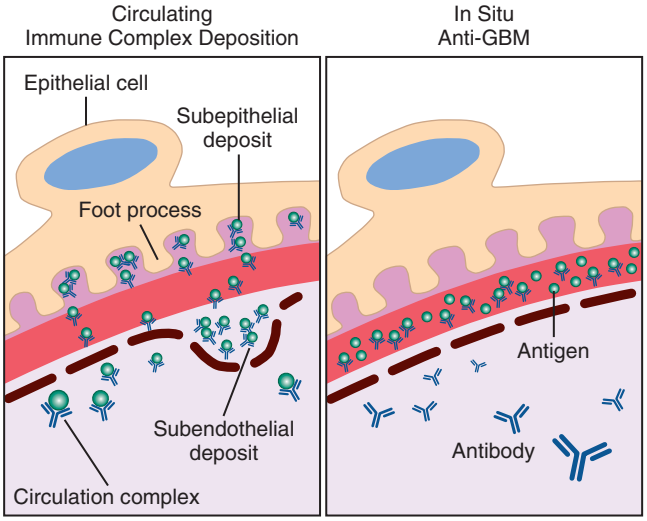


FIG 40.4
Immune complex glomerulonephritis. Shown are the deposition of subepithelial and subendothelial circulating immune complexes *(left panel)* and intramembranous complexes formed in situ *(right panel)*. (From Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology,* ed 2, St Louis, 2011, Elsevier Saunders.)

PATHOGENESIS

Glomerular injury may be immune-mediated or non–immune-mediated. Immune-mediated GN typically is associated with immune complex deposition in the glomeruli. Examples of non–immune-mediated glomerular disease include amyloid fibril deposition and glomerular damage caused by hyperfiltration. Minimal change nephropathy is a glomerular disease associated with loss of negative charge, foot process fusion, and severe proteinuria without immune complex deposition. It has been reported only rarely in dogs and cats.

Immune complex GN is caused by deposition of immunoglobulins or complement or both in the glomerular capillary wall. Immune complexes deposit in the glomerular filter via two different mechanisms (Fig. 40.4). Soluble

circulating immune complexes may become trapped in the glomeruli in conditions of antigen-antibody equivalence or slight antigen excess. Immune complexes also may be formed in situ in response to endogenous glomerular antigens, endogenous nonglomerular antigens, or exogenous antigens deposited or planted in the glomerular filter. Immune complexes may be deposited in subepithelial, subendothelial, or intramembranous locations in the glomerular capillary wall or in the mesangium. Factors affecting the location of these deposits include the size and charge of the complexes as well as the potential removal of complexes by phagocytosis. The location of deposition contributes to the histopathologic findings and severity of glomerular dysfunction.

Immune complexes can be detected in the glomeruli by staining renal tissue sections with fluorescein-labeled antibody against immunoglobulins or complement of the species being studied. This technique requires renal biopsy specimens to be collected and sent to the diagnostic laboratory in special preservative solutions (e.g., Michel's solution). More recently, immunohistochemistry using peroxidase-antiperoxidase methods have been applied to specimens preserved routinely in 10% buffered formalin. Glomerular deposition of preformed immune complexes usually results in a so-called lumpy bumpy or granular discontinuous immunofluorescence pattern on fluorescence microscopy (Fig. 40.5, *A*). In situ formation of immune complexes can occur within glomeruli when circulating antibodies react with endogenous glomerular antigens or planted nonglomerular antigens in the glomerular capillary wall. In this case, a smooth, linear, continuous pattern of immunofluorescence usually results (see Fig. 40.5, *B*). True autoimmune GN (anti-GBM GN) with antibodies against endogenous GBM antigens has not been conclusively identified in dogs and cats.

MECHANISMS OF IMMUNE INJURY

Immune complex deposition in glomeruli may decrease the amount of fixed negative charge and increase the filtration of negatively charged circulating macromolecules (e.g., albumin). Complement activation results in membrane damage and proteinuria, and soluble complement components recruit inflammatory cells. Platelet activation and aggregation may occur because of endothelial damage or antigen–antibody interaction, thus exacerbating glomerular damage by release of a variety of mediators. These mediators cause activation and proliferation of mesangial cells and endothelial cells, vasospasm, and local hypercoagulability. Neutrophils and macrophages localize in the glomeruli in response to soluble mediators, including complement components, platelet activating factor, platelet–derived growth factor, and eicosanoids. Activated neutrophils release reactive oxygen species and proteinases, leading to additional damage. Macrophages produce proteinases, oxidants, eicosanoids, growth factors, cytokines, complement fragments, and coagulation factors. Several infectious and inflammatory diseases have been associated with glomerular deposition or in situ formation of immune complexes in dogs and cats (Box 40.1). Often, however, the antigen source or underlying disease process is not identified and the glomerular disease is referred to as idiopathic.

PROGRESSION

The continued deposition of immune complexes and release of inflammatory mediators eventually leads to glomerular sclerosis. Obstruction of glomerular capillaries may result in ischemia of the tubules and tubulointerstitial disease, which may progress to CKD.

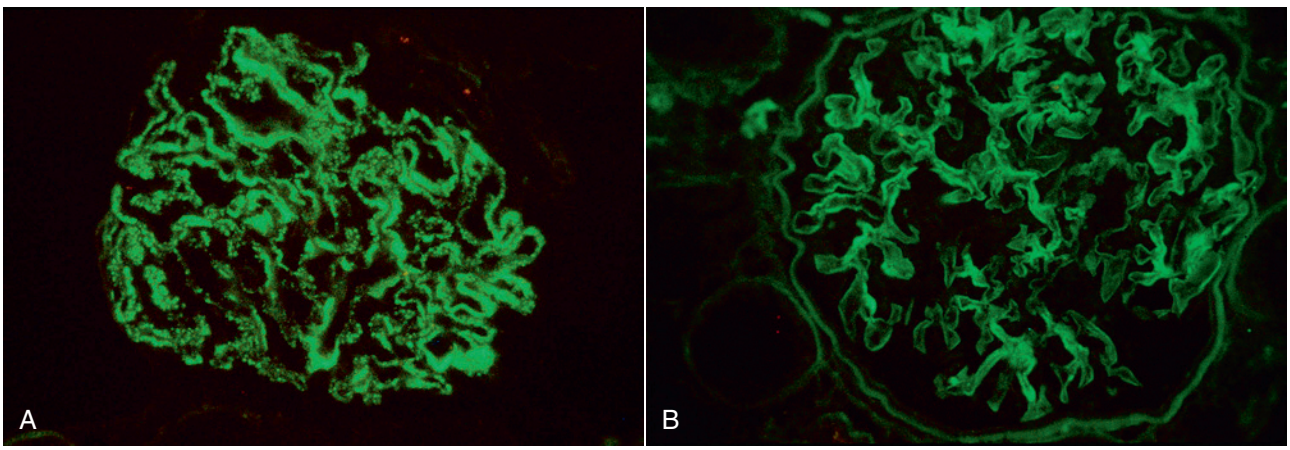


FIG 40.5
(A) So-called lumpy bumpy immunofluorescent appearance of discontinuous deposition of immune complexes in glomerulonephritis. Note discrete areas of immune complex deposition. **(B)** Linear immunofluorescent appearance of continuous deposition of immunoglobulins that have reacted with planted nonglomerular antigens (in this case associated with dirofilariasis) in the glomerulus. (**A** from Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology,* ed 2, St Louis, 2011, Elsevier Saunders.)

BOX 40.1

Causes of Immune-Mediated Glomerulonephritis in Dogs and Cats

Dogs

Infectious diseases
- Dirofilariasis*
- Blastomycosis
- Coccidioidomycosis
- Pyometra*
- Bacterial endocarditis
- Brucellosis
- Pyoderma
- Borreliosis*
  - Membranoproliferative glomerulonephritis (GN) in Bernese Mountain dogs inherited as an autosomal recessive trait has a strong association with seropositivity for *Borrelia burgdorferi*.
- Ehrlichiosis*
- Rocky Mountain spotted fever *(Rickettsia rickettsii)*
- Bartonellosis
- Other chronic bacterial infections
- Leishmaniasis
- Babesiosis
- Hepatozoonosis
- Trypanosomiasis
- Canine adenovirus-1 (infectious canine hepatitis)

Noninfectious inflammatory diseases
- Systemic lupus erythematosus (SLE)
- Immune-mediated polyarthritis
- Chronic inflammatory skin disease
- Pancreatitis

Neoplasia
- Lymphoma
- Mast cell tumor
- Other tumors

Other disease associations
- Exogenous or endogenous (e.g., hyperadrenocorticism) glucocorticoids (dogs treated with glucocorticoids develop proteinuria and glomerular lesions but not deposition of immune complexes).
- Drug reaction (e.g., trimethoprim-sulfonamide, masitinib, and minimal-change nephropathy in a dog).

Familial glomerular disease
- Familial glomerulopathy in soft-coated Wheaten Terriers associated with mutations in NPHS1 and KIRREL2 which encode slit diaphragm proteins nephrin and Neph3/filtrin
- Juvenile glomerulonephropathy in French Mastiff (Bordeaux) dogs
- Autosomal recessive collagen type III glomerulopathy
- Membranoproliferative GN associated with hereditary deficiency of complement component III in Brittany Spaniels
- Autosomal recessive type IV collagen defect in English Cocker Spaniels
- X-linked dominant type IV collagen defect in Samoyeds
- Suspected basement membrane disorders in Doberman Pinschers and Bull Terriers
- Glomerulopathy with increased collagen deposition and glomerular sclerosis in young Newfoundland dogs

Cats

Infectious diseases
- Feline leukemia virus infection
- Feline immunodeficiency virus
- Feline infectious peritonitis
- Chronic progressive polyarthritis (Mycoplasma gatae)
- Other chronic bacterial infections

Noninfectious inflammatory diseases
- Pancreatitis
- Systemic lupus erythematosus

Neoplasia
- Lymphoma
- Mastocytocytosis
- Other tumors

Familial (sibling cats with GN)

Note: Most cases of GN in cats are idiopathic, and many cases of GN in dogs (50% or more) are idiopathic.
*Most common causes of glomerulonephritis in dogs and cats.

Proteinuria itself may promote interstitial inflammation and contribute to tubulointerstitial disease. Increased protein in the glomerular ultrafiltrate is resorbed and degraded by proximal tubular cells. Overload of the lysosomal systems in these cells may lead to cell damage and death. Increased protein reabsorption also leads to upregulation of inflammatory mediators, which contribute to tubulointerstitial inflammation. GN also has the potential to resolve after removal of the causative antigen (e.g., ovariohysterectomy in dogs with pyometra, treatment of heartworm disease).

HISTOPATHOLOGIC LESIONS OF GLOMERULONEPHRITIS

GN is classified morphologically according to the presence of basement membrane thickening, hypercellularity, or both. Disease characterized primarily by basement membrane thickening is called membranous GN, whereas that characterized primarily by increased glomerular cellularity (due to inflammatory cell influx, mesangial cell proliferation, or both) is called proliferative GN. Disease characterized by basement membrane thickening and increased cellularity is called membranoproliferative GN. Disease characterized primarily by fibrosis of the glomeruli is called glomerular sclerosis. The prevalence of immune-complex GN was only 48% in a series of 501 dogs that underwent renal biopsy as part of diagnostic evaluation for suspected glomerular disease. The remaining dogs were diagnosed with primary glomerular sclerosis, amyloidosis, nonimmune complex glomerulopathy or nephropathy, and tubulointerstitial disease

The presence and location of immunoglobulin deposits in the glomerular capillary wall and podocyte foot process

fusion can be detected by electron microscopy. Ultrastructural changes include thickening or splitting of the basement membrane, podocyte foot process fusion, increased cellularity of the mesangial space, and the presence of electron-dense deposits (i.e., immune complexes).

AMYLOIDOSIS

Amyloidosis refers to a diverse group of diseases characterized by extracellular deposition of fibrils formed by polymerization of protein subunits, with a specific biophysical conformation called the β-pleated sheet. This specific biophysical conformation is responsible for the unique optical and tinctorial properties of amyloid deposits as well as their insolubility and resistance to proteolysis in vivo. Amyloid deposits have a homogeneous eosinophilic appearance when stained by hematoxylin and eosin (H&E) and viewed by conventional light microscopy (Fig. 40.6). They demonstrate green birefringence after Congo red staining when viewed under polarized light, and the clinical diagnosis of amyloidosis is based on this finding. Congo red-stained amyloid deposits from patients with reactive (secondary) amyloidosis lose their affinity for Congo red after permanganate oxidation; this feature is useful in the preliminary differentiation of reactive from other types of amyloidosis.

Amyloid syndromes may be classified by distribution of the deposits (systemic or localized) and by the nature of the responsible protein. Localized syndromes usually affect one organ and are uncommon in domestic animals. Examples of localized amyloidosis include pancreatic islet cell amyloid in domestic cats and solitary extramedullary plasmacytomas of the gastrointestinal tract or skin that produce immunoglobulin-associated amyloid. Systemic syndromes affect more than one organ and include reactive, immunoglobulin-associated, and heredofamilial syndromes.

Reactive (secondary) amyloidosis is a systemic syndrome characterized by tissue deposition of amyloid A protein (AA amyloid). Naturally occurring systemic amyloidosis in domestic animals is an example of reactive amyloidosis. Familial amyloid syndromes in the Abyssinian, Siamese, and Oriental Shorthair breeds of cat and in the Shar Pei, Beagle, and English Foxhound breeds of dog are examples of reactive systemic amyloidosis.

Tissue deposits in animals with reactive systemic amyloidosis contain amyloid A protein, which is an amino terminal fragment of an acute-phase reactant called serum amyloid A protein (SAA). Serum amyloid A protein is one of several acute-phase reactants synthesized by the liver in response to tissue injury. The normal serum concentration of SAA is approximately 1 mg/L, but its concentration increases 100- to 500-fold after tissue injury (e.g., inflammation, neoplasia, trauma, infarction). SAA concentration decreases to baseline by 48 hours if the inflammatory stimulus is removed. If inflammation persists, SAA concentration remains increased. Serum amyloid A protein serves as the precursor of amyloid A protein in tissues, and the concentration of SAA is increased in plasma before amyloid deposits are observed in tissues. Chronic inflammation and a prolonged increase in SAA concentration are necessary prerequisites for development of reactive amyloidosis. Despite this, only a small percentage of individuals with chronic inflammatory disease develop reactive amyloidosis. Thus other factors must also be important in development of amyloidosis.

Among domestic animals, reactive amyloidosis is most common in the dog. It is relatively uncommon in other species. Diseases that have been observed in association with reactive systemic amyloidosis in the dog include chronic infectious or noninfectious inflammatory diseases and

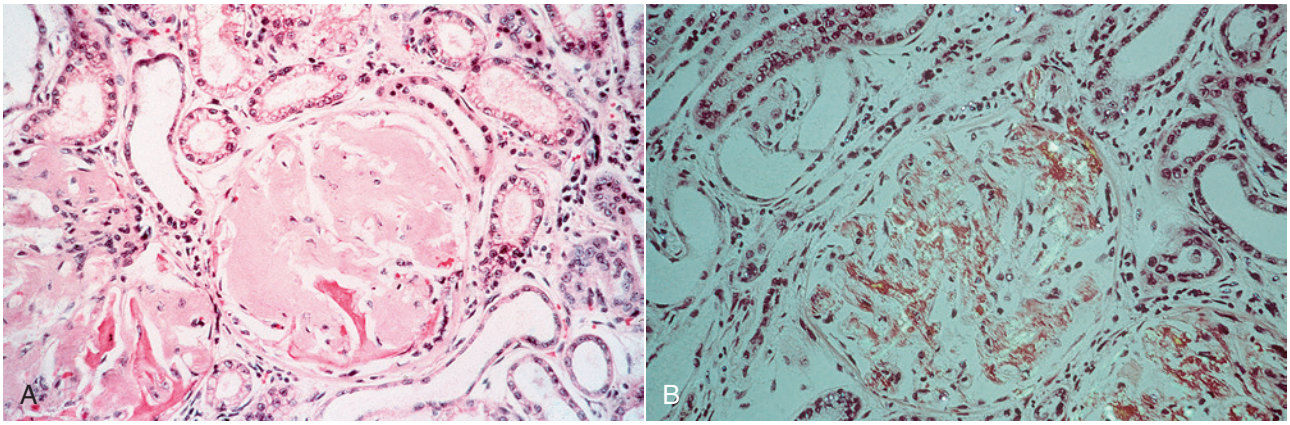


FIG 40.6
Light microscopic appearance of glomerular amyloidosis in a dog. **(A)** Note hypocellularity of the glomerulus caused by deposition of an eosinophilic extracellular material (amyloid; H&E, 400×). **(B)** Congo red stain viewed under polarized light. Note the green birefringence of Congo red-stained amyloid deposits (400×). (**A** from Chew DJ, DiBartola SP, Schenck PA: *Canine and feline nephrology and urology,* ed 2, St Louis, 2011, Elsevier Saunders.)

neoplasms, but there is no discernible associated inflammatory or neoplastic disease in up to 50% of dogs with reactive systemic amyloidosis.

The cause of species differences in the tissue tropisms of reactive amyloid deposits is unknown. In the dog, amyloid AA deposits are most common in the kidney, and clinical signs are caused by renal failure and uremia. The spleen, liver, adrenal glands, and gastrointestinal tract also may be involved, but associated clinical signs are rare. In the cat, there is widespread deposition of amyloid deposits, but clinical signs are due to renal failure and uremia. The Shar Pei dog, Siamese cat, and Oriental Shorthair cat can be exceptions to these general rules. Severe liver deposition of amyloid can cause rupture of the liver and acute hemoabdomen in these breeds. Within the kidney itself, the distribution of amyloid deposits varies among species. For example, amyloidosis is primarily a glomerular disease in the dog, whereas amyloid deposits may have a predominant medullary distribution in the cat.

CLINICAL FINDINGS

Most animals with glomerular disease are middle-aged or older at presentation. There is no sex predilection in dogs, but approximately 75% of cats with GN are males. Any breed can be affected by glomerular disease, but familial forms of membranoproliferative GN have been reported in soft-coated Wheaten Terriers (associated with mutations in the slit diaphragm proteins, nephrin, and Neph3/filtrin), Brittany Spaniels (associated with hereditary deficiency of the third component of complement), and Bernese Mountain dogs (often associated with positive serology for *Borrelia burgdorferi*). Hereditary defects of GBM type IV collagen occur as an autosomal recessive trait in English Cocker Spaniels and as an X-linked dominant trait in male Samoyeds. Basement membrane defects are also suspected to occur in Doberman Pinschers and Bull Terriers. Familial renal amyloidosis occurs in young Abyssinian, Siamese, and Oriental Shorthair cats and in Shar Pei dogs. Familial amyloidosis also has been reported in Beagles and English Foxhounds.

History and Physical Examination Findings

There are several possible clinical presentations of dogs and cats with glomerular disease. Clinical signs may be related to the presence of CKD if more than 75% of the nephron population has become nonfunctional (e.g., anorexia, weight loss, lethargy, polyuria, polydipsia, vomiting). This presentation is common. Signs may be related to an underlying infectious, inflammatory, or neoplastic disease, or proteinuria may be an incidental finding detected during diagnostic evaluation of another medical problem. Clinical signs occasionally may be related to classical nephrotic syndrome (e.g., ascites, subcutaneous edema). Signs may be related to thromboembolism (e.g., sudden onset of dyspnea with pulmonary embolism, sudden onset of paraparesis with iliac, or femoral artery embolism), or sudden blindness may occur because of retinal detachment resulting from systemic hypertension.

Physical examination findings usually are related to the presence of CKD and uremia (e.g., poor body condition, poor hair coat, dehydration, oral ulceration, small irregular kidneys). Other physical examination findings may be related to the presence of underlying infectious, inflammatory, or neoplastic diseases. Affected Shar Pei dogs may have a previous history of so-called Shar Pei fever, episodic joint swelling usually involving the tibiotarsal joints, and high fever that resolves within a few days, regardless of treatment. Some physical examination findings may be related to severe protein loss (e.g., ascites, edema, poor body condition and hair coat). Retinal hemorrhages, vascular tortuosity, and retinal detachment may occur because of systemic hypertension.

Laboratory Findings

A careful search for known associated diseases (see Box 40.1) is a crucial part of the diagnostic evaluation, despite the fact that the glomerular disease ultimately is idiopathic in most cases. Marked persistent proteinuria with inactive urine sediment is the hallmark of glomerular disease. Increased numbers of hyaline casts and occasionally lipid droplets may be observed in the urine sediment of animals with nephrotic range proteinuria. Isosthenuria (urine specific gravity, 1.007-1.015) may be observed if 67% or more of the nephron population has become nonfunctional, and earlier loss of concentrating ability may occur in animals with medullary deposition of amyloid (e.g., Abyssinian cats, Shar Pei dogs).

Glomerulonephritis or amyloidosis can lead to chronic renal failure with the expected biochemical abnormalities (e.g., azotemia, hyperphosphatemia, metabolic acidosis). Hypoalbuminemia occurs in many dogs with glomerular disease (up to 75% of dogs with amyloidosis and 60% of dogs with GN). Hypercholesterolemia occurs in most dogs with glomerular disease (up to 60% of dogs with GN and 90% of dogs with amyloidosis) but tends to be a nonspecific finding in cats with renal disease. Hypercholesterolemia may be caused in part by increased hepatic synthesis of cholesterol-rich lipoproteins secondary to chronic hypoalbuminemia.

The UPC ratio avoids the confounding effect of total urine solute concentration (i.e., specific gravity) on the qualitative assessment of proteinuria. It correlates well with 24-hour urinary protein loss but is much easier to measure—that is, it does not require a 24-hour urine sample. The magnitude of increase in UPC is roughly correlated with the nature of glomerular disease. UPCs are highest in dogs with glomerular amyloidosis (often >10) and lowest in those with interstitial renal disease (usually <10). Animals with GN have very variable UPC (normal to >30). The presence of hematuria or pyuria potentially can make the UPC difficult to interpret; it may cause a false-positive result. Normal UPC is < 0.5 in dogs and < 0.4 in cats. In one study of dogs, results of UPC obtained on three separate urine samples correlated well with a single determination made from a pooled sample of

the three specimens, suggesting a cost-effective alternative to repeated UPC determinations on individual samples. As glomerular disease advances and glomerular filtration rate decreases, less protein is filtered and the UPC may decrease, usually as the azotemia worsens. Such a decrease does not necessarily indicate clinical improvement and is a poor prognostic sign. Proteinuria is mild or absent in animals with renal medullary amyloidosis but without glomerular amyloidosis (e.g., some cats and Shar Pei dogs with amyloidosis).

In addition to being valuable for the diagnosis of glomerular disease, proteinuria also has been recognized as a factor in the progression of CKD. Dogs with CKD and a UPC ratio of 1.0 or higher had a threefold greater risk of uremic crises and death as compared with those with a UPC ratio less than 1.0. In cats with CKD, survival was correlated with UPC ratio; cats with a UPC ratio more than 0.4 had a 4.0 hazard ratio for death or euthanasia as compared with a hazard ratio of 2.9 for cats with a UPC ratio between 0.2 and 0.4. Treatment with angiotensin-converting enzyme inhibitors (ACEi) to decrease proteinuria and slow progression of CKD has become an important management strategy in patients with CKD (see later). The diagnostic approach to proteinuria is summarized in Box 40.2.

Renal biopsy is the only reliable way to differentiate GN from glomerular amyloidosis. A renal cortical biopsy will reliably differentiate GN from glomerular amyloidosis, but medullary tissue is needed to diagnose renal medullary amyloidosis. Light microscopic lesions may be minimal in GN.



BOX 40.2

Clinical Approach to Proteinuria

Localization: Proteinuria in a sample collected by cystocentesis and with an inactive urinary sediment is likely renal in origin.

Persistence: Proteinuria should be repeatable on at least three urine samples obtained at least 2 weeks apart.

Magnitude: The next steps should be determined by the magnitude of the proteinuria.

- Microalbuminuria based on results of enzyme-linked immunosorbent assay (ELISA) (1-30 mg/dL)
  - Monitor for persistence and progression when found in an otherwise healthy older animal.
  - Investigate previously unsuspected systemic disease when found in an older animal.
  - Progressive increases suggest ongoing renal injury and prompt further evaluation.
- Urine protein-to-creatinine (UPC) ratio
  - >0.5 to 1.0 suggests renal (but not necessarily glomerular) proteinuria.
  - >1.0 to 2.0 suggests increased risk for morbidity and mortality in animals with azotemic chronic kidney disease.
  - >2.0 suggests glomerular disease.

From Lees GE et al.: Assessment and management of proteinuria in dogs and cats: 2004 ACVIM Forum Consensus Statement (small animal), *J Vet Intern Med* 19:377, 2005.

Immunopathologic methods using fluorescence microscopy or peroxidase-immunoperoxidase staining and transmission electron microscopy are necessary to accurately diagnose and characterize immune complex GN. If ascitic fluid is available for analysis, evaluation typically indicates a pure transudate with low cell count and low total protein concentration. Measurement of plasma fibrinogen and antithrombin concentrations may identify animals at risk for thromboembolism.

MANAGEMENT OF PATIENTS WITH GLOMERULAR DISEASE

The primary guiding principle for the treatment of dogs and cats with glomerular disease is to identify and treat any underlying predisposing infectious, inflammatory, or neoplastic disease (i.e., remove the offending antigen if possible; Box 40.1). For example, ovariohysterectomy in a dog with pyometra or heartworm treatment in a dog with dirofilariasis can result in resolution of the underlying GN. If CKD is present, it is treated according to the principles outlined in Chapter 41.

Although it may seem logical that supplemental dietary protein would be beneficial in dogs and cats with protein-losing renal disease, doing so merely exacerbates urinary protein loss. On the other hand, feeding a low-protein diet decreases intraglomerular pressure and results in a reduction in proteinuria. In one study, feeding a 14% protein diet (on a dry matter basis) to dogs with X-linked hereditary nephropathy was associated with a mean UPC of 1.8 as compared with a mean UPC of 4.7 in those fed a 35% protein diet. In dogs, supportive treatment of hypertension may include a low-salt diet (<0.3% on a dry matter basis). A low-sodium diet also may enhance the antihypertensive effects of renin-angiotensin-aldosterone system (RAAS) inhibitors. Dietary supplementation with long chain n-3 polyunsaturated fatty acids (PUFA) may suppress glomerular inflammation and coagulation by interfering with production of proinflammatory prostanoids. Renal diets that provide 0.6% n-3 PUFA on a dry matter basis decrease the n-6/n-3 ratio from approximately 50:1 to 5:1. If preferred, the animal's food can be supplemented with 0.25-0.5 g/kg/day of long chain n-3 PUFA using fish oil. Such supplementation increases the requirement for antioxidants (e.g., 1.1 IU vitamin E per g fish oil added to the diet).

Inhibition of the RAAS decreases transcapillary glomerular pressure by decreasing efferent arteriolar resistance, and results in a decrease in proteinuria. Treatment with angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), or both has become standard treatment for patients with glomerular disease. Either enalapril or benazepril can be started at dosage of 0.5 mg/kg q24h and gradually increased to 2.0 mg/kg/day divided q12h based on monitoring the patient's UPC. Ideally, the UPC would return to normal (≤ 0.5), but a decrease of 50% from baseline UPC is considered a reasonable partial response. Worsening of

azotemia (i.e., increase in serum creatinine concentration > 30% above baseline) is uncommon when ACEi are used alone. If the patient fails to respond adequately to an ACEi alone, an ARB such as lorsartan or telmisartan can be added to the treatment regimen (Box 40.3). Finally, spironolactone can be added to the treatment regimen if aldosterone escape occurs, but any additional improvement must be weighed against the risk of hyperkalemia or worsening azotemia when these drugs are used in combination. Loop diuretics (e.g., furosemide) may be used in animals with ascites, but caution must be exercised to avoid dehydration and prerenal azotemia.

BOX 40.3

Drugs Used in the Management of Glomerular Disease

Drug	Initial Dosage	Dose Escalation
Ace Inhibitors		
Enalapril	0.5 mg/kg PO q24h	Increase by 0.5 mg/kg/day to a maximum of 2.0 mg/kg/day divided q12h
Benazepril	0.5 mg/kg PO q24h	Increase by 0.5 mg/kg/day to a maximum of 2.0 mg/kg/day divided q12h
Angiotensin Receptor Blockers		
Losartan	0.125 mg/kg/day in azotemic dogs; 0.5 mg/kg/day in nonazotemic dogs	Up to 0.25 mg/kg/day in azotemic dogs; up to 1.0 mg/kg/day in nonazotemic dogs
Telmisartan	1.0 mg/kg/day	Increase by 0.5 mg/kg/day to a maximum of 2.0 mg/kg/day
Aldosterone Receptor Blockers		
Spironolactone	1.0-2.0 mg/kg PO q12h	
Calcium Channel Blockers		
Amlodipine	0.1-0.75 mg/kg q24h	
Loop Diuretics		
Furosemide	1.0 mg/kg q6h to q12h	Incremental increases of 0.5-1.0 mg/kg q6h to q12h up to total of 4.0 mg/kg; or, constant rate infusion of 2-15 µg/kg/min after a loading dose of 2 mg/kg
Antithrombotic Therapy		
Aspirin	1.0-5.0 mg/kg/day	

Adapted from: IRIS Canine GN Study Group Standard Therapy Subgroup, S. Brown, chair, J. Elliott, T. Francey, D. Polzin, S. Vaden: Consensus recommendations for standard therapy of glomerular disease in dogs, *J Vet Int Med* 27:S27, 2013.

The ACEi and ARB have modest effects on systemic blood pressure (i.e., approximately 10%-15% decrease from baseline). Additional antihypertensive treatment is recommended if systolic blood pressure is > 160 mm Hg and diastolic pressure is > 100 mm Hg in a patient with glomerular disease already receiving ACEi and ARB. Typically, the calcium channel blocker amlodipine (0.1-0.2 mg/kg/day) is added to the treatment regimen to manage system blood pressure. In the glomerulus, its effect is primarily on the afferent arteriole and consequently it has little effect on proteinuria. The goal should be to decrease systolic blood pressure to < 150 mm Hg and diastolic pressure to < 95 mm Hg.

Platelet inhibition may decrease intraglomerular coagulation and decrease the risk of thromboembolism. In dogs, an aspirin dosage of 1 to 5 mg/kg PO, q24h, may inhibit platelet cyclooxygenase without preventing the beneficial effects of prostacyclin formation (e.g., vasodilatation, inhibition of platelet aggregation). An aspirin dosage of 5 mg PO, q72h, may be considered in cats.

Immunosuppressive drugs (e.g., corticosteroids, cyclosporine, cyclophosphamide, chlorambucil, azathioprine, mycophenolate, leflunomide) seem like logical candidates for treatment of immune-mediated GN, but no studies in veterinary medicine are available that clearly demonstrate their effectiveness. Corticosteroid administration can cause proteinuria in dogs, and one retrospective study suggested that corticosteroid therapy actually may be detrimental in dogs with idiopathic GN. A controlled trial of cyclosporine treatment (15 mg/kg PO, q24h) in dogs with GN failed to show a beneficial effect. Cyclophosphamide and chlorambucil are alkylating agents that can be considered, but studies in dogs with GN are lacking and adverse effects are a concern, especially with cyclophosphamide. Azathioprine (50 mg/m^2 PO, q24-48h) may be considered for immunosuppression in dogs with idiopathic GN, but only anecdotal evidence of effectiveness is available. Azathioprine is thought to require 2 to 5 weeks of treatment to be fully effective in dogs, and consequently it usually is combined initially with a more rapidly acting immunosuppressive drug. Azathioprine should not be used in cats because they metabolize the drug very slowly and develop bone marrow suppression and severe leukopenia when given dosages similar to those used in dogs; chlorambucil can be used as an alternative in cats. Whether corticosteroids are beneficial for the treatment of cats with GN is unclear. Mycophenolate inhibits purine synthesis and is less toxic than alkylating agents. Its adverse effects are primarily gastrointestinal and reversible upon discontinuation of the drug. Leflunomide inhibits pyrimidine synthesis and can be associated with unexplained hemorrhage and thrombocytopenia at higher dosages. These newer immunosuppressive drugs have potential in the treatment of immune-mediated disease but limited information is available for their use in GN in dogs. The mechanism of action, dosage, and adverse effects of immunosuppressive drugs potentially useful in the treatment of GN are presented in Box 40.4.

BOX 40.4

Immunosuppressive Drugs Potentially Useful in the Management of Glomerular Disease

Immunosuppressive Therapy			
Drug	***Mechanism of Action***	***Dosage***	***Adverse Effects***
Prednisone	Inhibits phospholipase A2, decreases cytokine release, inhibits neutrophil migration, decreases function and numbers of T cells and B cells, induces antiinflammatory phenotype during macrophage differentiation	1.0-2.0 mg/kg/day	Polyuria, polydipsia, polyphagia, pendulous abdomen, panting, worsening of proteinuria, hypercatabolism and muscle loss, increased hypercoagulability, sodium and fluid retention, hypertension, behavioral changes, adrenal suppression
Mycophenolate	Inhibits inosine monophosphate dehydrogenase, rate-limiting step in synthesis of guanosine nucleosides needed for DNA and RNA synthesis	10 mg/kg q12h	GI upset
Cyclosporine	Binds to cyclophilin and inhibits calcineurin essential for transcription of interleukin-2 needed for T-cell activation	5-20 mg/kg q12h	GI upset, gingival hyperplasia
Cyclophosphamide	Alkylating agent that interferes with DNA and RNA synthesis	Pulse therapy of 200-250 mg/M^2 q3wks or continuous therapy of 50 mg/M^2 4 days/wk	GI upset, myelosuppression, hemorrhagic cystitis
Chlorambucil	Alkylating agent that interferes with DNA and RNA synthesis	0.2 mg/kg q24-48h	GI upset, myelosuppression
Azathioprine	Purine analogue that interferes with DNA and RNA synthesis and lymphocyte proliferation	2 mg/kg q24h for 1-2 wks, then 1-2 mg/kg q48h	GI upset, myelosuppression, acute pancreatitis, hepatotoxicity
Leflunomide	Inhibits pyrimidine synthesis leading to decrease in DNA and RNA synthesis and lymphocyte proliferation	2 mg/kg/day	Diarrhea, lethargy, unexplained hemorrhage, thrombocytopenia, increased liver function tests (more common at dosages ≥ 3 mg/kg/day)

Adapted from: IRIS Canine GN Study Group Established Pathology Subgroup, G. Segev, chair, L.D. Cowgill, R. Heiene, M.A. Labado, D.J. Polzin: Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology, *J Vet Int* Med 27:S44, 2013.

Response to treatment of GN is gauged by the change in UPC as well as improvement in serum creatinine and albumin concentrations, if these were abnormal at the start of treatment. The patient should be assessed every 2 weeks during the initial phase of treatment. If the patient is tolerating immunosuppressive therapy without serious adverse effects, it can be continued for 8 to 12 weeks before beginning to taper the patient off treatment. If the response is minimal, increased dosage or alternative drugs can be tried, but if there is no response after 12 to 16 weeks, continued immunosuppressive therapy is unlikely to be worthwhile.

No specific therapy has been shown to be beneficial for the treatment of amyloidosis. Experimentally, dimethyl sulfoxide (DMSO) given during the rapid deposition phase can cause resolution of amyloid deposits and a persistent decrease in SAA concentration, and may improve renal function by decreasing interstitial inflammation and fibrosis. One case report in a dog with amyloidosis showed a beneficial effect (e.g., less proteinuria, improved glomerular filtration rate) of DMSO when used at a dosage of 90 mg/kg/wk administered subcutaneously. Another study of several affected dogs showed no effect of DMSO; the dogs had similar amounts of amyloid in their kidneys at necropsy as in renal biopsies taken before instituting DMSO treatment.

In human patients with systemic AA amyloidosis, amyloid deposits regress and prognosis is most favorable in patients when the SAA concentrations remain low (<10 mg/L). The drug eprodisate, which binds to glycosaminoglycan binding sites on serum amyloid A (SAA) protein and inhibits polymerization and deposition of amyloid fibrils in tissues, may slow the progression of renal disease in some human patients with systemic AA amyloidosis. Recently, tocilizumab (a monoclonal antibody directed against the interleukin-6 receptor) has shown promise in treatment of human patients with AA amyloidosis secondary to inflammatory diseases. It results in markedly decreased SAA concentration and, in some cases, it decreased proteinuria and stabilized renal function. Amyloid deposits in treated patients regressed or remained stable.

Colchicine impairs the release of SAA from hepatocytes by binding to microtubules and preventing its secretion. It prevents the development of amyloidosis in human patients with familial Mediterranean fever (FMF), a genetic disorder characterized by recurrent, self-limiting febrile episodes

associated with serosal inflammation. FMF is caused by mutations in the pyrin gene, which is expressed in neutrophils and normally inhibits inflammation provoked by minor insults. If untreated, most people with FMF develop reactive amyloidosis, nephrotic syndrome, and renal failure in middle age. Colchicine prevents most febrile attacks and prevents development of amyloidosis in this population. Colchicine (0.03 mg/kg/day) may be beneficial in Shar Pei dogs with recurrent fever and joint swelling (so-called Shar Pei fever) that may be at risk for the development of systemic amyloidosis, but no prospective placebo-controlled study is available to support this treatment. Adverse effects of colchicine include gastrointestinal upset and rare development of neutropenia.

COMPLICATIONS

HYPOALBUMINEMIA

The hypoalbuminemia of nephrotic syndrome is only partially explained by the urinary loss of albumin. Hepatic albumin synthesis is increased in nephrotic syndrome but this increase is insufficient for the degree of hypoalbuminemia. Low plasma oncotic pressure is thought to be the primary stimulus for increased hepatic synthesis of albumin in this syndrome. Renal catabolism of albumin is increased in nephrotic syndrome because of increased reabsorption of filtered protein. Although an increase in dietary protein stimulates hepatic albumin synthesis, it does not correct hypoalbuminemia in patients with nephrotic syndrome and only worsens the urinary loss of protein.

SODIUM RETENTION

The underfill hypothesis of edema and ascites formation in the nephrotic syndrome involves activation of the RAAS. Progressive loss of albumin through the glomeruli and inadequate hepatic synthesis of albumin lead to hypoalbuminemia, which in turn leads to decreased oncotic pressure with loss of water and electrolytes from the vascular compartment. Decreased circulating volume leads to decreased renal blood flow and activation of the RAAS with aldosterone release and consequent renal conservation of sodium and water. Attempted restoration of circulating volume is unsuccessful because hypoalbuminemia and decreased oncotic pressure prevent retention of water in the vascular compartment. In addition to the RAAS, nonosmotic stimulation of antidiuretic hormone (ADH) release and increased sympathetic nervous system activity could be invoked by decreased circulating volume and also would promote renal water and sodium retention.

The overfill hypothesis is based on evidence for a primary intrarenal mechanism of sodium retention in nephrotic syndrome. Aldosterone concentrations frequently are normal or even low in affected human patients, and treatment with ACEi does not always prevent sodium retention. Primary intrarenal sodium retention in nephrotic syndrome occurs in the distal nephron and contributes to extracellular fluid volume expansion and edema formation. Recent studies have suggested that upregulation of the electrogenic sodium channel (ENaC) in collecting duct epithelial cells may mediate this sodium retention.

The underfill and overfill hypotheses of sodium retention and edema formation in the nephrotic syndrome can be reconciled by considering the stage of disease. Earlier in the disease process, when the serum albumin concentration and intravascular oncotic pressure are adequate, intrarenal sodium retention may result in expansion of circulating volume and suppression the RAAS (overfill). Later in the disease process, when severe hypoalbuminemia and low circulating volume caused by decreased intravascular oncotic pressure develop, the RAS would be activated, despite the presence of an intrarenal mechanism for sodium retention (underfill).

THROMBOEMBOLISM

The nephrotic syndrome results in a hypercoagulable state. Occasionally, thromboembolic phenomena are responsible for the major presenting signs and overshadow the underlying renal disease, thus complicating the clinical course and delaying the primary diagnosis. Hypercoagulability and thromboembolism associated with the nephrotic syndrome occur secondary to several abnormalities in the coagulation system. Mild thrombocytosis and platelet hypersensitivity occur in association with hypoalbuminemia and result in increased platelet adhesion and aggregation. Plasma arachidonic acid normally is protein-bound, and more arachidonic acid is free to bind to platelets in the presence of hypoalbuminemia. This may result in increased thromboxane production by platelets and platelet hyperaggregability. Hypercholesterolemia also may contribute to platelet hyperaggregability by altering platelet membrane composition or affecting platelet adenylate cyclase response to prostaglandins.

Loss of antithrombin (AT; molecular weight [MW], 65,000) in urine also contributes to hypercoagulability. AT acts in concert with heparin to inhibit serine proteases (clotting factors II, IX, X, XI, and XII) and normally plays a vital role in modulating thrombin and fibrin production. Decreased plasma concentrations of factors IX, XI, and XII occur because of urinary loss of these proteins. Hyperfibrinogenemia and decreased fibrinolysis contribute to hypercoagulability. Decreased fibrinolysis occurs as a result of decreased concentration of plasminogen and increased concentration of α_2-macroglobulin (a plasmin inhibitor). Increased concentration of large-MW coagulation factors (factors II, V, VII, VIII, and X) may lead to a relative increase in coagulation factors as compared with regulatory proteins. This increase may result from increased protein synthesis by the liver as it attempts to correct hypoalbuminemia.

Thromboembolism has been reported to occur in 15% to 25% of dogs with nephrotic syndrome. It is rare but has been reported in cats with glomerular disease. Animals with fibrinogen concentrations more than 300 mg/dL and AT concentrations less than 70% of normal are considered at risk for thromboembolism, and anticoagulant therapy (e.g.,

aspirin) should be considered. In one study, the prevalence of hypercoagulability characterized by thromboelastography was 89% in 76 dogs with protein-losing nephropathy in which the diagnosis was based on the UPC results, but the prevalence of thromboembolism was only 6.6%. Hypercoagulability could not be predicted by the severity of proteinuria, hypertension, hypoalbuminemia, or low AT activity. The pulmonary artery is the most common site for thromboembolism, but emboli also may lodge in the mesenteric, renal, iliac, coronary, and brachial arteries and in the portal vein. Dogs with pulmonary thromboembolism usually are dyspneic and hypoxic, with minimal pulmonary parenchymal radiographic abnormalities. Treatment usually is unsuccessful, and the prognosis in dogs with glomerular disease and pulmonary thromboembolism is grave.

HYPERLIPIDEMIA

Hypercholesterolemia and hyperlipidemia are common in patients with nephrotic syndrome. Decreased plasma oncotic pressure caused by hypoalbuminemia and increased loss of regulatory factors for lipid metabolism in urine cause increased hepatic synthesis of lipoproteins and decreased peripheral catabolism of lipoproteins. Large-MW, cholesterol–rich lipoproteins that are not easily lost through the damaged glomerular capillary wall accumulate, whereas smaller MW proteins such as albumin and AT are lost in the urine. In nephrotic patients, cholesterol and lipid concentrations tend to increase as albumin concentration decreases. Decreased hepatic catabolism of lipoproteins occurs because of abnormal lipoprotein lipase function. Normal lipoprotein lipase function requires heparin sulfate as a cofactor, and concentrations of heparin sulfate frequently are decreased in nephrotic patients. The decrease in heparin sulfate has been linked to increased urinary loss of another glycoprotein, orosomucoid. Diversion of necessary sugar intermediates as the liver replaces the lost orosomucoid causes the decreased production of heparin sulfate. Orosomucoid also has an important role in maintaining normal glomerular permselectivity. Consequently, urinary loss of orosomucoid not only contributes to the hyperlipidemia of the nephrotic syndrome but also exacerbates proteinuria.

HYPERTENSION

Systemic hypertension may occur in dogs and cats with glomerular disease caused by sodium retention, activation of the RAAS, and impaired release of normal renal vasodilator substances. Systemic hypertension has been associated with immune–mediated GN, glomerular sclerosis, and glomerular amyloidosis and may occur in 50% or more of dogs with glomerular disease. Retinal hemorrhage, retinal vascular tortuosity, and retinal detachment may result from systemic hypertension, and blindness may be the presenting complaint in hypertensive dogs and cats with glomerular disease.

Prognosis

Amyloidosis is a progressive disease with a poor prognosis. Affected animals often are in renal failure at the time of presentation and generally live less than 1 year after diagnosis. GN has a variable course, and a poor prognosis should not be given unless there is evidence of progression to CKD. Dogs and cats with GN may experience spontaneous remission, may have a relatively stable clinical course with ongoing proteinuria for several months to years, or may progress to chronic renal failure over months to years.

Suggested Readings

Dember LM, et al. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med*. 2007;356:2349.

IRIS Canine GN Study Group Established Pathology Subgroup, et al. Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology. *J Vet Intern Med*. 2013;27:S44.

IRIS Canine GN Study Group Standard Therapy Subgroup, et al. Consensus recommendations for standard therapy of glomerular disease in dogs. *J Vet Intern Med*. 2013;27:S27.

Jacob F, et al. Evaluation of the association between initial proteinuria and morbidity rate or death in dogs with naturally occurring chronic renal failure. *J Am Vet Med Assoc*. 2005;226:393.

King JN, et al. Tolerability and efficacy of benazepril in cats with chronic kidney disease. *J Vet Intern Med*. 2006;20:1054.

Lachmann HJ, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*. 2007;356:2361.

Lane T, et al. Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature. *Clin Exp Rheumatol*. 2015;33(6 suppl 94):S46.

LeVine DN, et al. The use of pooled vs serial urine samples to measure urine protein:creatinine ratios. *Vet Clin Pathol*. 2010;39:53.

Littman MP, et al. Glomerulopathy and mutations in NPHS1 and KIRREL2 in soft-coated Wheaten Terrier dogs. *Mamm Genome*. 2013;24:119.

Sato M, et al. A retrospective study on the safety and efficacy of leflunomide in dogs. *J Vet Intern Med*. 2017.

Schneider SM, et al. Prevalence of immune-complex glomerulonephritis in dogs biopsied for suspected glomerular disease: 501 cases (2007-2012). *J Vet Intern Med*. 2013;27:S67.

Syme HM, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. *J Vet Intern Med*. 2006;20:528.

White CR, et al. Evaluation of the relationship between clinical variables and thromboelastographic findings in dogs with protein-losing nephropathy. *J Vet Emerg Crit Care (San Antonio)*. 2016;26:74.

Zacchia M, et al. Nephrotic syndrome: new concepts in the pathophysiology of sodium retention. *J Nephrol*. 2008;21:836.

CHAPTER 41

Acute Kidney Injury and Chronic Kidney Disease



It can be difficult sometimes to determine whether an animal is suffering from acute kidney injury (AKI) or chronic kidney disease (CKD), but differentiation is important because AKI is potentially reversible, whereas CKD is not. Several of the clinical findings that help differentiate AKI from CKD are specific but not sensitive for CKD (i.e., they are useful if present but not if absent). For example, the kidneys are expected to be normal-sized (or occasionally mildly enlarged) in patients with AKI, whereas small irregular kidneys signify CKD. Some animals with CKD, however, can have normal-sized kidneys, and some chronic renal diseases in cats are associated with enlarged kidneys (e.g., renal lymphoma, polycystic kidney disease). A history of previous polyuria (PU) and polydipsia (PD) often (but not always) is present in CKD, whereas this history is absent in AKI. Nonregenerative anemia often (but not always) is detected at presentation in dogs and cats with CKD, whereas anemia is not present initially in AKI. If present, weight loss, poor body condition, and poor hair coat suggest CKD, and these findings are not expected in animals with AKI. However some dogs and cats with CKD are in good body condition. The observation of enlarged parathyroid glands (>4 mm) on ultrasound examination of a dog with kidney disease suggests CKD, whereas a dog with AKI is expected to have normal-sized parathyroid glands (≤4 mm). Hyperkalemia may be observed with the development of oliguria or anuria in AKI or CKD. The clinical differentiation of AKI and CKD is summarized in Table 41.1.

ACUTE KIDNEY INJURY

AKI is a clinical syndrome characterized by abrupt increases in serum creatinine (SCr) and blood urea nitrogen (BUN) concentrations (azotemia). Early recognition of AKI is crucial because it can be reversed in patients with enough surviving nephrons, provided treatment is instituted early. AKI probably occurs more frequently than appreciated and may go undiagnosed or be confused with CKD. Recognizing situations in which AKI is likely to develop and taking appropriate preventive measures is preferable to treating established AKI. The clinicopathologic abnormalities in patients with AKI frequently are more severe than those observed in patients with CKD because most of the compensatory mechanisms that develop in CKD are not present in AKI.

Pathophysiology

Renal ischemia or exposure to nephrotoxins causes tubular injury that ranges from degeneration to necrosis and historically has been referred to as nephrosis or acute tubular necrosis (Fig. 41.1). In some cases, severe excretory failure can occur, despite minimal or no light microscopic lesions. Several factors may contribute to azotemia and oliguria in AKI, including tubular backleak, intraluminal tubular obstruction (e.g., casts, cellular debris, tubular swelling), extraluminal tubular obstruction (e.g., interstitial edema, cellular infiltrates), and primary filtration failure (e.g., afferent arteriolar vasoconstriction, efferent arteriolar vasodilatation, decreased glomerular permeability). Some combination of these pathophysiologic mechanisms likely occurs in clinical patients, depending upon the underlying cause of AKI (Fig. 41.2). Depending on duration and severity, renal ischemia can cause reversible prerenal azotemia or acute tubular necrosis. The renal cortex is richly supplied with adrenergic innervation, which results in vasoconstriction during renal ischemia. Because of a large reserve of blood supply, temporary or mild reductions in renal blood flow (RBF) do not result in tubular necrosis. Deprivation of blood supply, if severe and prolonged, results in decreased cellular energy production and loss of cellular integrity. Tubules with high metabolic activity are at greatest risk of injury during decreased oxygen delivery. The outer medulla is supplied with the lowest amount of oxygen relative to its high metabolic activity, and this region of the kidney is at increased risk for injury during hypoxia. Nonsteroidal antiinflammatory drugs (NSAIDs) can result in renal ischemia by blocking the renal production of vasodilatory prostaglandins that maintain RBF during dehydration. True nephrotoxins exert their deleterious effects directly on the kidney after binding

TABLE 41.1

Clinical Differentiation of Acute Kidney Injury and Chronic Kidney Disease

CLINICAL FEATURE	ACUTE KIDNEY INJURY	CHRONIC KIDNEY DISEASE
Renal size	Normal or mildly enlarged	Small and irregular or normal
Previous history of polyuria and polydipsia	Absent	Present or absent
Nonregenerative anemia	Absent	Present or absent
Weight loss	Absent	Present or absent
Poor body condition	Absent	Present or absent
Poor hair coat	Absent	Present or absent
Ultrasound appearance of parathyroid glands	Normal-sized	Enlarged

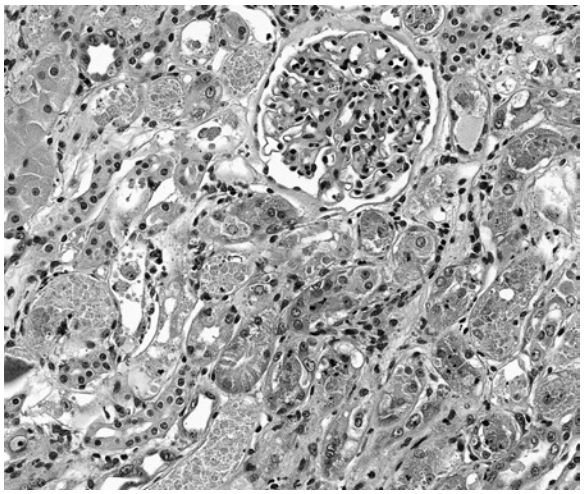


FIG 41.1
Photomicrograph of acute tubular necrosis showing normal glomerulus with areas of tubular necrosis. Note some tubules with loss of tubular epithelium, some with flattened epithelium, and tubular lumens filled with necrotic debris (200×). (Courtesy Dr. Steve Weisbrode.)

BOX 41.1

Some Causes of AKI in Dogs and Cats

Nephrotoxins

- Ethylene glycol
- Aminoglycosides
- Amphotericin B
- Easter lily (cats)
- Grape or raisin toxicity (dogs)
- Hypercalcemia
  - Cholecalciferol rodenticide
  - Calcipotriene (Dovonex)
- Anticancer drugs
  - Cisplatin
- Radiocontrast dyes administered intravenously
- Heavy metals (e.g., thiacetarsamide)
- Tainted food (melamine, cyanuric acid)
- Hydroxyethyl starch (increased risk with 10% solution but not 6%)

Renal Ischemia

- Dehydration
- Trauma
- Anesthesia
- Sepsis
- Heat stroke
- Pigment nephropathy
  - Myoglobinuria
- Shock
- Hemorrhage
- Surgery
- Nonsteroidal antiinflammatory drugs (NSAIDs)

Other

- Leptospirosis—acute tubulointerstitial nephritis
- Borrelia—rapidly progressive glomerulonephritis
- Cutaneous and renal glomerular vasculopathy—renal thrombotic microangiopathy (especially Greyhounds)

Acute Hyperphosphatemia

- Tumor lysis syndrome

to tubular cell membranes. The term *nephrotoxicant* refers to a chemical or drug that can result in renal injury regardless of whether it is caused by direct nephrotoxic injury (e.g., aminoglycosides) or renal ischemia (e.g., NSAIDs). Patients with underlying renal disease may develop AKI more readily than patients with kidneys that were normal before the insult. Concurrent dehydration also may increase the severity of AKI after renal ischemia or exposure to nephrotoxins, in part because dehydration activates renal vasoconstriction, which can contribute to additional ischemic damage. Causes of AKI in dogs and cats are presented in Box 41.1.

AKI passes through three clinical phases (Fig. 41.3). The latent phase represents the time after exposure to a nephrotoxin or renal ischemia before the onset of azotemia. It is associated with an increasing number and severity of renal tubular lesions over time if the renal insult is not removed. The latent phase often is not detected because clinical signs are absent or minimal. Prompt removal of the inciting cause will result in rapid return to normal renal function.

Entry into the maintenance phase signifies that a critical amount of lethal injury has occurred in the renal tubules, and a course of 1 to 3 weeks of AKI is expected before restoration of renal function can occur. Removal of the inciting cause during the maintenance phase will not result in

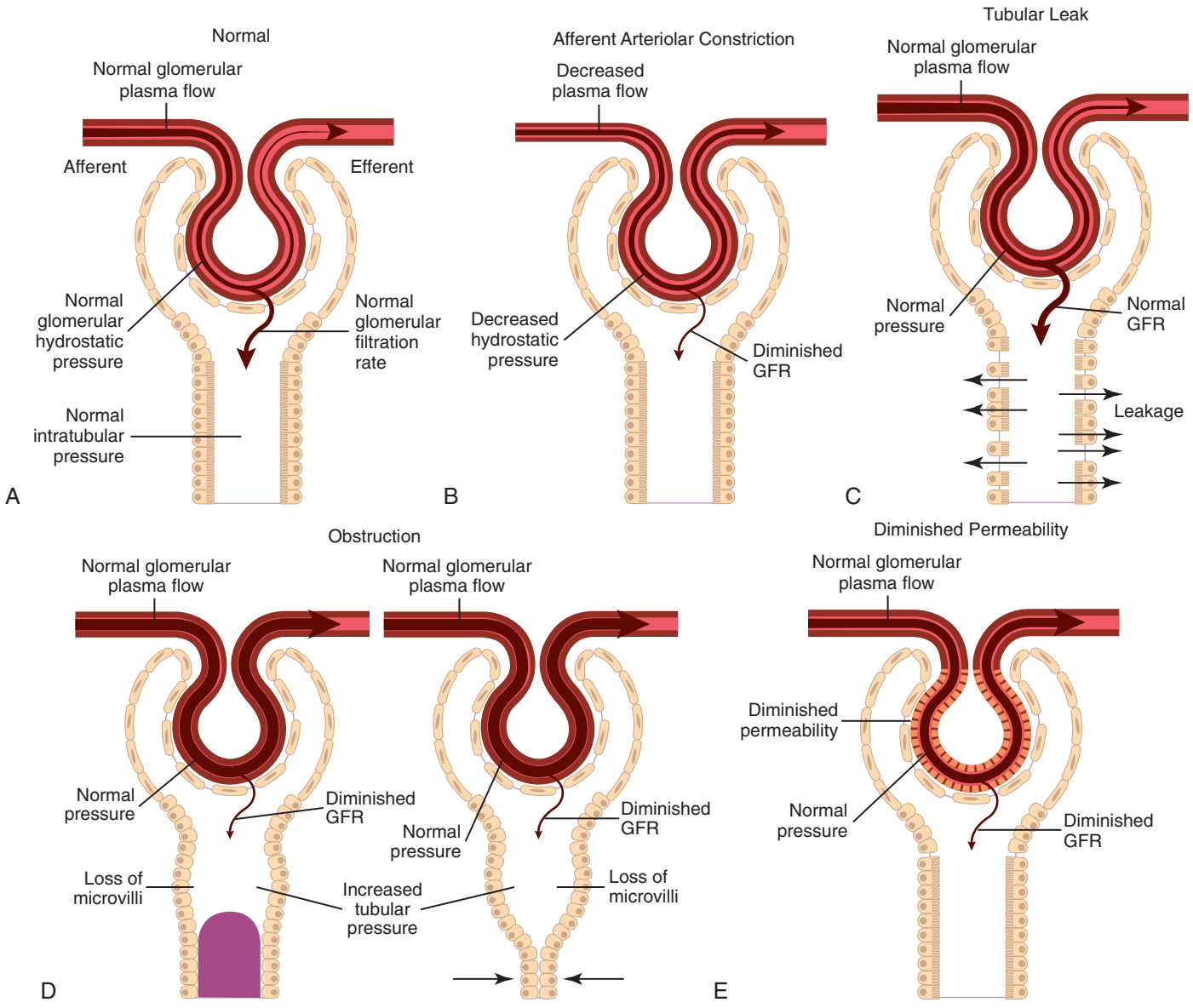


FIG 41.2
Mechanisms contributing to decreased GFR and oliguria in AKI. **(A)** Normal nephron. Glomerular filtration pressure normally is not impeded to any appreciable extent by the normally low intratubular pressure. The healthy renal tubular epithelium prevents tubular fluid from leaking between or across tubular cells. No obstructing material is present within the tubular lumen and the lumen is completely patent. **(B)** Afferent arteriolar vasoconstriction (i.e., vasomotor nephropathy). Glomerular filtration is severely decreased by constriction of the afferent arteriole. Decreased intraglomerular pressure can result in azotemia and decreased urine production. **(C)** Tubular backleak. Filtration pressure may be normal, but filtered fluid leaks back across the damaged tubular epithelium into the interstitium. Some fluid also may accumulate within the damaged tubule. Tubular backleak occurs in patients with more severe tubular injury. Backleak is increased by any concurrent increase in tubular pressure (see **D**). **(D)** Obstruction-increased intratubular pressure. Increased intratubular pressure occurs proximal to the obstructed segment of the nephron. The obstruction can be intraluminal or extraluminal, and the resultant increase in pressure opposes glomerular filtration. The obstructing material can be cellular debris, precipitated proteins, or occasionally crystalline precipitates. Interstitial edema or cellular infiltrates can cause extraluminal obstruction and decrease renal blood flow by compressing interstitial blood vessels. Tubular swelling also can contribute to increased intraluminal pressure. **(E)** Decreased glomerular permeability. In this example, the disease process has decreased the surface area available for glomerular filtration. Decreased glomerular permeability can arise as a consequence of mesangial cell contraction and decreases in the number and diameter of the glomerular fenestrae (pores).

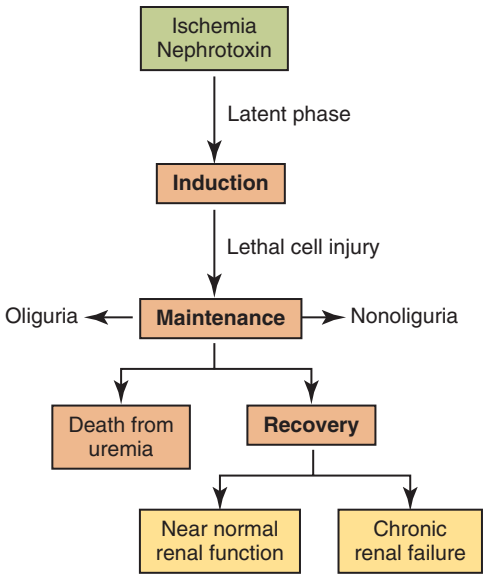


FIG 41.3
Phases of AKI and potential outcomes.

immediate return of normal renal function. Anuria, oliguria, normal urine production, or PU may occur, depending on the specific cause and severity of renal injury. Anuria or marked oliguria occurs in patients with the most severe renal injury (e.g., ethylene glycol, lily toxicity in cats), whereas normal urine production or PU is more likely in those with aminoglycoside nephrotoxicity. Persistently increased SCr characterizes the maintenance phase of AKI, despite correction of all prerenal factors (i.e., restoration of extracellular fluid volume and renal perfusion). With severe renal injury, the patient may not survive the maintenance phase. RBF may be restored by volume expansion during the maintenance phase, but the glomerular filtration rate (GFR) remains very low.

During the recovery phase, BUN and SCr return to normal as GRF and RBF recover, and diuresis ensues in patients that previously were anuric or oliguric. Maximal urinary concentrating ability and urinary acidification may not return to normal, but these limitations are usually not of clinical consequence. BUN and SCr also may not completely normalize, depending on the amount of renal injury sustained. These patients, however, may show sufficient improvement to have a reasonable quality of life as a CKD patient.

Clinical Findings

The clinical findings in AKI are nonspecific and include anorexia, lethargy, vomiting, and diarrhea. These signs are of recent onset, and a longstanding history of PU or PD should not be present. In one study of dogs with AKI, approximately 18% had anuria, 43% had oliguria, 25% had normal urine output, and 14% had PU. Recent trauma, shock, surgery, or general anesthesia suggests the possibility of ischemic AKI. Recent administration of known nephrotoxicants increases the likelihood of nephrotoxic AKI. Physical examination findings in AKI patients tend to be more severe than those observed in animals with prerenal azotemia and include dehydration, uremic breath, and oral ulceration. Mucous membrane pallor, as may be observed in patients with CKD, should not be detected. Fever may be present in animals with AKI caused by nephritis (e.g., dogs with leptospirosis). Overhydration may be present in oligoanuric animals with AKI that have received an excessive amount of fluids intravenously. The kidneys are normal or enlarged and not small and irregular, as may be observed in animals with CKD. Bladder size will vary depending on urine output. If present, bradycardia suggests the need to evaluate the serum potassium concentration.

Clinicopathologic Findings

Anemia should be absent early in the course of AKI, but may develop with repeated blood sampling and ongoing gastrointestinal (GI) blood loss. Total protein concentration may be normal or high, depending on the extent of dehydration. A stress response (e.g., mature neutrophilia, lymphopenia) is common on the complete blood count (CBC). Leukocytosis with left shift and thrombocytopenia may be seen in dogs with acute leptospirosis. The urine specific gravity (USG) typically is in the isosthenuric range (1.007-1.015), regardless of whether the animal is oliguric or nonoliguric. Proteinuria, hematuria, or glucosuria may be observed, and the urine sediment may be active with many casts (e.g., renal tubular cellular casts, coarsely and finely granular casts).

The absence of casts, however, does not exclude a diagnosis of AKI. The presence of oxalate crystals in the urine sediment of an animal with AKI supports a diagnosis of ethylene glycol poisoning. BUN and SCr are high and continue to increase until a plateau is established. It may take days to reach a steady-state SCr after severe acute renal injury, and SCr may continue to increase as additional lethal renal cell injury occurs (i.e., ongoing undetected ischemia or nephrotoxic insult). The magnitude of increase in BUN or SCr is not helpful in the differentiation of AKI from CKD or in the differentiation of prerenal, intrinsic renal, and postrenal azotemia. Rapid increases in BUN, SCr, and serum phosphorus concentrations may occur during AKI. Depending on urine output, serum potassium concentrations may be normal or high, whereas normal or low serum potassium concentrations are expected in polyuric CKD patients. Hyperphosphatemia is present and often severe in AKI patients. Renal secondary hyperparathyroidism maintains phosphorus balance in slowly progressive CKD, a compensatory effect that does not have sufficient time to develop in AKI patients. The serum total calcium concentration usually is normal or low. Blood gas analysis during the maintenance phase usually shows moderate to severe metabolic acidosis. Fractional excretion of sodium is increased in animals with AKI and may be a useful biomarker because it decreases over time in survivors. Recently, other urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) have been shown to be valuable in the detection and monitoring of patients with AKI (see Chapter 39).

The kidneys are normal-sized or enlarged and of normal shape in patients with AKI. Renal ultrasonography may show increased cortical or medullary echogenicity, but normal ultrasonographic examination findings do not exclude AKI. The kidneys of animals with ethylene glycol intoxication are extremely hyperechoic, and this observation may be helpful diagnostically (Fig. 41.4). Radiographic signs of pulmonary disease (e.g., alveolar pattern, alveolar mineralization) were more common in dogs with AKI than in those with CKD in one study, but these findings did not affect survival. Acute and convalescent serology testing is useful to establish a diagnosis of leptospirosis in dogs with acute nephritis.

Renal biopsy is used to confirm that azotemia is caused by primary renal lesions, to characterize the lesions as acute or chronic, and to establish a prognosis. Renal lesions compatible with AKI include tubular degeneration, tubular necrosis, and intratubular casts. The presence of intact tubular basement membranes with evidence of tubular regeneration is a good prognostic sign, whereas disrupted basement membranes suggest a worse prognosis. Interstitial inflammation is minimal in AKI caused by nephrosis but substantial in AKI caused by nephritis. Lack of fibrosis is supportive of a diagnosis of AKI rather than CKD. Histopathologic changes on light microscopy may be minimal to absent in some animals with AKI. Renal biopsy during a prolonged recovery phase can be helpful to evaluate whether healing is occurring by fibrosis and nephron loss or by tubular regeneration and repopulation of intact basement membranes.

Treatment

The ultimate goal in management of the maintenance phase of AKI is to provide adequate supportive care and time for healing to occur. Prevention of additional renal injury is an important treatment goal; this requires conscientious fluid therapy to provide optimal renal perfusion while at the same time avoiding overhydration. It may take as long as 3 weeks of supportive care to determine whether adequate renal function is likely to return. The severity of residual azotemia will determine whether the animal can be managed successfully as a CKD patient.

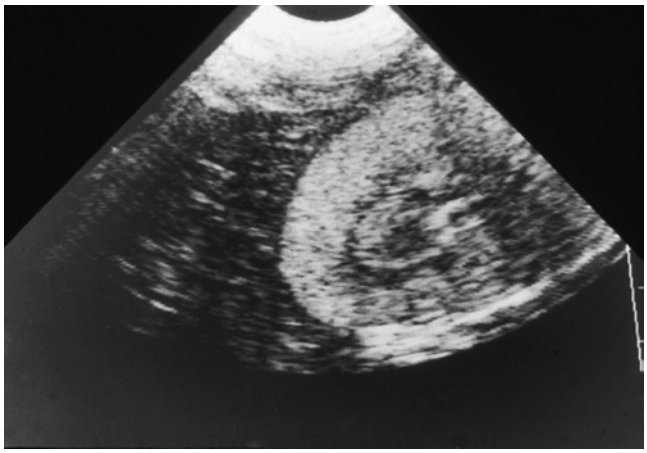


FIG 41.4
Ultrasound appearance of kidney of a dog with ethylene glycol poisoning. Note the extremely hyperechoic renal cortex.

Initially, the most life-threatening disturbances should be identified and corrected while searching for the underlying cause of AKI. Administration of nephrotoxic drugs should be discontinued and no nephrotoxic drugs should be prescribed. Because of the loss of renal autoregulation, AKI patients cannot protect themselves against ongoing episodes of decreased renal perfusion, so general anesthesia and surgery should be avoided.

An indwelling intravenous catheter should be placed to administer fluids and medications. A jugular catheter is preferred so that central venous pressure (CVP) can be monitored. Fluid administration should be decreased or discontinued temporarily if the CVP exceeds 13 cm H_2O or increases rapidly by 2 cm H_2O or more in any 10-minute period. A volume challenge of 20 mL/kg can be administered over 10 minutes to assess the likelihood of impending volume overload. Central venous pressure should not increase by more than 2 cm H_2O if the heart is normal. Dehydration should be corrected rapidly, ideally within 6 to 8 hours to prevent additional renal injury as a result of ongoing ischemia. Once dehydration has been corrected, additional fluids are given to match sensible (i.e., measured urine volume), insensible (i.e., GI and respiratory losses of approximately 20 mL/kg/day), and ongoing contemporary fluid losses (estimated losses from vomiting and diarrhea). An indwelling urinary catheter is needed to monitor urine output and facilitate fluid therapy in the initial 24 to 48 hours. The presence of oliguria necessitates meticulous attention to fluid therapy to prevent overhydration. Weighing the patient twice daily on the same scale will provide useful information about fluid balance. Normal urine output is 1 to 2 mL/kg/h, and a urine output of 2 to 5 mL/kg/h is expected in normal dogs and cats receiving adequate fluid volume expansion. Urine output less than 2 mL/kg/h in an adequately hydrated animal receiving fluid therapy is considered relative oliguria.

Normal saline (0.9% NaCl) usually is the initial fluid of choice for rehydration because of its sodium content (154 mEq/L) and lack of potassium. When rehydration has been accomplished, hypotonic fluids (0.45% sodium chloride in 2.5% dextrose) can be provided for maintenance needs to prevent hypernatremia.

Potassium supplementation, if required, must be adjusted carefully based on serial determinations of serum potassium concentration. Serum potassium concentration will vary depending on urine output, renal excretory function, severity of metabolic acidosis, and oral intake.

Treatment of hyperkalemia may be necessary in oligoanuric patients. Electrocardiography can be useful for detecting the physiologic effects of hyperkalemia, including bradycardia, prolongation of the P-R interval, widening of the QRS complexes, blunting or absence of P waves (atrial standstill), and tenting of T waves. Electrocardiographic

abnormalities usually occur when the serum potassium concentration exceeds 8 mEq/L. Serum potassium concentrations of 8 to 10 mEq/L are considered dangerous for cardiac function, and concentrations of 10 mEq/L or higher are life-threatening. If electrocardiographic changes associated with hyperkalemia are present, treatment should be instituted immediately. Sodium bicarbonate (0.5-1.0 mEq/kg IV) usually is infused first, especially if metabolic acidosis is present. Alternatively, infusion of 20% to 30% hypertonic glucose can stimulate endogenous insulin release and translocation of potassium into cells. Glucose infusion may be selected over sodium bicarbonate when the total or ionized calcium concentration is low, seizures have occurred, or metabolic alkalosis is present. Administration of insulin in combination with hypertonic glucose infusion is controversial. A 10% calcium gluconate solution (0.5-1.0 mL/kg) can be infused to counteract the effects of potassium on the heart, but this approach does not lower the serum potassium concentration. Calcium salts may be beneficial in patients with hypocalcemia, but they also may promote soft tissue mineralization in the presence of hyperphosphatemia. The electrocardiogram (ECG) should become normal within minutes of these treatments, but they only provide temporary relief from the effects of hyperkalemia. Maximizing renal excretory function and maintaining serum pH and bicarbonate concentration in the normal range will promote normalization of the serum potassium concentration. Chronic hyperkalemia may be treated with an ion exchange resin (sodium polystyrene sulfate, 2 g/kg, divided into three doses/day and administered orally or as a retention enema) or may require dialysis.

Metabolic acidosis may be severe and require treatment during the maintenance phase of AKI. If blood gas analysis is not available, total CO_2 concentration (<15 mEq/L) can be used to identify metabolic acidosis. Alkali therapy should be provided if the total CO_2 is less than 15 mEq/L. To correct metabolic acidosis, sodium bicarbonate (1-3 mEq/kg) can be added to maintenance fluids that do not contain calcium (e.g., 0.9% NaCl). Hypernatremia, hyperosmolality, metabolic alkalosis, and ionized hypocalcemia are potential complications of alkali therapy.

Hyperphosphatemia may be severe during the maintenance phase of AKI and may contribute to a worsening of renal lesions and excretory function by several mechanisms, including renal mineralization, direct nephrotoxicity, and vasoconstriction. Hyperphosphatemia also contributes to metabolic acidosis and ionized hypocalcemia. Intestinal phosphate binders may lower serum phosphorus concentration to some degree, even in anorexic patients, by binding with phosphorus in GI secretions. Aluminum hydroxide and aluminum carbonate can be used at a dosage of 30 to 90 mg/kg/day. The dosage should be modified based on serial measurements of the serum phosphorus concentration. Excessive administration of aluminum-containing phosphate binders may result in aluminum toxicity, which is manifested as dementia that may be difficult to distinguish from the effects of uremia.

It is easier to manage nonoliguric patients because hyperkalemia and overhydration are less likely to develop and the severity of nitrogenous waste product retention may be less. Therefore diuretics often are administered in an attempt to convert oliguria to nonoliguria after rehydration. Patients that remain oliguric despite diuretic therapy have a poor prognosis because of limited access to dialysis in veterinary practice. Usually, conversion to nonoliguria occurs without a detectable increase in GFR, as typified by an increase in urine volume with no concomitant decrease in the BUN and SCr. To prevent dehydration and additional renal injury, it is important to replace excessive urinary fluid losses in patients that respond dramatically with increased urine volume after diuretic administration.

Osmotic diuretics are freely filtered, low-molecular-weight substances that undergo little or no tubular reabsorption. The increased osmolality of the glomerular ultrafiltrate obligates water excretion. Mannitol can be administered intravenously at a dosage of 0.25 to 0.50 g/kg and repeated once if no increase in urine volume is observed within 30 to 60 minutes. A total daily dose of 2 g/kg should not be exceeded. The effects of mannitol exceed those observed with isotonic volume expansion (e.g., 0.9% NaCl) and are more potent than those achieved with hypertonic dextrose. Adverse effects include volume overload and hyperosmolality.

Loop diuretics (e.g., furosemide) are probably the diuretics most widely used in AKI patients. Furosemide may be administered intravenously at a dosage of 1 to 2 mg/kg IV followed by an infusion of 1 mg/kg/h for up to 6 hours in an attempt to convert oliguria to nonoliguria. If urine output increases, a constant rate infusion of 0.1 mg/kg/h of furosemide may be administered or intermittent doses may be given as necessary to maintain urine output. If urine output does not increase, furosemide should be discontinued and dopamine or fenoldopam considered. Furosemide may potentiate aminoglycoside toxicity, and its use in this setting is contraindicated.

Dopaminergic receptors are found in renal cortical vasculature and renal tubules. Cats originally were thought to lack dopaminergic receptors in their renal vasculature but recent reports have documented their presence. Dopamine increases RBF and occasionally GFR in normal animals at low dosages (<10 μg/kg/min). Higher dosages cause vasoconstriction, which reduces GFR and RBF. Dopamine contributes to natriuresis by blocking sodium reabsorption in the proximal tubules. Renal dose dopamine usually is defined as 2 to 5 μg/kg/min. The use of renal dose dopamine has never been documented in human or veterinary medicine to be superior to supportive care, and IV administration requires an infusion pump to deliver the calculated dose accurately. The use of furosemide and dopamine together has resulted in conversion from oliguria to nonoliguria in experimental dogs with severe nephrotoxicity, and this combination may be tried when other treatments have failed.

Fenoldopam is a dopamine-1 receptor agonist that causes peripheral vasodilatation, increased RBF, and diuresis. When

administered to normal dogs at an infusion rate of 0.8 µg/kg/min, it significantly increased GFR and fractional excretion of sodium. In a study of dogs and cats with AKI, however, no significant differences in BUN or SCr, length of hospital stay, and survival were found between animals treated with fenoldopam and those not treated with the drug.

Dialysis may be the only way for a dog or cat with AKI to survive the metabolic consequences of advanced uremia, especially in the presence of oliguria or anuria. Hemodialysis removes uremic waste products and retained water very efficiently but is technically demanding, very expensive, and available for dogs and cats only at a limited number of treatment facilities. Even with intermittent hemodialysis, overall survival at time of discharge was only 53% for dogs and 50% for cats with AKI in one study. Peritoneal dialysis requires less technical expertise, is less expensive, and is more widely available than hemodialysis. Historically, dialysis has been attempted mainly late in the clinical course of dogs and cats with AKI when fluid, acid-base and electrolyte abnormalities, and azotemia are advanced. Early institution of dialysis in severe AKI may provide greater opportunity for survival and recovery

Prognosis

Oliguria or anuria that persists or develops during treatment is associated with a poor prognosis. The most common causes for death or euthanasia during initial management of AKI in the maintenance phase are hyperkalemia, metabolic acidosis, or severe azotemia. Overhydration with resultant pulmonary edema as a consequence of aggressive fluid therapy is another important cause of death or euthanasia. The underlying cause of AKI also affects prognosis because some causes of AKI are worse (e.g., ethylene glycol intoxication) than others (e.g., leptospirosis). Aminoglycoside nephrotoxicity and NSAID-induced AKI also often are associated with a poor prognosis. Other organ system disease or failure also worsens the prognosis (e.g., heart failure, diabetes mellitus, liver disease, pancreatitis, disseminated intravascular coagulation, neoplasia, sepsis). AKI patients require intensive care and major surveillance, so the level of medical care available also affects prognosis. Overall, death or euthanasia can be expected in approximately 50% of dogs and cats with AKI. Of those that survive, approximately half can be expected to develop CKD and the other half to become clinically normal, based on the SCr.

CHRONIC KIDNEY DISEASE

CKD culminates in renal failure when compensatory mechanisms are no longer able to maintain the normal excretory, regulatory, and endocrine functions of the kidneys. The resultant retention of nitrogenous solutes, derangements of fluid, electrolyte, and acid-base balance, and failure of hormone production constitute the syndrome of CKD. A diagnosis of CKD is made when these abnormalities have been present for 3 months or longer. Causes of CKD in dogs and cats are listed in Box 41.2 and familial diseases of dogs and cats are listed in Box 41.3.

Staging

The term *chronic kidney disease* is used by the National Kidney Foundation to refer to human patients with five stages of renal disease. Patients in stage 5 CKD have a GFR less than 17% of normal (<15 mL/min/1.73 m^2), are azotemic, and are classified as being in chronic renal failure. Those in stage 4 CKD have a GFR 17% to 32% of normal (15-29 mL/min/1.73 m^2), and might also be azotemic and in chronic renal failure. CKD in dogs and cats can be staged similarly using guidelines proposed by the International Renal Interest Society (IRIS), an international group whose mission is to help veterinarians better understand the diagnosis and management of CKD in dogs and cats. Guidelines for staging CKD in dogs and cats based on SCr are shown in Table 41.2. According to IRIS guidelines, dogs and cats with stages 2, 3, and 4 CKD are azotemic and thus have mild, moderate, or severe CKD, respectively. SCr always should be interpreted along with USG and the physical examination and diagnostic imaging findings, especially renal size. Guidelines established by IRIS also include substaging based on the extent of proteinuria (i.e., magnitude of UPC ratio) and hypertension (see http://www.iris-kidney.com/guidelines/).



BOX 41.2

Causes of CKD in Dogs and Cats

Dog

- Chronic interstitial nephritis (CIN) of unknown cause (most common pathologic diagnosis)
- Chronic pyelonephritis (can be difficult to distinguish histologically from CIN)
- Chronic glomerulonephritis (can be difficult to distinguish histologically from CIN)
- Amyloidosis
- Familial renal disease (several dog breeds can be affected)
- Healing of acute kidney injury

Cat

- CIN of unknown cause (most common pathologic diagnosis)
- Chronic pyelonephritis (can be difficult to distinguish histologically from CIN)
- Chronic glomerulonephritis (can be difficult to distinguish histologically from CIN)
- Amyloidosis (uncommon in mixed-breed cats but familial in Abyssinians)
- Polycystic kidney disease (familial in Persians)
- Healing of acute kidney injury
- Neoplasia (renal lymphoma)
- Pyogranulomatous nephritis caused by feline infectious peritonitis

BOX 41.3

Familial Renal Diseases in Dogs and Cats*

Amyloidosis
- ***Abyssinian cat,*** Beagle, English Foxhound, Oriental Shorthair cat, ***Shar pei,*** Siamese cat

Basement membrane disorder
- Bull Terrier, Bullmastiff, Dalmatian, Doberman Pinscher, English Cocker Spaniel, Newfoundland, Rottweiler, ***Samoyed***

Juvenile glomerulopathy
- Beagle, French Mastiff (Bordeaux)
- Familial glomerulopathy in ***soft-coated Wheaten Terriers*** associated with mutations in NPHS1 and KIRREL2, which encode slit diaphragm proteins nephrin and Neph3/filtrin

Membranoproliferative GN
- Bernese mountain dog, Brittany Spaniel, Soft-C Wheaten Terrier

Multiple renal cystadenocarcinomas
- German Shepherd

Periglomerular fibrosis
- Norwegian Elkhound

Polycystic kidney disease
- ***Bull Terrier***, Cairn Terrier, ***Persian cat***, West Highland White Terrier

Renal dysplasia
- Alaskan Malamute, Chow, Golden Retriever, ***Lhasa apso and Shih tzu***, Miniature Schnauzer, ***Soft-Coated Wheaten Terrier***, Standard Poodle

Renal telangiectasia
- Pembroke Welsh Corgi

Fanconi syndrome
- Basenji

Renal glucosuria
- Norwegian Elkhound

Unilateral renal agenesis
- Beagle

*Most common, well-characterized disorders are shown in ***bold italics***.

Pathophysiology

UREMIA AS INTOXICATION

A uremic toxin is any compound retained because of decreased renal function that can contribute to the clinical signs of uremia (Box 41.4). Many compounds are involved in the pathophysiology of uremia, and no single compound can explain the diversity of uremic symptoms. Parathyroid hormone (PTH) probably is the best-characterized uremic toxin; it plays a major role in development of renal secondary hyperparathyroidism and bone demineralization.

HYPERFILTRATION

Renal disease tends to be progressive when a critical number of nephrons has been destroyed. Glomerular hyperfiltration has been incriminated as an important factor contributing to the progressive nature of renal disease. The total GFR represents the sum of single-nephron GFR (SNGFR) in all nephrons of both kidneys. In a healthy animal, the range of SNGFR is fairly narrow (Fig. 41.5, *lower panel*). During progressive renal disease, the decline in total GFR initially is offset by an increase in SNGFR in functional remnant nephrons (so-called glomerular hyperfiltration). Thus the normally narrow range of SNGFR widens during the development of CKD because diseased nephrons have low SNGFR and

TABLE 41.2

International Renal Interest Society Stages of Chronic Kidney Disease in Dogs and Cats Based on Serum Creatinine Concentration*

	SERUM CREATININE CONCENTRATION (mg/dL)	
STAGE	**DOGS**	**CATS**
1	<1.4 (with impaired concentrating ability, abnormal renal palpation or abnormal renal imaging, or both)	<1.6 (with impaired concentrating ability, abnormal renal palpation or abnormal renal imaging, or both)
2	1.4-2.0 (with mild or no clinical signs)	1.6-2.8 (with mild or no clinical signs)
3	2.1-5.0 (with systemic clinical signs)	2.9-5.0 (with systemic clinical signs)
4	>5.0 (with systemic signs and increased risk of uremic crisis)	>5.0 (with systemic signs and increased risk of uremic crisis)

*Substaging guidelines according to proteinuria and systemic blood pressure also are provided by IRIS (http://www.iris-kidney.com/guidelines/)

BOX 41.4

Pathophysiologic Features of Chronic Kidney Disease

- Uremic intoxication (i.e., retention of uremic solutes)
- Hyperfiltration
  - Proteinura
  - Glomerular sclerosis
- Maintenance of external solute balance, despite progressively declining glomerular filtration rate
- Development of polyuria and polydipsia and defective urinary concentrating ability
- Maintenance of calcium and phosphorus balance and development of renal secondary hyperparathyroidism
- Maintenance of acid-base balance and development of metabolic acidosis
- Development of nonregenerative anemia
- Hemostatic disorders (e.g., platelet dysfunction)
- Gastrointestinal disturbances
- Cardiovascular complications (e.g., hypertension)
- Metabolic disturbances (e.g., insulin resistance, euthyroid sick syndrome)

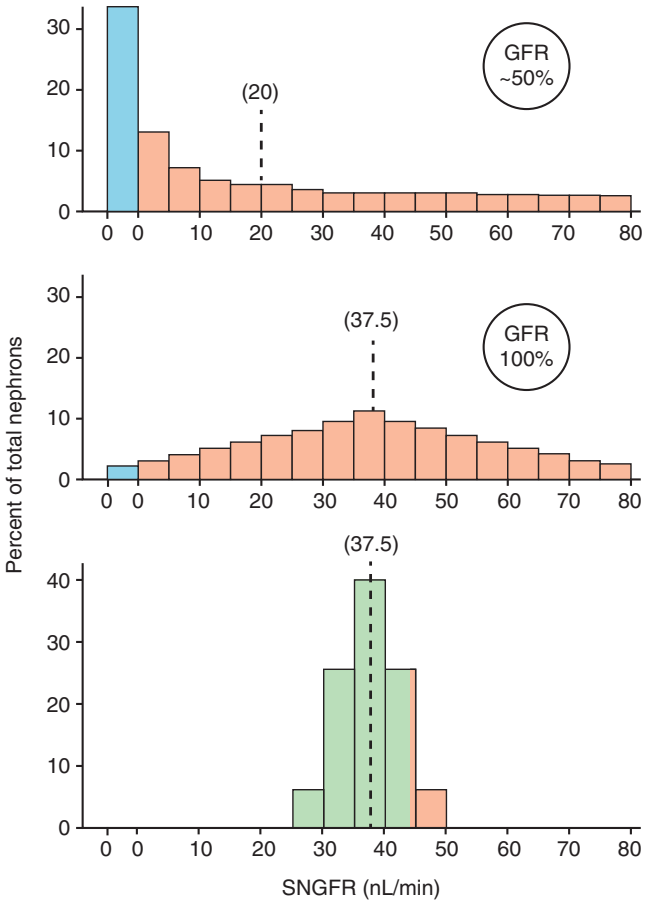


FIG 41.5
Widening range of SNGFR as renal disease progresses. *Lower panel,* Normal situation. *Middle panel,* Situation in which some nephrons are nonfiltering or have decreased SNGFR and others have increased SNGFR but the mean SNGFR remains unchanged and total GFR is still normal. *Upper panel,* The total GFR has been reduced by 50%. In this setting, the mean SNGFR is decreased, many nephrons are nonfiltering or hypofiltering, and many are hyperfiltering. (From Brenner BM: Nephron adaptation to renal injury or ablation, *Am J Physiol* 249:F332, 1985.)

remnant nephrons have supranormal SNGFR (see Fig. 41.5, *middle and upper panels*). This adaptation occurs to such an extent that total GFR increases approximately 40% to 60% in remnant renal tissue over a period of 4 to 6 weeks after experimental renal ablation. For example, if one kidney is removed from a dog with a GFR of 40 mL/min, GFR immediately will decrease to 20 mL/min but within 1 to 2 months will stabilize at approximately 30 mL/min because of hyperfiltration in the remnant nephrons.

FUNCTIONAL AND MORPHOLOGIC CHANGES IN REMNANT RENAL TISSUE

Hyperfiltration increases protein movement across the glomerular capillaries into Bowman's space and the mesangium. Proteinuria and glomerular sclerosis in remnant nephrons are adverse functional and morphologic consequences of glomerular hyperfiltration that contribute to the progression of renal disease. Tubular cells have receptors for hormones and growth factors, some of which are small-MW proteins that are filtered excessively and taken up by the proximal tubular cells, where they promote cellular proliferation and extracellular matrix deposition, leading to tubulointerstitial damage. Tubular cell overload caused by increased reabsorption of filtered proteins also upregulates inflammatory and vasoactive genes that contribute to damage. Ischemia of portions of the nephron downstream from the damaged glomerulus, mineralization in the kidney, and local ammonia accumulation are additional factors that contribute to tubulointerstitial lesions. This progressive damage is independent of the activity of the underlying primary renal disease.

Factors that may affect the progression of CKD include species differences, extent and duration of reduction in renal mass, dietary modifications, and complications. In dogs and cats, 85% to 95% of renal tissue must be destroyed to result in progression, whereas progression occurs in humans and rats after 75% to 80% renal ablation. Dogs with 75% reduction in renal mass followed for 4 years did not show evidence of progression, whereas dogs with 94% reduction in renal mass developed progression over 24 months. In rats, dietary restriction of protein can reverse glomerular hyperfiltration. In one study of dogs, however, a diet containing 17% protein did not prevent glomerular hyperfiltration in dogs with 94% renal ablation. On the other hand, a diet containing 8% protein has been shown to result in malnutrition (e.g., weight loss, hypoalbuminemia) and increased mortality in dogs with experimentally induced renal disease. Decreasing dietary phosphorus content can reverse renal secondary hyperparathyroidism and slow progression of renal disease. Improvement in proteinuria and renal morphologic changes also may be associated with decreased caloric intake. Dietary supplementation with ω-3 polyunsaturated fatty acids (PUFAs) also may have beneficial effects. Hypertension and urinary tract infection are examples of complications that may contribute to progression.

EXTERNAL SOLUTE BALANCE

The concept of external solute balance is important in understanding the compensatory response of the kidneys to chronic, progressive renal disease. An individual animal consumes different amounts of water and solutes each day, and the kidneys must adjust their output of water and solutes to keep the volume and composition of body fluids constant. The challenge to the kidneys in a patient with CKD is to maintain balance, despite advancing disease and progressively declining GFR. In health, as spontaneous increases or decreases in GFR occur, the absolute tubular reabsorption of filtered solutes changes in a similar direction. Thus the fraction of the filtered load that is resorbed remains constant, despite changes in GFR. This principle has been termed the *glomerulotubular balance.* For any given solute, the diseased kidney maintains glomerulotubular balance as the GFR declines by decreasing the fraction of the filtered load of that solute that is resorbed and increasing the fraction of the filtered load of that solute that is excreted. In some cases, the

mechanisms responsible for the adaptive changes have adverse effects on the animal.

This trade-off hypothesis was articulated by Dr. Neil Bricker in 1972, as follows: "The biological price to be paid for maintaining external solute balance for a given solute as renal disease progresses is the induction of one or more abnormalities of the uremic state." Hyperfiltration is an example of the trade-off hypothesis in that total GFR is preserved, but at the expense of proteinuria, glomerular sclerosis, and progressive deterioration of residual renal tissue. Another classic example is the maintenance of normal calcium and phosphorus balance by renal secondary hyperparathyroidism but at the expense of bone density. Buffering of accumulated fixed acid by bone carbonate at the expense of bone density is yet another example. Some maladaptive mechanisms and their consequences can be prevented by a proportional reduction in the intake of the solute in question. This strategy will avoid the need for the kidneys to alter fractional reabsorption and excretion of the solute being manipulated. Using this approach with dietary phosphorus has been shown to prevent or reverse renal secondary hyperparathyroidism and slow the progression of CKD.

The kidneys respond differently to different solutes during development of CKD (Fig. 41.6). Solutes that experience no regulation are handled by glomerular filtration alone (e.g., urea, creatinine). At any given time, the plasma concentrations of these solutes reflect the prevailing GFR. Solutes that experience limited regulation are handled by glomerular filtration and some combination of tubular reabsorption and secretion (e.g., phosphate, hydrogen ions). Normal plasma concentrations of these solutes are maintained until the GFR decreases to below approximately 15% to 20% of normal. Solutes that experience complete regulation also are handled by glomerular filtration and some combination of tubular reabsorption and secretion (e.g., sodium, potassium), but normal plasma concentrations of these solutes are maintained until the GFR decreases below 5% of normal or until oliguria or anuria develops.

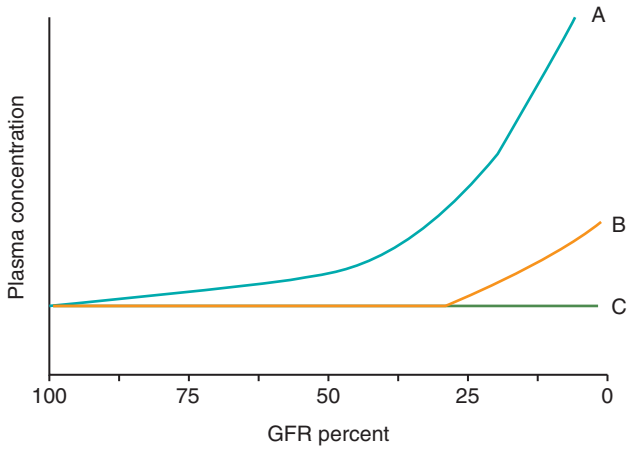


FIG 41.6
Renal regulation of solute balance. Curve A represents solutes experiencing no regulation. Curve B represents solutes experiencing limited regulation. Curve C represents solutes experiencing complete regulation. (From Bricker NS, Fine LG: The renal response to progressive nephron loss. In Brenner BM, Rector FC: *The kidney,* ed 2, Philadelphia, 1981, WB Saunders, p 1058.)

DEVELOPMENT OF POLYURIA AND POLYDIPSIA

The ability to produce concentrated urine (i.e., conserve water) and the ability to excrete a water load are impaired in CKD. The development of this concentrating defect is heralded clinically by the onset of PU and compensatory PD. Increased solute load per residual functioning nephron rather than architectural damage to the tubules and interstitium is the single most important factor contributing to the concentrating defect—that is, the remnant nephrons are functioning under conditions of osmotic diuresis. In most cases, defective concentrating ability develops when 67% of the nephron population has become nonfunctional and is recognized clinically by isosthenuria, a urine osmolality of 300 to 600 mOsm/kg or USG of 1.007 to 1.015. The example in Box 41.5 demonstrates how PU develops in CKD, despite a progressive decline in GFR.

CALCIUM AND PHOSPHORUS BALANCE

Normal calcium and phosphorus metabolism requires the interaction of PTH, 1,25-dihydroxycholecalciferol (calcitriol), fibroblast growth factor-23 (FGF-23), and calcitonin with the kidneys, GI tract, and bone. The kidneys are the site of conversion of 25-hydroxycholecalciferol to

BOX 41.5

Case Example

Consider a normal 10-kg dog with normal daily urine output of 333 mL and urine osmolality of 1500 mOsm/kg. These values imply a solute load of 0.333 × 1500 or 500 mOsm/day. The same dog with CKD might have a relatively fixed urine osmolality of 500 mOsm/kg and would require a urine output of 1000 mL to excrete the same 500 mOsm. Renal handling of water in this dog might change as shown here after the development of chronic renal disease.

	Normal	Diseased
Number of nephrons	1,000,000	250,000
Total GFR (mL/min)	40	15
SNGFR (nL/min)	40	60
Urine output (mL/day)	333	1000
Urine output (mL/min)	0.23	0.69
Urine output per nephron (nL/min)	0.23	2.76
Filtered water reabsorbed	99.4%	95.4%
Filtered water excreted	0.6%	4.6%

Note that the fraction of filtered water that is resorbed is decreased in the disease state and the fraction that is excreted is increased.

1,25-dihydroxycholecalciferol by 1α-hydroxylase. Total serum calcium concentrations are decreased in approximately 10% of dogs with CKD, but decreased serum ionized calcium concentration is found in 40% of dogs with CKD. Ionized hypocalcemia may occur in association with hyperphosphatemia in CKD as a consequence of the mass law effect. The amounts of calcium and phosphorus that can remain in solution together are defined by the $[Ca] \times [P_i]$ product, where [Ca] is the serum calcium concentration and $[P_i]$ is the serum phosphorus concentration. When this value is more than 60 to 70, soft tissue mineralization occurs. In one study, the proportion of CKD dogs with $[Ca] \times [P_i]$ product >70 increased with increased stage of disease, and mortality was higher (and survival time shorter) in dogs with $[Ca] \times [P_i]$ product >70. Decreased production of calcitriol by the diseased kidneys impairs intestinal absorption of calcium, and complexing of calcium with phosphate in the lumen of the intestinal tract further impairs calcium absorption. Approximately 5% to 10% of dogs with CKD develop hypercalcemia, which may damage the kidney additionally by causing renal vasoconstriction and interstitial mineralization. The serum ionized calcium concentration, however, usually is normal or low when measured in dogs with CKD that have increased total serum calcium concentrations.

Hyperparathyroidism is a consistent finding progressive CKD. Development of renal secondary hyperparathyroidism typically has been explained by the effect of phosphorus retention on serum ionized calcium concentration (Fig. 41.7, *A*). Reduction in GFR decreases phosphate excretion and results in hyperphosphatemia, which in turn causes a reciprocal decrease in serum ionized calcium concentration by the mass law effect ($[Ca] \times [P_i]$ = constant). Ionized hypocalcemia stimulates the parathyroid glands to synthesize and secrete PTH. The increase in PTH stimulates increased renal excretion of phosphate and increased release of calcium and phosphate from bone, which returns the serum phosphorus and ionized calcium concentrations to normal. PTH decreases the fractional reabsorption of phosphate in the kidney by decreasing the tubular maximum for phosphate reabsorption. The limit of this compensatory response is reached when the GFR declines to approximately 15% to 20% of normal; when the GFR declines further, hyperphosphatemia develops. Thus calcium and phosphorus balance is maintained by a progressive increase in the serum PTH concentration. A chronically increased PTH concentration leads to bone demineralization and other toxic effects of uremia (e.g., bone marrow suppression, uremic encephalopathy). This sequence of events represents a trade-off for the maintenance of calcium and phosphorus balance in progressive CKD.

The effect of phosphorus retention on renal calcitriol production suggests an additional factor in the development of renal secondary hyperparathyroidism. Phosphorus retention and hyperphosphatemia inhibit renal 1α-hydroxylase, which impairs the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (calcitriol). Impaired production of calcitriol decreases the GI absorption of calcium, which in turn contributes to ionized hypocalcemia and

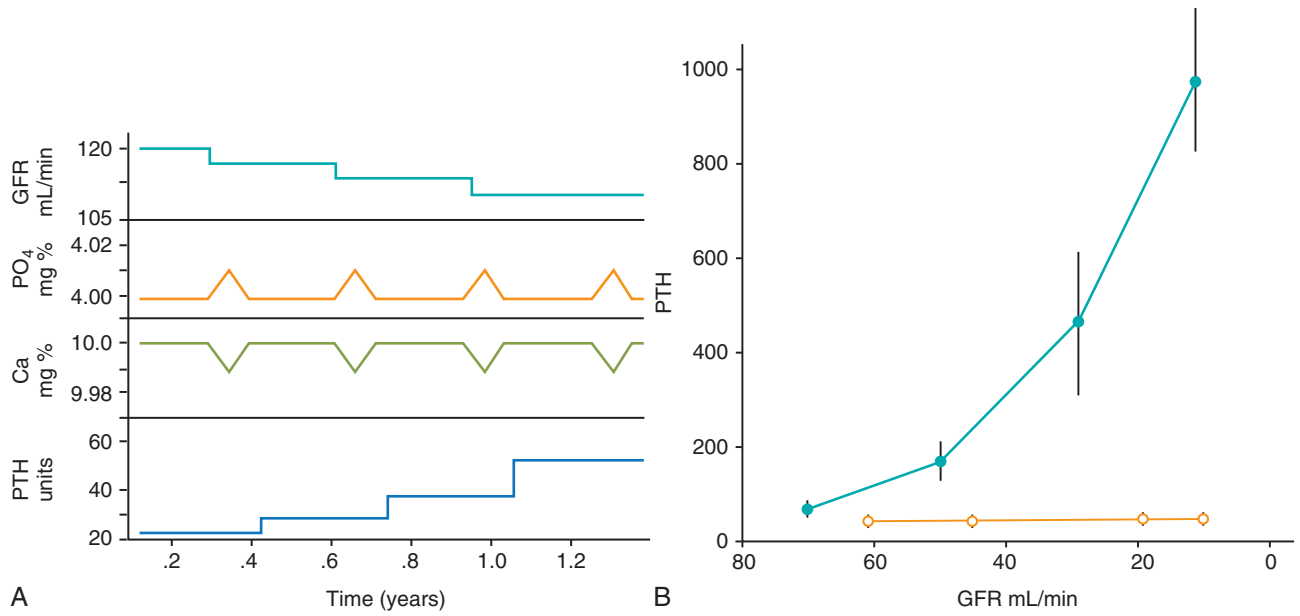


FIG 41.7
(A) Classic theory of the development of renal secondary hyperparathyroidism according to Slatopolsky (see text for explanation). **(B)** Effect of proportional restriction of dietary phosphorus in progressive CKD on serum PTH concentration *(open circles)* as compared with normal unrestricted dietary intake of phosphorus *(closed circles)*. (From Slatopolsky E, et al.: On the pathogenesis of hyperparathyroidism in chronic experimental renal insufficiency in the dog, *J Clin Invest* 50:492, 1971.)

stimulation of PTH secretion. Calcitriol normally feeds back to receptors on the parathyroid gland cells and decreases the synthesis and secretion of PTH. This negative feedback loop is impaired in CKD because of decreased renal production of calcitriol and further contributes to increased PTH secretion.

FGF-23 is a phosphatonin produced in bone that inhibits proximal renal tubular reabsorption of phosphate and also inhibits 1α-hydroxylase activity in the kidney, thus decreasing calcitriol production. It increases in CKD to facilitate phosphate excretion, and may contribute to renal secondary hyperparathyroidism by decreasing the negative feedback of calcitriol to the parathyroid glands. FGF-23 increases with increasing stage of CKD in dogs and cats and has been shown to be predictive of disease progression in cats with CKD. Baseline FGF-23 concentrations were higher in nonazotemic geriatric cats that went on to develop azotemia over 12 months of follow-up as compared with those that did not.

Renal secondary hyperparathyroidism can be prevented or reversed in dogs with experimentally induced CKD by decreasing the dietary intake of phosphorus in proportion to the decrease in GFR (see Fig. 41.7, *B*). Feeding a renal diet decreased FGF-23 concentrations in both normophosphatemic and hyperphosphatemic cats with stable azotemic CKD, indicating that dietary phosphorus restriction allows maintenance of normal serum phosphate concentrations with lower FGF-23 concentrations.

Early in the course of CKD, decreased phosphorus intake stimulates renal 1α-hydroxylase, which results in increased calcitriol production. This increase in calcitriol results in enhanced intestinal absorption of calcium, increased serum ionized calcium concentration, and decreased PTH secretion. Later in the course of CKD, the kidneys are unable to produce sufficient calcitriol to promote normal intestinal absorption of calcium. Phosphorus restriction slows the progression of CKD by blunting renal secondary hyperparathyroidism and limiting renal interstitial mineralization, inflammation, and fibrosis. These observations form the basis for the use of phosphorus restriction in the medical management of dogs and cats with CKD.

ACID-BASE BALANCE

The main cause of metabolic acidosis in CKD is limitation of renal ammonium excretion. The chronically diseased kidney maintains hydrogen ion balance by increased renal ammoniagenesis from glutamine. Absolute ammonium excretion falls during progressive CKD, but ammonium excretion is markedly increased when expressed per remnant nephron. On a per nephron basis, the diseased kidney can increase its ammonium excretion by threefold to fivefold. This adaptive mechanism reaches its limit when the GFR falls to 10% to 20% of normal. At this point, the diseased kidneys can no longer cope with the daily fixed acid load effectively, and a new steady state is established at a lower than normal plasma bicarbonate concentration. The metabolic acidosis of CKD usually is not severe, and the relatively mild decrease in plasma bicarbonate concentration is a consequence of the large reservoir of buffer (e.g., calcium carbonate) in bone. Buffering of metabolic acidosis by the release of calcium carbonate from bone contributes to bone demineralization, and accumulation of ammonia in the kidney may elicit tubulointerstitial inflammation, another example of the trade-off hypothesis. Alkali therapy to correct metabolic acidosis may slow the progression of CKD.

ANEMIA

Erythropoietin is a glycoprotein hormone that regulates red cell production by the bone marrow, and the kidney is the major source of erythropoietin in the adult animal. A nonregenerative (i.e., normochormic normocytic) anemia is common in CKD but variable in severity. Its main cause is inadequate production of erythropoietin by the diseased kidneys to meet the demand for new red cells because of loss from hemolysis and hemorrhage. The life span of red cells in uremic patients is approximately 50% of that of healthy individuals, which is thought to be caused by a uremic toxin in plasma. Platelet dysfunction in CKD promotes insidious, ongoing blood loss (e.g., GI hemorrhage). Recombinant human erythropoietin has been used successfully to correct the anemia of CKD in human patients. This product also is effective in correcting the anemia of CKD in dogs and cats, but the potential for antibody formation limits its usefulness in these species.

HEMOSTATIC DEFECTS

Uremia is characterized by abnormal hemostasis and a predisposition to hemorrhage. GI blood loss is observed more commonly in dogs than cats. A qualitative platelet function defect (platelet numbers are normal) is most important. Risk of hemorrhage is best correlated with the buccal mucosal bleeding time (normally <2-3 minutes). Other coagulation test results (e.g., prothrombin time, partial thromboplastin time, activated coagulation time) usually are normal. Abnormalities of platelet function include abnormal platelet adhesiveness and aggregation, decreased clot retraction, and decreased thromboxane production by platelets. Platelet dysfunction also is thought to be the consequence of uremic toxins (e.g., guanidines, PTH).

GASTROINTESTINAL DISTURBANCES

Erosions and ulcers of the buccal mucosa and tongue may be observed in uremic dogs but much less commonly in cats. Ulcers may be caused by the excretion of urea into saliva and breakdown to ammonia by oral bacteria. Tongue tip necrosis may occur in uremic dogs; it results from fibrinoid necrosis and arteritis with focal ischemia, necrosis, and ulceration. Gastroenteritis with GI hemorrhage is relatively common in dogs with CKD. It arises as a consequence of bleeding caused by platelet dysfunction, ammonia production from urea by bacteria in the GI tract, ischemia caused by vascular lesions, and increased concentrations of gastrin because of impaired renal excretion. In one study, gastric ulceration, edema, and vascular fibrinoid change were not observed in the stomachs of cats with CKD. Serum gastrin concentrations were high

in these CKD cats, but the primary gastric lesions observed were fibrosis and mineralization. Vomiting is more common in uremic dogs than in cats, possibly as a consequence of the differences in gastric lesions observed in cats and dogs with CKD. Stimulation of the chemoreceptor trigger zone by a uremic toxin may contribute to vomiting in patients with CKD.

CARDIOVASCULAR COMPLICATIONS

Systemic hypertension is present in 20% to 30% of dogs and cats with CKD and in 50% to 80% of dogs with glomerular disease. Normal blood pressure in dogs and cats is similar to that of humans (i.e., systolic 120 mm Hg, diastolic 80 mm Hg), but interactions in the hospital setting increase the blood pressure of dogs and cats (so-called white coat effect), making identification of mild to moderate hypertension difficult. Factors contributing to hypertension include renal ischemia associated with CKD that results in activation of the renin-angiotensin system and increased sympathetic nervous system activity. An intrarenal mechanism for sodium retention plays an important role in the hypertension in patients with glomerular disease. Clinical and pathologic manifestations of systemic hypertension include ocular abnormalities (e.g., retinal detachment, retinal hemorrhages, retinal vascular tortuosity) and cardiovascular abnormalities (e.g., left ventricular enlargement, medial hypertrophy of arteries, murmurs, gallop rhythms).

METABOLIC COMPLICATIONS

Many small peptides are normally filtered by the kidney, reabsorbed, and degraded in the proximal tubular cells. Loss of this clearance function can result in metabolic derangements because many of these peptides are hormones. Peripheral insulin resistance and mild fasting hyperglycemia (<150 mg/dL) are common in uremia, but not clinically relevant. Excess gastrin increases the stimulation of acid secretion in the stomach and contributes to uremic gastroenteritis, and excess glucagon may contribute to negative nitrogen balance and tissue catabolism. CKD is an important nonthyroidal illness, which can cause confusion in diagnosis of hyperthyroidism in older cats and must be taken into consideration when evaluating treatment options. Plasma cortisol concentrations may be slightly increased, and increased mineralocorticoids may contribute to hypertension.

Clinical Findings

PU and PD may be the first abnormalities noted by observant owners of dogs and cats with CKD. In dogs, nocturia may be noted first because the animal begins waking the owner up at night to be allowed outside to urinate. If PU and PD are not recognized, nonspecific signs of uremia may be the first abnormalities the owner detects. Anorexia, weight loss, and lethargy are common in dogs and cats with CKD. Client surveys have shown that poor appetite is common in cats with CKD and may negatively impact the animal's quality of life as perceived by the owner. In a study of cats with CKD, affected animals were shown to have lost a median of 8.9% of body weight in the year preceding diagnosis, and weight loss accelerated as the disease progressed. Body weight <4.2 kg at the time of diagnosis was associated with significantly shorter survival time. In a study of dogs with CKD, higher body condition score at the time of diagnosis was associated with improved survival. Vomiting is more common in dogs with CKD than in cats.

On physical examination, poor body condition and dull dry hair coat are evidence of chronic disease. Dehydration is common because of inadequate food intake and insufficient water intake to keep pace with PU. Oral ulcers may be observed in dogs with CKD. Pallor may be evident if anemia is present. Clinical manifestations of bone demineralization are extremely rare in adult dogs and cats with CKD, but fibrous osteodystrophy can be dramatic in young growing dogs with uremia (so-called rubber jaw). Despite a lack of clinical signs, CKD has been shown to be associated with histologic evidence of decreased cancellous and cortical bone mineral density in cats. The presence of subcutaneous edema or ascites suggests the possibility of glomerular disease.

Clinicopathologic Findings and Imaging

Nonregenerative anemia may be observed on the CBC but can be masked by dehydration—that is, the hematocrit should be evaluated in conjunction with total protein concentration. Mature neutrophilia and lymphopenia reflect the stress of chronic disease. Platelet numbers typically are normal, but platelet function may be abnormal. Serum potassium concentrations usually are normal in patients with CKD unless oliguria or anuria develop. Azotemia is present if 75% or more nephrons are nonfunctional, and hyperphosphatemia is observed if 85% or more nephrons are nonfunctional. Serum total calcium concentration is normal to slightly low or, rarely, high. Bicarbonate concentration usually is only mildly decreased, and moderate to severe metabolic acidosis is a late finding in dogs and cats with CKD.

In dogs, isosthenuria develops when 67% or more nephrons become nonfunctional (USG, 1.007-1.015), but some cats with CKD retain concentrating ability after the onset of azotemia. In one study, cats with a 58% to 83% loss of functional nephrons could produce concentrated urine (USG, 1.022-1.067). Thus a cat with azotemia and relatively concentrated urine does not necessarily have prerenal azotemia. The magnitude of proteinuria is a reflection of intraglomerular hypertension and may be an indicator of the rate of progression of renal disease. In one study, a urine protein-to-creatinine (UPC) ratio >1.0 was associated with more rapid progression and increased risk of developing uremic crisis or death. Severe persistent proteinuria with an inactive urine sediment suggests primary glomerular disease. Microalbuminuria refers to urine protein concentrations >1 mg/dL but <30 mg/dL. Microalbuminuria is an early indicator of endothelial damage and may be a risk factor for progression of renal disease. It increases with age and in association with other systemic diseases, but its prognostic value is uncertain

in dogs and cats. Pyuria and bacteriuria suggest the presence of urinary tract infection.

The kidneys may be observed to be irregularly shaped or small on plain abdominal radiographs (<2.5 times the length of the L2 vertebra on the ventrodorsal view) in dogs or cats with CKD, but normal renal shape and size do not rule out CKD. Similarly, renal ultrasonography may show increased echogenicity of renal tissue and loss of corticomedullary distinction when medullary echogenicity increases and becomes similar to cortical echogenicity, but normal ultrasonographic findings do not exclude CKD.

CONSERVATIVE TREATMENT

General Principles

Do not be overly pessimistic when presented with a severely dehydrated dog or cat with CKD. If the patient is dehydrated, appropriate IV fluid therapy to resolve prerenal azotemia should be provided (Box 41.6). Rehydration may require 1 to 5 days. Frequently, the patient and laboratory results look much better after rehydration with a balanced crystalloid solution (e.g., lactated Ringer's). Next, search for potentially reversible causes of renal failure (e.g., pyelonephritis, hypercalcemia, obstructive nephropathy) and treat them appropriately. Finally, treat reversible factors that may be aggravating the renal disease (e.g., urinary tract infection, ongoing electrolyte or acid-base disturbances, hypertension). After these steps, a treatment plan should be devised to maintain fluid, electrolyte, acid–base, and caloric balance while preventing the accumulation of metabolic waste products and minimizing the detrimental effects of lost endocrine functions of the kidney.

Dietary Management

Dogs and cats with CKD should have access to fresh water at all times. Renal diets for dogs and cats have been shown to prolong survival. In one study, 12- to 14-month survival was observed in CKD cats on renal diets as compared with 6 to 12 months for cats eating regular diets. These studies do not necessarily show the effect of a specific nutrient because renal diets differ from regular diets in several ways, such as decreased protein, phosphorus, and sodium and increased B vitamins, soluble fiber, ω-3 PUFA, and antioxidants, but they represent grade I evidence (i.e., evidence obtained from randomized controlled clinical studies in clinical patients of the target species) for the use of renal diets in dogs and cats with CKD. Commercial renal diets designed for dogs and cats with CKD are preferable to homemade diets, which can be highly variable in composition and sometimes nutritionally inadequate.

Theoretical benefits of protein restriction are a reduction in clinical signs associated with uremia by decreasing production of toxic metabolites of protein metabolism and decreasing hyperfiltration in remnant nephrons. A low-protein diet, however, does not lessen the metabolic workload of the kidney because the metabolites of protein catabolism are excreted primarily by glomerular filtration, and most of the metabolic energy expended by the kidneys arises from sodium reabsorption. Moderate protein restriction is indicated to relieve clinical signs of uremia and promote patient well-being, but it is not likely that moderate protein restriction will reverse hyperfiltration in dogs and cats with CKD.

When in the course of progressive renal disease protein restriction should be started is controversial. It is not recommended early in the course of renal disease before symptomatic accumulation of protein catabolic products has become a problem. Dietary modification often is recommended when moderate azotemia is present in a stable, hydrated patient with CKD (e.g., IRIS stage 2 in cats or stage 3 in dogs). Feeding moderately restricted protein diets (e.g., 15%-17% protein) to dogs with CKD is preferable to feeding extremely high- or low-protein diets. A gradual transition

BOX 41.6

Treatment Options for Chronic Kidney Disease

In hospital
- IV crystalloid fluid therapy to restore hydration and resolve prerenal azotemia
- Correction of acid-base disturbances
- Correction of electrolyte disturbances
- Identification and resolution of reversible causes of renal failure (e.g., pyelonephritis, hypercalcemia, obstructive nephropathy)
- Identification and resolution of complicating problems (e.g., lower urinary tract infection, hypertension)

At home
- Dietary management
  - Access to fresh water at all times
  - Provision of a renal diet—decreased protein, phosphorus, sodium; increased B vitamins, soluble fiber, ω-3 PUFAs, antioxidants
  - Provision of adequate nonprotein calories (40-60 kcal/kg/day)
- Additional phosphorus restriction (phosphorus binders)
  - Aluminum hydroxide
  - Aluminum carbonate
  - Calcium carbonate
  - Calcium acetate
  - Sevelamer HCl
  - Lanthanum carbonate
  - Chitosan, calcium carbonate
- Alkali and potassium supplementation (e.g., potassium citrate, potassium gluconate)
- H_2 receptor blockers (e.g., famotidine)
- Angiotensin-converting enzyme inhibitors (e.g., enalapril, benazepril) and angiotensin receptor blockers (e.g., losartan, telmisartan)
- Recombinant human erythropoietin
- Calcitriol
- Additional antihypertensive medications (e.g., amlodipine)
- Crystalloid fluids (e.g., lactated Ringer's solution) administered by the owner

from the previous diet to the prescribed diet over 2 to 4 weeks is recommended. On a low-protein diet, the BUN concentration will decrease as a result of dietary modification alone and will no longer be a good indicator of renal function. SCr is not influenced by diet. It is, however, affected by loss of muscle mass, which can confound interpretation of SCr in cachectic animals with CKD.

The nutritional needs of cats differ from dogs. Dogs require that a minimum of approximately 5% of calories come from protein, whereas cats require that a minimum of 20% of calories come from protein. These represent minimum requirements and do not provide for nitrogen reserves. Healthy adult cats typically maintain lean body mass on 32% to 34% of calories from protein. Cats also seem to prefer diets higher in fat and require a source of taurine in their diet. Stable body weight, stable serum albumin concentration, and decreased BUN concentration are indications that a low-protein diet is being used effectively. Accelerated weight loss, on the other hand, indicates the need for dietary modifications.

Adequate nonprotein calories to maintain body condition should be provided by carbohydrate and fat. Approximately 60 kcal/kg/day are recommended as a general guideline, but older animals may eat fewer calories normally (e.g., 40 kcal/kg/day). Supplementation of the diet with ω-3 PUFAs may be renoprotective. Increasing the amount of ω-3 PUFAs relative to ω-6 PUFAs in the diet decreases the production of proinflammatory, platelet-aggregating, vasoconstrictive prostaglandin (PG) TXA2 and increases the production of vasodilatory prostaglandins (PGE, PGI). Studies of dogs with remnant kidneys have shown beneficial effects of supplementation, including decreased proteinuria, preservation of GFR, and less severe renal morphologic changes. These studies used very low ω-6–to–ω-3 ratios, which may not be easily achievable using commercial diets. An ω-6–to–ω-3 ratio of 2 : 1 may be reasonable in a renal diet. Alternatively, the diet can be supplemented with 1 to 5 g/day of ω-3 PUFAs.

Increased fractional sodium excretion allows maintenance of sodium balance during the course of progressive CKD. Dietary sodium restriction may be advisable in dogs with CKD and hypertension and in those with glomerular disease that have sodium retention and edema. Patients with CKD are less flexible in adjusting to changes in dietary sodium load. Many commercial pet foods provide more sodium than needed, often about 1%, and commercial products marketed for dogs and cats with CKD provide approximately 0.2% to 0.3% sodium.

The metabolic acidosis of CKD generally is well compensated. If metabolic acidosis is severe (serum bicarbonate concentration ≤ 12 mEq/L), sodium bicarbonate may be added to the treatment regimen. The dosage should be adjusted to maintain the serum bicarbonate concentration at 14 mEq/L or higher and the additional sodium intake should be taken into consideration. Potassium gluconate and potassium citrate are alternative sources of alkali that provide potassium and do not pose the problem of an additional sodium load. Hyperkalemia usually is not a problem in dogs and cats with CKD. The kidneys can maintain normal serum potassium concentrations at 5% of normal GFR if urine volume is adequate. Hypokalemia in dogs and cats with CKD may be treated with oral potassium gluconate or potassium citrate.

Phosphorus restriction

Early phosphorus restriction in CKD has been shown to blunt or reverse renal secondary hyperparathyroidism. In a study of dogs with 94% nephrectomy that were fed diets containing 17% protein with 0.5% or 1.5% phosphorus, progression was more rapid and outcome worse in the dogs fed the higher phosphorus diet. Tubulointerstitial lesions also were worse in dogs on the higher phosphorus diet. In another study, renal secondary hyperparathyroidism was documented in 84% of cats with naturally occurring CKD and, as assessed by serum phosphorus and PTH concentrations, responded to dietary phosphorus restriction. Because extremely phosphorus–depleted diets are unpalatable, phosphorus–binding agents may be given orally to trap phosphorus in the gut and hasten its excretion. These drugs should be given with meals or within 2 hours of feeding to maximize their effectiveness. When CKD is diagnosed, phosphorus restriction is initiated by feeding a low-phosphorus, low-protein diet. If necessary, oral phosphorus–binding agents can be added as necessary to the treatment regimen for additional reduction in serum phosphorus concentration.

In humans, chronic aluminum intoxication causing bone disease and encephalopathy has been recognized as an important complication of aluminum-containing phosphorus binders; it is thought that there is no safe dosage of aluminum-containing phosphorus binder that will provide sufficient phosphorus restriction without risking aluminum intoxication. Consequently, other phosphorus binders have replaced aluminum-containing phosphorus binders in humans with CKD. It is not yet clear that aluminum intoxication is a problem in dogs and cats with CKD, but it has been reported in two dogs with AKI. Aluminum-containing phosphorus binders are still used by many veterinary clinicians in dogs and cats with CKD. Aluminum hydroxide (Amphojel) can be used at a dosage of 45 mg/kg q12h given with food. In general, an attempt should be made to maintain the serum phosphorus concentration at less than 5.0 mg/dL. If preferred, calcium carbonate can be used instead, at a starting dosage of 45 mg/kg q12h given with food. It has the advantage of not containing aluminum, which may be toxic if absorbed from the GI tract. Calcium acetate is more effective than the aluminum- or other calcium-containing phosphorus binders and may be used at a slightly lower dosage. The animal should be monitored for the development of hypercalcemia whenever calcium-containing phosphorus binders are used. Constipation may be a complication of phosphorus binders and may be managed by addition of polyethylene glycol 3350 (Miralax) or lactulose to the treatment regimen. Sevelamer HCl is a phosphorus binder that does not contain aluminum or calcium. A dosage of 10 to 20 mg/kg q8h given with food may be considered for dogs

and cats. The use of sevelamer may be associated with adverse GI effects, including constipation, and at extremely high dosages may impair the absorption of folic acid and vitamins K, D, and E. Lanthanum carbonate is not absorbed from the GI tract and should not be retained in patients with CKD. It has no known toxicity and may be used as a phosphorus binder beginning at a dosage of 30 mg/kg/day. It has been shown to be safe and well tolerated in cats up to a dosage of 1 g/kg/day. Lanthanum carbonate decreased digestibility of phosphorus and shifted phosphorus excretion from the urine to the feces of treated cats. Epakitin decreases the absorption of dietary phosphorus and may have additional beneficial effects as an oral adsorbent for urea and ammonia. Used at a dosage of 1 g/5 kg body weight q12h, it provides 20 mg/kg calcium carbonate q12h. There is limited information about its effectiveness in dogs and cats with CKD.

If the patient is not hyperphosphatemic at the time of initial evaluation, phosphorus restriction still may be beneficial in reversing existing renal secondary hyperparathyroidism. The patient must be monitored carefully for hypophosphatemia. All measurements should be made in the fasting state to avoid the effect of feeding on the serum phosphorus concentration, and an attempt should be made to maintain the serum phosphorus concentration in the 2.5- to 5.0-mg/dL range. Serial PTH determinations are an ideal way to monitor treatment of renal hyperparathyroidism, but validated assays for dogs and cats are not widely available.

Therapy for gastrointestinal signs

Hypergastrinemia in uremic patients can result in increased gastric acidity. H_2 receptor antagonists block gastrin–mediated increases in gastric acid secretion and may be helpful in the treatment of gastrointestinal signs such as decreased appetite, nausea, vomiting, and gastrointestinal hemorrhage. Famotidine (1 mg/kg PO, q24h) is commonly used. Failure to observe gastric ulceration in cats with CKD and absence of differences in stomach pH and serum gastrin concentrations between normal cats and cats with CKD are recent observations that cast doubt on the clinical value of using famotidine or other H_2 blockers in cats with CKD.

Antiemetics also may be used to manage vomiting. Drugs used include metoclopramide (0.1-0.4 mg/kg PO or SQ, q8-12h), 5-HT3 (serotonin type 3) receptor antagonists such as ondansetron (0.6-1.0 mg/kg PO, q12h), and the NK1 (neurokinin) receptor antagonist maropitant citrate (1 mg/kg SQ or 2 mg/kg PO, q24h). The 5-HT3 receptor antagonist mirtazapine (1.88 mg PO q48h) increased appetite, activity and body weight and decreased vomiting compared with placebo in a randomized crossover study of 11 CKD cats, indicating that it may be helpful in the management of GI complications in cats with CKD. Gastroprotectants such as sucralfate (0.5-1.0 g/dog PO, q8-12h) can be used in dogs if GI ulceration and hemorrhage are suspected, but sucralfate has been associated with adverse effects in CKD cats (e.g., anorexia, vomiting, constipation, worsening azotemia) and therefore is not recommended for cats with CKD.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, benazepril) are renoprotective and may slow the progression of CKD. Angiotensin II increases efferent arteriolar vasoconstriction, which contributes to intraglomerular hypertension and proteinuria. Increased protein traffic in the mesangium promotes glomerular sclerosis. ACE inhibitors decrease the filtration of protein into Bowman's space and the mesangium by lowering intraglomerular hydrostatic pressure. Enalapril can be used at a dosage of 0.5 mg/kg PO, q24h or q12h, or benazepril can be used at a dosage of 0.25 to 0.5 mg/kg PO, q24h or q12h. Benazepril is well tolerated by cats with CKD and decreases proteinuria.

Angiotensin receptor blockers

The angiotensin receptor blockers also may be used alone or in conjunction with ACE inhibitors to decrease proteinuria. Losartan may be used at a dosage of 0.5 mg/kg/day in nonazotemic patients or at a dosage of 0.125 mg/kg/day in azotemic patients. Telmisartan may be used at a dosage of 1.0 mg/kg/day and has been shown to be similar to benazepril in its effectiveness at decreasing the UPC ratio in cats with CKD.

Endocrine replacement therapy

Erythropoietin. Recombinant human erythropoietin or EPO (epoetin alfa [Epogen], darbepoetin alfa [Aranesp]) has been used to correct the nonregenerative anemia in dogs and cats with CKD. Dogs and cats treated with EPO experience resolution of anemia, weight gain, improved appetite, improved hair coat, and improved sociability with their owners. The use of epoetin alfa in dogs and cats carries a 20% to 40% risk of anti-EPO antibody formation within 30 to 90 days of initiating therapy, and antibody development may result in severe anemia and subsequent transfusion dependence. The starting dosage of epoetin alfa is 100 U/kg SQ, three times/wk. The hematocrit must be monitored closely during therapy and the dosage adjusted to achieve and maintain a target hematocrit of 30% to 40%. The frequency of administration is decreased to twice a week as soon as the animal's hematocrit enters the target range. Small sequential decreases in the hematocrit value while an animal is being treated with epoetin alfa are presumptive evidence of anti-EPO antibody formation. Other observed adverse effects include vomiting, seizures, hypertension, uveitis, and mucocutaneous hypersensitivity-like reactions. Because of the potential for adverse effects and expense, epoetin alfa is reserved for animals with severe and symptomatic anemia (e.g., hematocrit < 12%-15%). Iron supplementation should be provided during (and ideally before) EPO treatment to ensure that the animal is iron replete.

Darbepoetin alfa has two additional glycosylation sites that extend its biologic half-life 3-fold. It can be given at a low dosage (0.25-0.5 μg/kg SQ once weekly) and then once every 2 weeks when the lower end of the target range of the hematocrit (30%) is achieved. When the upper end of the target range of the hematocrit (40%) is reached, it can be given every 3 weeks. In one study, 14 of 25 anemic CKD cats responded to darbopoietin at a dosage of 0.45 to 1.0 μg/kg/

wk. Presumptive adverse effects included vomiting, hypertension, seizures, and fever. Because of its structure and lower dosage, darbepoetin alfa is thought to be less likely to result in antibody formation when used in dogs and cats. Canine and feline recombinant erythropoietin have been synthesized and been shown to be effective but are not commercially available.

Calcitriol. In the kidney, 25–hydroxycholecalciferol is converted to the active form of vitamin D_3, 1,25–dihydroxycholecalciferol (calcitriol), by 1α–hydroxylase in the tubular cells. The 1α-hydroxylase is stimulated by PTH and hypophosphatemia and inhibited by calcitriol and FGF-23. The major effects of calcitriol are to increase the intestinal absorption of calcium (and phosphate), facilitate PTH–mediated bone resorption of calcium and phosphorus, increase renal tubular reabsorption of calcium (and phosphate), and provide negative feedback control on PTH synthesis by the parathyroid glands; a relative lack of this effect plays an important role in the development of renal secondary hyperparathyroidism in patients with CKD.

Calcitriol is helpful in the management of renal secondary hyperparathyroidism because of its ability to feed back to calcitriol receptors in the parathyroid glands and decrease PTH synthesis and secretion. If the [Ca] × [P_i] solubility product is more than 60 to 70, calcitriol therapy should be avoided because of the risk of soft tissue mineralization. Calcitriol should only be used after hyperphosphatemia has been adequately controlled by a low-phosphorus diet and oral phosphorus binders, if necessary. A very low dosage of calcitriol (2.5–3.5 ng/kg/day) has been used in dogs and cats with CKD to prevent or reverse renal secondary hyperparathyroidism. Serial serum calcium concentrations should be monitored to detect hypercalcemia. Serum PTH concentrations fall dramatically in dogs and cats with CKD treated with calcitriol, and survival time may be increased.

Anabolic steroids

Many products are available but there are no long-term studies demonstrating the efficacy of anabolic steroids in dogs and cats with CKD. The anabolic steroid stanozolol (Winstrol-V) has equivocal effects in dogs with CKD. In cats, it is hepatotoxic and has been associated with increased liver enzyme activities, vitamin K-responsive coagulopathy, cholestasis, and hepatic lipidosis. Anabolic steroids usually are not recommended for dogs and cats with CKD.

Blood pressure control agents

The presence of systemic hypertension is a risk factor for uremic crises, more rapid progression, and mortality in dogs with CKD. In cats, it can be difficult to decide whether hypertension really is present because of the white coat effect. Dogs and cats with a systolic blood pressure of 150 to 159 mm Hg and evidence of end-organ damage (e.g., cardiovascular or ocular complications) are candidates for antihypertensive treatment. Those with a systolic blood pressure of 160 to 179 mm Hg or higher are candidates for treatment, regardless of evidence of target organ damage.

Most commercial diets formulated for dogs and cats with CKD are low in salt. Sodium restriction may have a limited effect on systemic blood pressure and in cats may contribute to increased urinary loss of potassium and hypokalemia by activation of the renin-angiotensin system. Diuretics (e.g., furosemide, hydrochlorothiazide) generally are not used to treat hypertension in dogs and cats with CKD because of concern about dehydration and prerenal azotemia. The effect of ACE inhibitors on systemic blood pressure may be modest, but other potentially beneficial effects warrant their use in dogs and cats with CKD (see earlier). Dihydropyridine calcium channel blockers (e.g., amlodipine) are effective for treatment of hypertension in cats at a dosage of 0.625 to 1.25 mg PO, q24h. Amlodipine can be used in dogs at a dosage of 0.1 to 0.5 mg/kg PO, q12h. Gingival hyperplasia is an uncommon and reversible adverse effect in dogs. Nondihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) may decrease proteinuria and be renoprotective in humans but have not been evaluated for this purpose in dogs and cats.

SUPPORTIVE CARE

Some owners can be taught to administer fluids subcutaneously to their animals at home. This is particularly convenient for cats and small dogs. For example, if the owner is willing to learn the technique and the cat is cooperative, 60 mL of lactated Ringer's solution can be given subcutaneously two or three times per day. If the owner has noticed that the cat did not absorb previously administered fluids, additional fluid should not be given. Also, if the owner experiences technical difficulty administering fluids subcutaneously, it is preferable for fluids to be administered on an outpatient basis at the veterinary clinic. The additional fluid support appears to have beneficial effects on the animal's quality of life, and in one study, 47% of cats with CKD were reported to be receiving subcutaneous fluids as part of their treatment. If the owner is having difficulty getting the animal to eat, a feeding tube should be considered to ensure adequate caloric intake and facilitate administration of medications. Most cats tolerate percutaneously placed gastrostomy tubes well for extended periods of time, and this approach can make medical management much easier and less stressful for the owner and the cat.

Course and Prognosis

The rate of progression of CKD varies among individual animals, and affected dogs and cats may live months to years. The slope of the relationship of the reciprocal of the SCr (1/SCr) versus time may give a rough indication of the rate of progression of CKD. Findings that warrant a poor prognosis include severe intractable anemia, inability to maintain fluid balance, and progressive azotemia, despite fluid therapy and conservative medical management.

Suggested Readings

Chalhoub S, et al. The use of darbepoetin to stimulate erythropoiesis in anemia of chronic kidney disease in cats: 25 cases. *J Vet Intern Med*. 2012;26:363.

Chew DJ. Acute renal failure. In: Chew DJ, DiBartola SP, Schenck PA, eds. *Canine and feline nephrology and urology*. St Louis: Elsevier Saunders; 2011:63.

Finch NC, et al. Fibroblast growth factor 23 (FGF-23) concentrations in cats with early nonazotemic chronic kidney disease (CKD) and in healthy geriatric cats. *J Vet Intern Med*. 2013;27:227.

Freeman LM, et al. Evaluation of weight loss over time in cats with chronic kidney disease. *J Vet Intern Med*. 2016;30:1661.

Geddes RF, et al. Relationship between plasma fibroblast growth factor-23 concentration and survival time in cats with chronic kidney disease. *J Vet Intern Med*. 2015;29:1494.

Geddes RF, et al. Fibroblast growth factor 23 (FGF-23) concentrations in cats with early nonazotemic chronic kidney disease (CKD) and healthy geriatric cats. *J Vet Intern Med*. 2013;27:227.

Geddes RF, et al. Fibroblast growth factor 23 in feline chronic kidney disease. *J Vet Intern Med*. 2013;27:234.

Harjes LM, et al. Fibroblast growth factor-23 concentration in dogs with chronic kidney disease. *J Vet Intern Med*. 2017;31:784.

Kelly KL, et al. Effect of fenoldopam continuous infusion on glomerular filtration rate and fractional excretion of sodium in healthy dogs. *J Vet Intern Med*. 2016;30:1655.

King JN, et al. Tolerability and efficacy of benazepril in cats with chronic kidney disease. *J Vet Intern Med*. 2006;20:1054.

McLeland SM, et al. Relationship among serum creatinine, serum gastrin, calcium-phosphorus product and uremic gastropathy in cats with chronic kidney disease. *J Vet Intern Med*. 2014;28:827.

Nielsen LK, et al. Administration of fenoldopam in critically ill small animal patients with acute kidney injury: 28 dogs and 34 cats (2008-2012). *J Vet Emerg Crit Care (San Antonio)*. 2015;25:396.

Parker VJ, et al. Association between body condition and survival in dogs with acquired chronic kidney disease. *J Vet Intern Med*. 2011;25:1306.

Plantinga EA, et al. Retrospective study of the survival of cats with acquired chronic renal insufficiency offered different commercial diets. *Vet Rec*. 2005;157:185.

Quimby JM, et al. Mirtazapine as an appetite stimulant and antiemetic in cats with chronic kidney disease: a masked placebo-controlled crossover clinical trial. *Vet J*. 2013;197:651.

Roudebush P, et al. An evidence-based review of therapies for canine chronic kidney disease. *J Small Anim Pract*. 2010;51:244.

Shipov A, et al. The effect of naturally occurring chronic kidney disease on the microstructural and mechanical properties of bone. *PLoS ONE*. 2014;9:e110057.

Sparkes AH, et al. ISFM Consensus guidelines on the diagnosis and management of feline chronic kidney disease. *J Feline Med Surg*. 2016;18:219.

Syme HM, et al. Survival of cats with naturally occurring chronic renal failure is related to severity of proteinuria. *J Vet Intern Med*. 2006;20:528.

Tolbert MK, et al. Evaluation of gastric pH and serum gastrin concentrations in cats with chronic kidney disease. *J Vet Intern Med*. 2017.

CHAPTER 42

Bacterial Cystitis, Pyelonephritis, and Prostatitis in the Dog and Cat



INTRODUCTION

The entire urinary tract has several built-in defense mechanisms to prevent external pathogens from adhering to the urinary mucosa. Normal micturition itself and frequent and complete voiding can help remove bacteria. Furthermore, the proximal urethra is sterile and contains microplicae that expand as urine is voided, aiding in the removal of the bacteria. Although the distal urethra, preputial tissues, and vulva contain normal flora, some of these bacteria can help prevent access of the pathogens into the urinary tract by producing bacteriocin, which can interfere with the metabolism of other bacteria. In addition, mucosal secretions such as immunoglobulins and glycosaminoglycans can help prevent the adherence of uropathogens to the epithelium. High urine osmolality and high concentrations of urea can also inhibit bacterial growth. Although isosthenuria itself does not appear to be a sole risk factor for bacteria cystitis, diseases that result in isosthenuria (e.g., chronic kidney disease [CKD] and hyperthyroidism) may predispose the dog or cat to bacteria cystitis. In dogs and cats, submitting a urine culture based only on a low urine specific gravity (<1.013) does not appear to be cost-effective in the absence of active urine sediment and high clinical suspicion based on clinical signs.

Bacterial cystitis in general is more common in dogs (females more so than males). The prevalence of bacterial cystitis in cats presenting to referral institutions with lower urinary tract signs (LUTS) ranges from 1% to 3%; higher percentages have been reported from cats presenting to private practices in Europe. Most young cats with LUTS have disorders such as feline idiopathic cystitis (see Chapter 44), which are not associated with bacterial infections. When bacterial cystitis occurs in cats, comorbidities such as diabetes mellitus, hyperthyroidism, CKD, or a combination of these diseases are present. The prevalence of bacterial cystitis in cats with diabetes mellitus is 11% to 13%. In young adult cats, the prevalence of bacterial cystitis is higher in those who have had urinary catheterization and/or perineal urethrostomy. Other factors that may predispose cats to bacterial cystitis are female sex, older age, and lower body weight, although some of these risk factors may also be associated with the comorbidities mentioned earlier. Furthermore, asymptomatic bacteriuria has been associated with these comorbidities in cats, and therefore treatment with antimicrobials may not always be indicated (see later).

The most common uropathogen isolated in sporadic bacterial cystitis in dogs is *Escherichia coli,* which accounts for approximately 50% of all isolates, followed by *Staphylococcus, Proteus, Klebsiella, Enterococcus,* and *Streptococcus* spp. Mycoplasma have also been isolated from the urinary tract of dogs, although its clinical relevance has been unclear because they are usually isolated from dogs that have other disorders of the lower urinary tract, such as underlying neoplasia, urolithiasis, or micturition disorders. The bacteria species isolated from cats with bacterial cystitis are similar to those in dogs.

CLASSIFICATION OF BACTERIAL CYSTITIS

Bacterial cystitis can be classified according to several definitions (Table 42.1). Sporadic bacterial cystitis (which will also be referred to as sporadic UTI in this chapter for simplicity; all other types and locations of urinary infections will be clearly stated) suggests that the animal is otherwise healthy and has no underlying comorbidity that may predispose it to the infection. This term also implies the animal has clinical signs associated with the infection. Complicated bacterial cystitis implied an underlying comorbidity, which can include such disorders as anatomic problems (e.g., ectopic ureters, ureterocoeles), systemic diseases (e.g., diabetes mellitus, hyperthyroidism, hyperadrenocorticism, systemic neoplasia, immunocompromised animals), and those problems related to the urinary tract itself (e.g., urolithiasis, cystic neoplasia, deep seated bacterial cystitis). Subclinical bacteriuria is the presence of bacteria identified in urine and the presence of a positive bacterial urine culture despite the lack of the typical LUTS. These clinical signs can include the following: stranguria, hematuria, pollakuria, peruirua, and

TABLE 42.1

Definitions Applied to Urinary Tract Infections

TERM	DEFINITION
Sporadic bacterial cystitis (i.e., sporadic UTI)	Sporadic bacterial infection of the bladder in an otherwise apparently healthy individual with normal urinary tract anatomy and function
Complicated UTI	UTI that occurs in the presence of an anatomic or functional abnormality or comorbidity that predisposes to persistent UTI, recurrent infection, or treatment failure
Subclinical bacteriuria	Presence of bacteria in the urine as determined by a positive bacterial culture in the absence of lower urinary tract signs (LUTS). Differentiation from subclinical UTI may be difficult.

From Westropp J, Sykes JE: Bacterial infections of the genitourinary tract. In Sykes JE, editor: *Canine and feline infectious diseases,* St. Louis, 2013, Elsevier.

dysuria. In the author's experience, some dogs with urinary incontinence and positive bacterial urine culture respond to antimicrobial therapy suggesting this is a clinical sign associated with UTI. Subclinical bacteriuria has also been referred to as occult UTI and asymptomatic bacteriuria in human medicine.

Animals with comorbidities can have unique bacterial infections such as *Corynebacterium urealyticum,* a gram-positive bacterium that can result in encrusting cystitis (Fig. 42.1). This pathogen also can produce urease, which results in the precipitation of calcium phosphate and struvite plaques that adhere to the uroepithelium. The most common cause is *E. coli,* which ferments the glucose to gas products; *Clostridium* spp. may also be involved. In the absence of glucose, proteins such as albumin may be fermented to gas. Dogs and cats with diabetes mellitus may present with emphysematous cystitis (EC), characterized by the production of gas by bacteria within the bladder wall or lumen (Fig. 42.2). Gas was most commonly detected in the bladder lumen and wall in 14/27 (51%) of dogs with EC in a recent report. Comorbidities were identified in 26/27 (96%) cases reported, the most common of which were diabetes mellitus in 33% of dogs, neurologic disease in 26% of dogs, and adrenal disease in 19% of dogs.

Recurrent bacterial cystitis (UTI) implies that the animals have had three or more infections in a 12-month time period. Recurrent UTI can be subclassified as relapsing infection, reinfection, refractory infection, or persistent infections. Although urine bacterial cultures may help distinguish these types of recurrent infections, advanced molecular diagnostic

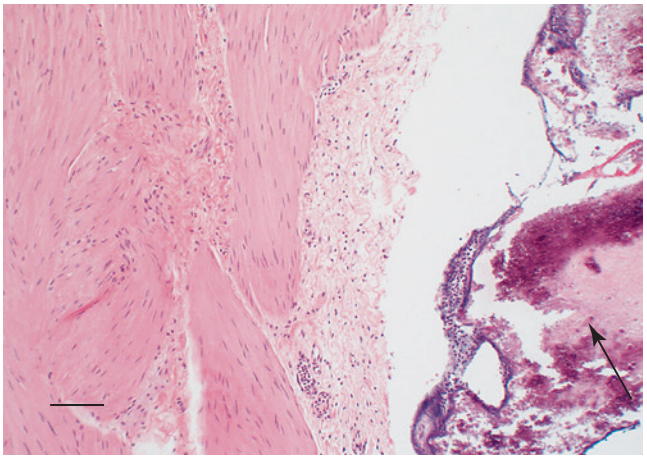


FIG 42.1
Photomicrograph of a section of the urinary bladder from a dog with *C. urealyticum* cystitis. Transitional epithelium overlying the smooth muscle is completely denuded and replaced by a thick mat of partially mineralized (basophilic) degenerate cellular debris and fibrin exudates *(arrow)* (H&E; bar = 100 µm). These plaques must be removed (cystoscopically or surgically) to allow antibiotics to penetrate the bladder wall.

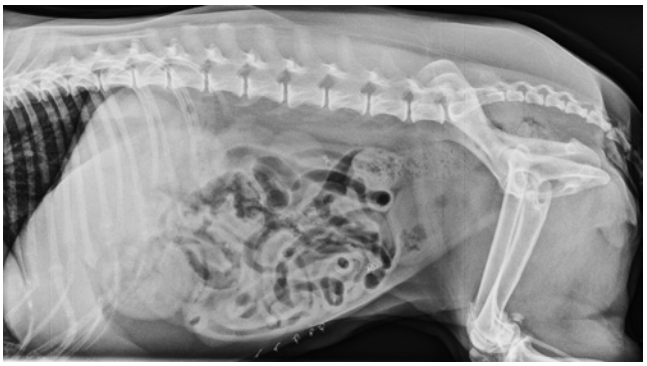


FIG 42.2
Lateral radiograph of a 13-year-old female spayed Terrier mix with diabetes mellitus with emphysematous cystitis caused by *E. coli*. Note the irregular gas pattern within the bladder lumen.

procedures are often required, and these tests are not clinically available. It is easy to identify a reinfection when the quantitative urine culture reveals a different bacterial genus and species than the original isolate. The same organism isolated initially causes a relapsing infection; it can be caused by the persistence of an organism that was never completely eradicated. Relapse suggests the organism may be deep-seated in the tissues—inaccessible to the antimicrobial, as in the kidney, prostate, or polyps—or that subtherapeutic concentrations of the antimicrobial were achieved in the urine and/or urinary tissues, or that the organism is resistant to the chosen antimicrobial. A study reported that there was a 17% disagreement between bladder mucosa cultures compared with urine cultures suggesting deep-seated infections may occur in dogs. This difference was not significant

though. A persistent infection implies the bacterial cultures remain positive with the same organism during antimicrobial treatment. In this case, the organism has not been eradicated, even transiently, despite administration of the appropriate urinary antimicrobial agent. Persistent infections imply severe abrogation of local host defenses or that the organism is highly resistant to the administered antimicrobial drug. Animals that present with recurrent UTI should have a thorough diagnostic evaluation (see later) to search for underlying predisposing diseases. See Table 42.2 for a list of disorders and diagnostic considerations for animals with various forms of recurrent bacterial cystitis.

Subclinical bacteriuria is a term used in human medicine to describe the presence of bacteria in the urine, as determined by a positive bacterial culture, in the absence of LUTS. This has generally been referred to as subclinical UTI in the veterinary literature. Subtle signs of bacterial cystitis may be difficult to discern in small animals. Subclinical bacteriuria has been variably reported in dogs and cats with prevalence rates in cats reported from 0.9% to 28.8%, and in one study evaluating 101 healthy adult dogs, it was 8.9%. Cats were oftentimes noted to be older and female. Subclinical bacteriuria is also anecdotally reported more often in animals with underlying endocrinopathies, kidney disease, or micturition disorders; in dogs and cats treated with glucocorticoids or immunosuppressive agents; or in those animals that have had perineal urethrostomies. Choosing what, if any, antimicrobial treatment for dogs or cats with subclinical bacteriuria is not always clear (see later).

Physical Examination Findings

The physical examination in dogs and cats with a simple uncomplicated bacterial cystitis is usually unremarkable. The bladder may be small and thickened, in some cases, because of persistent inflammation and pollakiuria; caudal abdominal discomfort may be present in some patients. On rectal examination, the urethra may be prominent or more severely thickened in cases in which urethral neoplasia or proliferative urethritis (Video 42.1) is present. Urethral stones may also be palpable, if present. Rarely, in more complicated cases, a large bladder is palpated in patients with secondary urethral obstruction caused by neoplasia, usually transitional cell carcinoma (TCC), proliferative urethritis, or urethrolith. In females, the vulva should be examined to be certain no evidence of a recessed vulva and/or perivulvar pyoderma is present (Fig. 42.3). Similarly, the prepuce should be examined for discharge, foreign bodies, or mass lesions.

Diagnosis

For simple sporadic UTI, a quantitative aerobic bacterial urine culture from urine obtained by cystocentesis is indicated, followed by identification and susceptibility testing of

TABLE 42.2

Recurrent Infections

		DIFFERENTIALS DIAGNOSES	DIAGNOSTICS TO CONSIDER
Relapsing	Clinical and microbiologic cure of bacterial cystitis with subsequent recurrence of disease.	Urolithiasis Bladder polyps Cystic neoplasia Deep seated bladder infections Pyelonephritis Chronic prostatitis Altered mucosal immune responses	Abdominal radiographs Contrast cystourethrograms Abdominal ultrasound CBC Serum biochemical panel Cystoscopy with biopsy
Persistent	Continued presence of the same bacterial strain in urine despite clinical cure	Immunocompromised Cystic neoplasia Encrusting cystitis Severe micturition abnormalities Altered mucosal immune responses	Radiographs Abdominal ultrasound CBC Serum biochemistry
Reinfection	Isolation of a different microorganism after apparent resolution of a previous infection	Hooded vulva Cystic diverticulum Ectopic ureter Urinary incontinence (USMI or anatomic) Ureterocele Immunosuppression	Check external confirmation CBC, serum biochemical panel Abdominal ultrasound Contrast cystourethrogram Cystoscopy
Refractory	Lack of clinical and microbiologic response to treatment	Poor owner compliance In appropriate drug or dosing regimen Undetected antimicrobial resistance Inability of antimicrobial(s) to penetrate the site of infection	Review dosing and compliance Radiographs Abdominal ultrasound Cystoscopy

Adapted from *ISACID guidelines for the diagnosis and management of bacterial UTI in dogs and cats,* Weese, et al., submitted, 2017.



FIG 42.3
Recessed vulva with pronounced perivulvar erythema. Dogs with recurrent UTIs and a recessed (or hooded) vulva may improve after an episioplasty. (Courtesy Dr. Dennis Chew, The Ohio State University.)

TABLE 42.3

Significant Bacteriuria in Dogs and Cats

COLLECTION METHOD	DOG	CAT
Cystocentesis	≥1000 cfu/mL	≥1000 cfu/mL
Catheterization (male)	≥10,000 cfu/mL	≥10,000 cfu/mL
Catheterization (female)	≥100,000 cfu/mL	Unknown
Midstream voided	Not recommended	Not recommended

the pathogen isolated. Although any pathogen isolated from specimens collected by cystocentesis is likely significant, bacterial contamination from the skin is possible; therefore the presence of more than 10^3 cfu/mL of bacteria is considered clinically relevant. See Table 42.3 for clinically relevant bacterial numbers based on the urine collection method. A complete blood count (CBC), serum biochemical panel, and imaging studies are not usually warranted in those cases in which the animal is otherwise healthy and the suspected infection is an isolated event.

The drugs chosen for susceptibility testing by individual laboratories vary. Similarly, the method of susceptibility testing used is subject to laboratory preference and has direct implications on how results are reported. The clinician should consult with his or her microbiologist to determine whether the susceptibilities reported are based on concentrations of the antimicrobials in the serum or urine. Attainable urine concentrations of some antimicrobials can be much higher than in the serum as long as kidney function is normal and polyuria and polydipsia are not present. Consequently, sterility within the urinary tract can be achieved at times when it would otherwise appear that these drugs would fail to do so at concentrations achieved in the plasma.

Although a urine culture is the gold standard for the diagnosis of a bacterial cystitis, it can be costly; in practice, culture kits, paddles, and other rapid bacterial immunoassays have been marketed for companion animal use. These can be helpful when screening animals for infections; however, inaccuracies with one veterinary specific culture paddle has been reported, particularly when multiple organisms were present. When growth is identified in any "in house" kit, the urine should be submitted to a commercial microbiology laboratory for identification and antimicrobial susceptibility testing. Furthermore, appropriate laboratory facilities and biosafety level 2 containment and waste management protocols need to be followed.

For dogs and cats with a recurrent UTI, not only is a urine culture indicated, but an appropriate diagnostic workup to evaluate the animal for predisposing factors is warranted, assuming the previous infections were treated appropriately (see later). Predisposing factors facilitate the ascent of bacteria and development of an initial infection and also can make it more difficult to eradicate a UTI once established in the urinary tissues. A search for anatomic or structural defects, such as a recessed vulva, ectopic ureter(s), urachal diverticulum, polypoid cystitis, proliferative urethritis, urolithiasis, foreign bodies, prostatic disease, and neoplasia within the urethra or bladder (Video 42.2), should be undertaken. Infection in the kidney is inherently more difficult to eradicate than in the lower urinary tract, especially when chronically infected or if there is a nidus for infection, such as a nephrolith, ureterolith, or partial ureteral obstruction. Micturition problems such as urinary incontinence or urine retention should be identified and corrected when possible. Those with metabolic abnormalities such as diabetes mellitus, hyperadrenocorticism, hyperthyroidism, and CKD may more readily acquire new infections or fail to easily resolve an existing UTI, as is also true for animals receiving corticosteroid therapy or other immunosuppressive drugs. It can be difficult to impossible to achieve long-term urinary tract sterility in patients that continue to receive immunosuppressive drug treatment. The clinician must decide if the animal has subclinical bacteriuria during these cases and if treatment is warranted every time bacteria is isolated. If clinical signs are present or progressive azotemia is noted, treatment should always be initiated.

Imaging studies that include survey abdominal radiography and abdominal ultrasonography are an important part of the evaluation of patients with recurrent lower bacterial cystitis to rule out structural and anatomic problems. Contrast cystourethrography should be considered when ultrasonography is not readily available, and in male dogs and

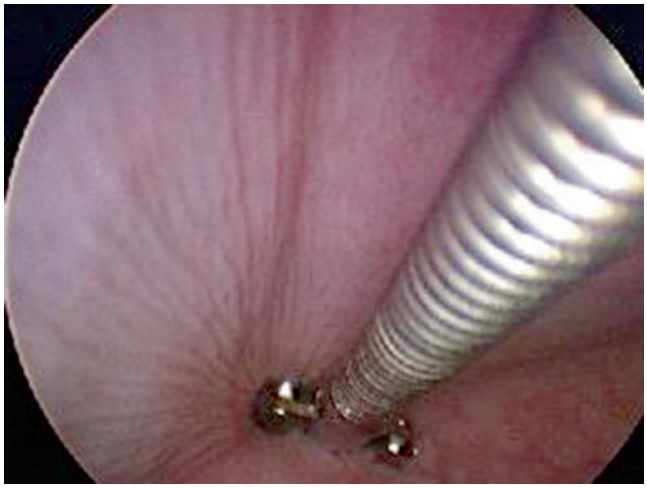


FIG 42.4
Cystoscopic view of biopsy forceps inserted through the working channel of a rigid cystoscope to obtain a mucosal biopsy from a female dog with recurrent UTIs. When obtaining biopsies in this manner, they can be submitted for histopathology as well as cultures for aerobic bacteria and mycoplasma.

cats for proper examination of the urethra. Excretory urography and renal ultrasonography may be needed to evaluate the kidneys more completely, especially to help exclude an element of obstruction within the upper urinary tract. Cystoscopy should be considered if the initial imaging tests do not document structural or anatomic abnormalities and is also excellent to evaluate the urethra. Even when no obvious lesions are observed during cystoscopy, submitting a biopsy of the bladder mucosa for culture to evaluate the patient for a deep-seated infection is ideal (Fig. 42.4; Video 42.3). If uroliths are removed from the patient with a recurrent UTI, a culture of the stone can also be performed.

Treatment

TREATMENT OF UNCOMPLICATED URINARY TRACT INFECTIONS

For empiric therapy, the Antimicrobial Use Working Group of the International Society for Companion Animal Infectious Diseases (ISCAID) recommends urinary antibacterial drugs that are likely to be effective against more than 90% of the urinary isolates when this information is available (Weese et al., 2011). In general, ISCAID recommends initial therapy for sporadic bacterial cystitis with amoxicillin (11-15 mg/kg orally [PO] q8h) or trimethoprim-sulfamethoxazole (15 mg/kg PO q12h). Newer guidelines are in preparation at the time of this writing and, although amoxicillin is still recommended, amoxicillin with clavulanate is a reasonable empiric choice when regional susceptibility data support a high likelihood or resistance to amoxicillin alone. Ampicillin is not recommended due to poor oral bioavailability. Although ciprofloxacin is routinely used in human medicine and often used in veterinary medicine due to lower cost, it is difficult to justify in veterinary medicine due to its lower oral bioavailability in dogs. Clinical and Laboratory Standards Institute (CLSI) have not established ciprofloxacin breakpoints for bacterial isolates from dogs. CLSI breakpoints are only available for other approved fluoroquinolones for dogs.

By convention, sporadic UTI has routinely been treated for 7 to 14 days. In human medicine, numerous studies have evaluated the efficacy of short-duration antimicrobial therapy for uncomplicated UTI in women. In veterinary medicine, one study in dogs with uncomplicated (i.e., sporadic) UTI showed that treatment with enrofloxacin (20 mg/kg) for 3 days was not inferior to treatment with amoxicillin–clavulanic acid for 14 days (Westropp et al., 2012). Adverse effects were rare and similar in both groups. In another clinical trial, cefovecin was administered subcutaneously (8 mg/kg) to 61 dogs with an uncomplicated UTI and was reported to be effective (Passmore et al., 2007). At this time, the ISCAID guidelines recommend short duration for bacterial cystitis (5-7 days). It is possible that 3 to 5 days of therapy may be all that is needed to achieve clinical and microbiologic cure. Reevaluation of sporadic UTI for aerobic bacterial cultures after clinical cure has been achieved in dogs and cats not clinically indicated.

Recurrent and Complicated Bacterial Cystitis

The correction of underlying predisposing factors increases the likelihood for successful long-term eradication of organisms from the animal's urine and urinary tissues. Empiric antimicrobial therapy should be avoided, and drugs should be selected based on culture and susceptibility results. The clinician should be certain that the proper doses of antimicrobials are used and the use of higher doses (for concentration-dependent) and increased number of doses (for time-dependent) should be considered, especially for drugs that are intermediate in their susceptibility.

By convention, treatment for dogs and cats with recurrent UTI has been recommended for up to 4 weeks, but a shorter course of therapy is likely effective in these cases as well. The clinician can consider obtaining urine shortly after beginning the drug regimen and again 7 days after completing the antimicrobial. If a positive culture is found, further diagnostic tests to investigate for underlying comorbidities should be performed. Although prophylactic, daily antimicrobial therapy and pulse therapy have been advocated by some clinicians, no studies exist regarding these protocols, and there is concern for emerging bacterial resistance if pathogens are exposed to daily suboptimal doses of antimicrobials. Nitrofurantoin has been anecdotally considered for clinical recurrent bacterial cystitis that is refractory to other oral antimicrobials but should never be used in animals with prostatitis or pyelonephritis because this drug does not achieve good tissue concentrations.

Adjunct Treatment

Alternative approaches for prevention and treatment of recurrent bacterial cystitis that have been investigated in

human beings as well as animal models include the use of cranberry extract. The efficacy of cranberry extract in women has been mixed but most recently has shown no significant difference in placebo-controlled studies. Although cranberry has been shown to prevent adherence of *E. coli* strains in in vitro studies, one study in dogs with intervertebral disk disease did not appear to reduce the risk of UTI in that placebo-controlled trial. Live biotherapeutic products appear promising for treatment of recurrent UTI for several reasons. Intravesicular administration of *E. coli* ASB 83972 in human beings with recurrent UTI reduced symptoms of UTI and protected some patients from recurrent UTI after serial catheterizations, which might reduce the need to antimicrobial therapy. In a recent veterinary pilot study, intravesicular administration of ASB *E. coli* 2-12 to dogs with recurrent UTI resulted in complete or nearly complete clinical cures in four of nine dogs and three also had microbiologic cures at 2 weeks; one of these dogs had subclinical bacteriuria (in addition to ASB *E. coli* 2-12 and did not require antimicrobial therapy). Three of these four dogs had ASB *E. coli* 2-12 isolated from their urine at day 14. Further studies are underway to investigate this live biotherapeutic in a larger population.

Subclinical Urinary Tract Infections

In humans with asymptomatic bacteriuria, treatment with antimicrobials is not always administered because of potential adverse effects of the drugs, as well as the concern for emerging bacterial resistance. Although prospective studies regarding this issue in cats and dogs are very limited, subclinical bacteriuria in dogs and cats may not always require treatment. In nine healthy dogs with subclinical bacteriuria followed for 3 months, four had persistent bacteriuria and four transient; none developed signs during this time period. The author has carefully followed several dogs with subclinical bacteriuria for many months with no treatment, and no adverse outcomes were noted at this time. If no underlying cause for the bacteriuria is found and the risk for ascending pyelonephritis is low (e.g., an otherwise healthy dog or cat or a very stable animal), antimicrobials may not always be indicated. If the clinician is not certain if clinical signs or labwork abnormalities are due to the bacteria, a short course of antimicrobials can be considered and the animal should be reevaluated. If no improvement is noted, cessation of the antimicrobial should be considered. In mixed infections that involve *Enterococcus* spp., anecdotal evidence suggests that the *Enterococcus* spp. infection will resolve when other organisms present are successfully treated. The need for antimicrobial therapy should be based on a case-by-case basis, and the pros and cons of using an antimicrobial should be considered and discussed with the owner.

Pyelonephritis

Acute pyelonephritis (APN) usually results when bacteria ascend into the renal pelvis and parenchyma from the lower urinary tract; less commonly, hematogenous spread to the kidney occurs. APN can also be classified as noncomplicated and complicated according to human medicine, which we have adapted to veterinary medicine. Complicated implies the presented of a systemic disease such as diabetes mellitus, neoplasia, or an immunocompromised animal or the presence of an anatomic or obstructive lesion in the urinary tract such as a nephrolith or ectopic ureter. Pyelonephritis may also be chronic as well; the diagnosis of chronic pyelonephritis can be challenging, as no sensitive and specific biomarkers are clinically available to aid in this diagnosis. Usually, a single organism is isolated from the urine. The medulla is more sensitive to colonization than the cortex, possibly because of impaired host defenses in a high-osmolality, low-pH, and low–blood flow milieu. Organisms adhere to pelvic and distal and proximal tubular epithelium and have been observed intracellularly. Considerable renal injury results from the inflammatory response to infection. Aggregation of neutrophils within capillaries and induction of vascular spasm by bacterial toxins and/or cytokines can contribute to renal ischemia.

In animals with APN, flank or dorsal abdominal pain may be present. Furthermore, these animals may be dehydrated and show signs of acute kidney injury.

A urinalysis and urine culture with susceptibility testing should be submitted on all patients suspected of having pyelonephritis. Imaging studies can help support the diagnosis of pyelonephritis. Although ultrasonographic findings are not specific, they can include renal pelvic dilation, blunting of the renal papilla, echogenic debris within the renal pelvis, ureteral dilation, or a combination of these findings. Nephropyelocentesis can be considered when renal pelvic dilation is present, particularly when the cystocentesis does not result in positive urine culture results. Blood cultures can also be considered if hematogenous spread is suspected or the animal is immunocompromised. Antimicrobials that reach high tissue levels are recommended; ISCAID suggests the use of the fluoroquinolones.

Empiric antimicrobial therapy should be started to help prevent further renal damage. Enrofloxacin is often prescribed (10-20 mg/kg q24h for dogs; 5 mg/kg PO once daily for cats), but 25% to 50% dose reductions may be required, depending on the severity of renal compromise. Intravenous therapy should be given to dogs and cats requiring hospitalization, and therapy for acute kidney injury should be implemented (see Chapter 44) for more severe cases. Oral antimicrobials can be administered if the patient is stable and not vomiting. Antimicrobial therapy has conventionally been recommended for as long as 4 weeks; shorter courses (7-14 days) in human medicine using both intravenous and oral antimicrobials have been published. Longer duration therapy in dogs is likely not indicated, and these shorter course therapies are likely to be effective in dogs and cats. The author routinely treats APN for 14 days then reassesses the animal. The animal should be reevaluated, including the CBC, serum creatinine, and urine culture results. The urine cultures results must be interpreted in conjunction with the other clinicopathologic parameters.

BACTERIAL PROSTATITIS

Bacterial prostatitis is a chronic or acute condition that usually occurs in sexually intact male dogs and should be suspected in any intact male dog with a positive urine culture. Acute prostatitis can have serious systemic ramifications, including fever, depression, dehydration, vomiting and diarrhea, and even septic shock. A leukocytosis with left shift may be present. Dogs may have LUTS as well as purulent or hemorrhagic urethral discharge and abdominal pain. Tenesmus may also occur because of the enlarged prostate causing compression of the distal colon. On rectal examination, the prostate may be asymmetric, enlarged, and painful. Dogs with chronic prostatitis may be lethargic, have mild LUTS, or have no clinical signs, and the prostate can be symmetric and nonpainful on palpation. Prostatic abscesses can also occur after acute or chronic prostatitis and can cause life-threatening peritonitis if the abscess were to rupture.

Most dogs with bacterial prostatitis also have a bacterial cystitis. The commonly isolated pathogens are similar to isolates that cause UTIs. Although a urine culture will suffice in most dogs, cultures of the prostate can be necessary when there is a negative urine culture or the animal has clinical signs despite appropriate treatment based on the urine susceptibility test results. Diagnostic imaging such as an abdominal ultrasonography (Fig. 42.5) or a retrograde contrast study (Fig. 42.6) should be performed to evaluate the prostate for size, cysts, and abscesses, and to evaluate for findings compatible with neoplasia (e.g., mineralization). Prostatic fluid can be obtained by ejaculation, prostatic massage, and usually by ultrasound-guided fine-needle aspiration of the prostate. The fluid should be analyzed for cytologic abnormalities as well as aerobic culture.

Antimicrobial treatment for acute prostatitis should be continued for at least 4 weeks; longer treatment regimens are often warranted for chronic prostatitis. Because of the blood–prostate barrier, it can be difficult to achieve levels of antimicrobials above the desired minimum inhibitory concentration (MIC) for the bacterial pathogen. Although the blood–prostate barrier is often broken in acute prostatitis, antimicrobials should still be chosen that would penetrate this barrier, which is important as the infection resolves. Because of this barrier, an antibiotic with high lipid solubility, low protein binding, and an appropriate pK_a should be used. Nonionized forms of antibiotics pass through lipid membranes, whereas the ionized forms do not. For gram-negative infections in the prostate, trimethoprim-sulfamethoxazole, chloramphenicol, and the fluoroquinolones are the most appropriate choices. Enrofloxacin is considered the drug of choice for canine bacterial prostatitis because of its high lipid solubility, low protein binding, low MIC profile, and broad spectrum of activity against many uropathogens. Furthermore, unlike the other two antibiotics, adverse effects with enrofloxacin are rare. Oral ciprofloxacin should not be used as a substitute for enrofloxacin because the bioavailability of ciprofloxacin is only approximately 40% in dogs and is widely variable. The typical dose of enrofloxacin for prostatitis is 10 to 20 mg/kg PO q24h. The higher doses may be needed for certain strains of *Pseudomonas* spp. Once-daily dosing is preferred because higher maximum concentrations of the antibiotic are achieved compared with dividing the dose over the day.

In addition to antimicrobials, castration should be performed as soon as the animal is stable for anesthesia and surgery. If castration is not an option for a breeding animal, the 5α-reductase inhibitor, finasteride (0.1-0.5 mg/kg PO

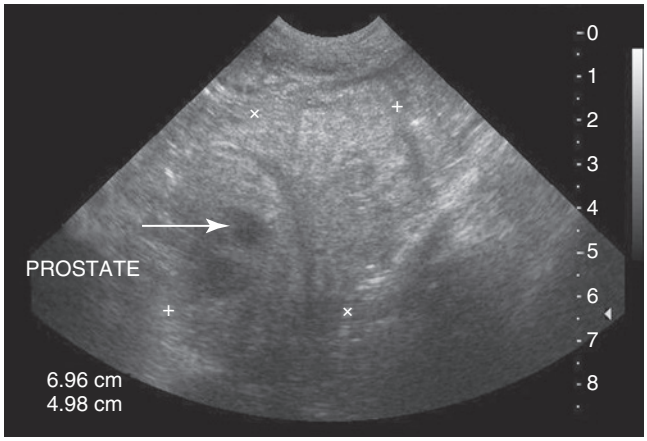


FIG 42.5
Abdominal ultrasonography of a 6-year-old male intact Borzoi that presented for weight loss and tenesmus. The prostate was enlarged, with ill-defined, irregular margins; gas was visualized within the parenchymal tissue and multiple hypoechoic cyst-like regions were noted *(arrow)*. Severe prostatitis and ultrasonographic evidence of septic peritonitis were also evident.

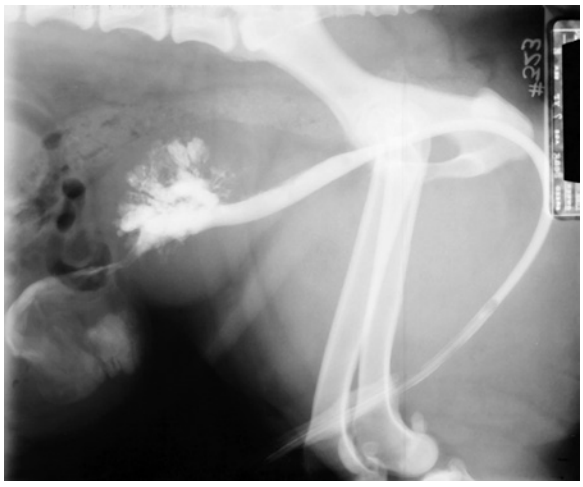


FIG 42.6
Contrast cystourethrogram in a male dog with severe prostatitis, which is evident because of the enlarged prostate and extravasation of contrast material into the prostatic parenchyma.

q24h), can be used to help decrease the size and secretions from the prostate. Prostatic abscesses may need to be addressed surgically, and omentalization of the prostatic abscess is often performed to prevent fluid and purulent material from accumulating in the area. Ultrasonography-guided drainage of the prostatic cyst can also be carried out, but this may need to be repeated several times and is usually more effective for small cysts.

Suggested Readings

Johnson JR, et al. Identification of urovirulence traits in *Escherichia coli* by comparison of urinary and rectal *E. coli* isolates from dogs with urinary tract infection. *J Clin Microbiol*. 2003;41:337.

Ling GV, et al. Interrelations of organism prevalence, specimen collection method, and host age, sex, and breed among 8,354 canine urinary tract infections (1969-1995). *J Vet Intern Med*. 2001;15:341.

Ling GV. Therapeutic strategies involving antimicrobial treatment of the canine urinary tract. *J Am Vet Med Assoc*. 1984;185:1162.

Litster A, et al. Occult bacterial lower urinary tract infections in cats—urinalysis and culture findings. *Vet Microbiol*. 2009;136:130.

McGuire NC, et al. Detection of occult urinary tract infections in dogs with diabetes mellitus. *J Am Anim Hosp Assoc*. 2002;38:541.

Merkel, et al. Clinicopathologic and microbiologic findings associated with emphysematous cystitis in 27 dogs JAAHA. Sept 11 2017.

Passmore CA, et al. Efficacy and safety of cefovecin (Convenia) for the treatment of urinary tract infections in dogs. *J Small Anim Pract*. 2007;48:139.

Puchot ML, et al. Subclinical bacteriuria in cats: prevalence, findings on contemporaneous urinalyses and clinical risk factors. Jan 1 JFMS 2017.

Segev, et al. Evaluation of the live biotherapeutic product, asymptomatic bacteriuria Escherichia coli 2-12 in healthy dogs and dogs with clinical recurrent UTI. JVIM In press. 2017.

Seguin MA, et al. Persistent urinary tract infections and reinfections in 100 dogs (1989-1999). *J Vet Intern Med*. 2003;17:622.

Sycamore KF, et al. Comparison of urine and bladder or urethral mucosal biopsy culture obtained by transurethral cystoscopy in dogs with chronic lower urinary tract disease: 41 cases (2001to 2011). *J Small Anim Pract*. 2014;55(7):364–368.

Tivapasi MT, et al. Diagnostic utility and cost-effectiveness of reflex bacterial culture for the detection of urinary tract infection in dogs with low urine specific gravity. *Vet Clin Pathol*. 2009;38:337.

Wagenlehner FM, et al. Emergence of antibiotic resistance and prudent use of antibiotic therapy in nosocomially acquired urinary tract infections. *Int J Antimicrob Agents*. 2004;23(suppl 1):S24.

Weese JS, et al. Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats: antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *Vet Med Int*. 2011;1:2011.

Westropp JL, et al. Evaluation of the efficacy and safety of high-dose, short-duration enrofloxacin treatment regimen for uncomplicated urinary tract infections in dogs. *J Vet Intern Med*. 2012;26:506.

CHAPTER 43

Canine and Feline Urolithiasis



INTRODUCTION

Urolithiasis is a common urinary tract disorder of dogs and cats. Clinical signs of urolithiasis are variable, depending on the location of the urolith. Pollakiuria, stranguria, dysuria, and hematuria may be noted by owners and suggest a problem in the lower urinary tract of their cat or dog. Clinical signs in cats and dogs with upper urinary tract uroliths are variable and can include hematuria or clinical signs compatible with acute kidney injury secondary to ureteral obstruction; ureterolithiasis may also be an incidental finding.

The most common uroliths in dogs and cats, calcium oxalate (CaOx) and struvite, are radiodense and can usually easily be identified on plain radiography. Cystine and urate uroliths are less radiodense, and contrast cystourethrograms or ultrasonography are often required to identify these stones. Although ultrasonography is a sensitive diagnostic for bladder and proximal urethral uroliths (Fig. 43.1), it is not a good imaging modality for visualizing the entire urethra of male dogs and cats, and urethroliths could be missed if abdominal radiography is not performed. It is important to position the animal's legs properly to obtain diagnostic images of the lower urinary tract (Fig. 43.2). Although ultrasonography does limit exposure to radiation, the size of the stone may be more accurately predicted by radiography. Furthermore, radioopacity can be determined. This information is clinically relevant when developing surgical and minimally invasive strategies for urolith removal.

Urolithiasis as well as other lower urinary tract disorders (e.g., neoplasia, granulomatous urethritis, urethral foreign body, obstructive feline idiopathic cystitis [FIC], functional urethral outflow tract obstruction) can result in urethral obstruction. Obstruction with urethroliths is more common in male dogs because of their longer, narrower urethra. Uroliths will often obstruct the area of the pelvic urethra or become lodged at the base of the os penis. Managing a urethral obstruction is described in Chapter 44; the principles described in that section are similar for dogs.

PRINCIPLES OF STONE ANALYSIS

Stones can be analyzed by a variety of methods. Calculi submitted to the Gerald V. Ling Urinary Stone Analysis Laboratory at the University of California at Davis (http://www.vetmed.ucdavis.edu/usal/index.cfm) are analyzed by quantitative crystallographic analysis primarily with the oil immersion method of optical crystallography using polarized light microscopy. In addition to optical crystallography, infrared spectroscopy (IR) is routinely used to process all calculus specimens suspected of containing uric acid crystals and/or salts of uric acid crystals to determine the presence of xanthine, hypoxanthine, allopurinol, or oxypurinol, a metabolite of allopurinol, which may be present in the specimens. Polarized light microscopy alone is insufficient to identify these metabolites. Other advanced analytic techniques (e.g., microprobe analysis, X-ray diffractometry) are available for certain stones if the mineral composition is not well identified with optical crystallography or IR. The author recommends that stones removed from animals be submitted to a veterinary stone analysis laboratory in order to help properly tailor the best management strategies and track research trends.

STONE REMOVAL

A consensus statement regarding the most common uroliths in small animals has been recently published (Lulich et al., 2016), and the reader is referred to that statement for additional details regarding upper and lower urinary tract urolithiasis and minimally invasive stone removal techniques. The panel agreed that minimally invasive stone removal should be discussed with all clients if clinically appropriate and available in one's area. These include laparoscopic-assisted cystostomy, percutaneous cystolithotomy, voiding urohydropropulsion (VUH) (Video 43.1), basket retrieval of a stone via the cystoscope (Fig. 43.3; Video 43.2), and holmium:YAG laser lithotripsy (Fig. 43.4; Video 43.3). Some uroliths such as struvite, urate, and cystine may be amenable to medical dissolution. Although protocols for dissolution of struvite uroliths in cats and dogs can be successful, protocols for dissolution of suspected urate and cystine stones are

often not as rewarding but can be attempted. It is important when attempting to dissolve struvite stones in dogs, in addition to dietary therapy (see later), to use appropriate antimicrobial therapy as well.

VUH can be performed when small calculi are present in the bladder (Fig. 43.5). The urolith size and shape, as well as the size of the dog or cat, need to be assessed; smoother stones generally pass through the smallest diameter of the urethra easier than those with irregular surfaces. Large uroliths can be removed more easily from larger dogs, although the procedure can be more cumbersome. To perform a VUH, the dog or cat should be anesthetized to help prevent increased urethral pressure and facilitate easier bladder expressions. A urinary catheter is then inserted into the bladder, and the bladder should be distended with sterile saline. The bladder should feel full but not so taut that bladder rupture could occur. With the catheter still in place, the animal should be held upright so that the vertebral column is vertical, and the bladder should be agitated to help promote movement of the stones into the bladder neck. As soon as the catheter is removed, the clinician should express the bladder to create a forceful stream and collect the voided contents. When expressing the bladder, the palm of the hand (not the fingertips) should be used to help prevent trauma to the bladder. Several voids may be required to remove all the stones and stone debris present. Hematuria

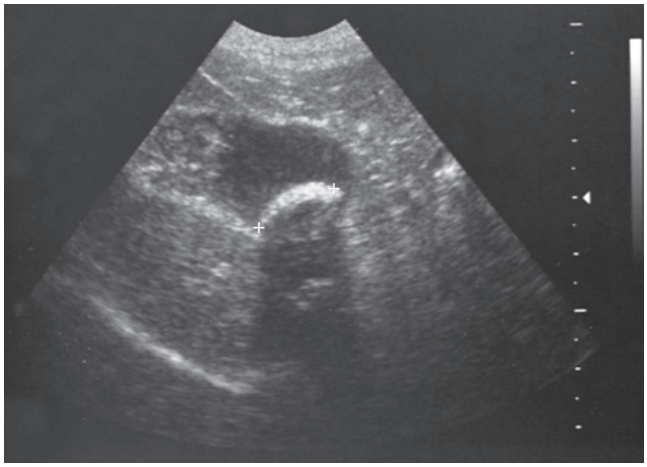


FIG 43.1
Ultrasonogram of a large cystolith in the bladder of a dog. Note the intense shadowing produced by the urolith.

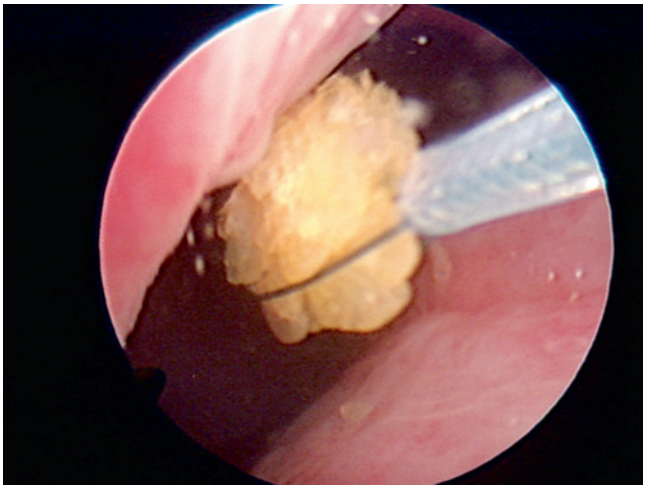


FIG 43.3
Cystoscopic view of basket retrieval of a CaOx stone from a female dog.

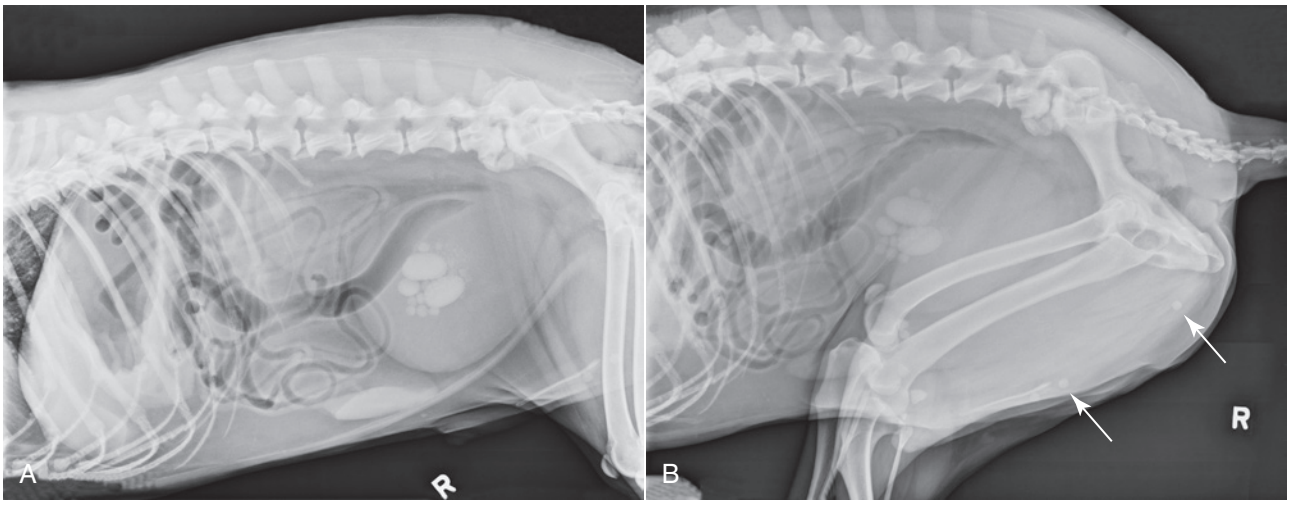


FIG 43.2
(A) Lateral abdominal radiograph of a male dog with multiple cystoliths. **(B)** The same dog, but this radiograph illustrates the importance of proper leg position to fully evaluate the urethra. The urethroliths *(arrows)* are not easily identified if the legs are not pulled forward to move the fabellae and the dog is positioned to include the perineal area.

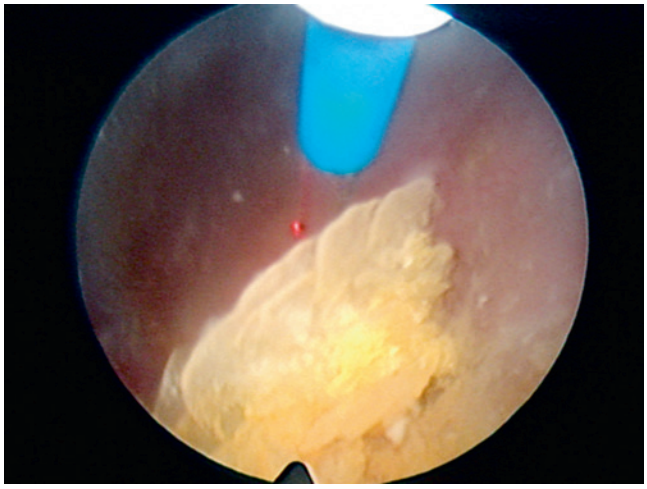


FIG 43.4
Cystoscopic view of a holmium:YAG laser inserted through the scope to fractionate larger cystic calculi for minimally invasive stone removal. All uroliths have been reported to fractionate in vitro.



FIG 43.5
Dog positioned for VUH. Although this dog also had a cystoscopy, a catheter can be used to fill the bladder with sterile saline before lifting the dog and expressing the bladder, as shown.

can result from this procedure but usually resolves within 24 hours.

Holmium:YAG laser lithotripsy has become widely available at referral institutions and uses laser energy to fragment stones. After fragmentation, the pieces can be removed using a basket inserted through the cystoscope and VUH for the smaller pieces that remain.

CALCIUM OXALATE CALCULI

Etiology

CaOx is the most common urolith from dogs submitted to several veterinary stone laboratories. They appear to be more common in older, castrated male dogs; small-breed dogs such as the Bichon Frise, Miniature Schnauzer, Pomeranian, Cairn terrier, and Maltese are at higher risk for CaOx urolith formation. The Keeshond has also been reported to have a higher risk for forming CaOx uroliths, which may be linked to its genetic predisposition for primary hyperparathyroidism causing hypercalcemia and hypercalciuria. Dogs with CaOx have been reported to have a higher body condition score than dogs without CaOx in a recent study.

CaOx is also the most common urolith removed cats. The most common location for CaOx in both species is the bladder, however, a significant increase in the number of upper urinary tract calculi (kidneys and ureters) was found for CaOx-containing calculi in the cat. Usually when upper tract calculi are seen on abdominal radiographs in cats, they primarily contain CaOx.

Unfortunately, there is a lack of published studies in cats to document specific risk factors for CaOx. There are likely intrinsic and extrinsic factors that predispose certain cats to form CaOx, including breed, age, and environment. Himalayan and Persian cats have been reported to have a higher relative risk for CaOx-containing uroliths. Male cats appear to be predisposed to CaOx urolithiasis. Stress-related events and obesity have not been critically evaluated in cats with urolithiasis, but some hypothesize that they may contribute to stone formation in some cats. Studies evaluating urolithiasis in human beings have supported a relationship among increased body weight, body mass index, waist circumference, and kidney stones. Furthermore, some studies have suggested that stressful life events can result in more clinical events of urinary stone disease in humans. Studies of body mass index, body weight, and environmental stressors as related to urinary stone disease are warranted in cats to see if any relationship exists.

URETEROLITHIASIS IN DOGS AND CATS

Struvite-, CaOx-, urate-, and cystine-containing calculi have been reported to occur in the upper urinary tract of dogs. Renal and ureteral struvite uroliths in dogs are generally associated with infection, and dissolution can be attempted, as long as the dog is stable. Surgical or interventional procedures may be required if the dog has complete ureteral obstruction (see later).

Most ureter and nephroliths in cats are composed primarily of CaOx, sometimes mixed with calcium phosphate or urate, but struvite renal and ureterolithiasis is not reported in the cat in recent literature. The increased incidence of CaOx-containing ureterolithiasis in cats may be associated with increased prevalence of CaOx ureterolithiasis, increased awareness of ureterolithiasis, and/or increased use of

diagnostic imaging in cats with renal disease. Ureterolithiasis tends to develop in middle-aged to older cats, with a median age of 7 years at the time of diagnosis.

Although reported less often, other causes of ureteral obstruction can include soft tissue plugs, which sometimes contain flakes of mineralized material, inflammatory debris in cats with pyelonephritis, and calculi composed of 100% dried solidified blood (DSB). In cats with a chronic upper tract urolithiasis, in which calculi have passed previously, it is relatively common for significant ureteral inflammation and/or stricture to develop, further decreasing the luminal diameter through which material can pass. This can lead to an even higher risk for the development of ureteral obstruction with minerals, whereby debris that would pass in a normal ureter leads to obstruction.

CLINICAL SIGNS OF URETEROLITHIASIS

Because ureterolithiasis is much more common in cats compared with dogs, the discussion will focus on this species, but principles of therapy can be applied to dogs, and the reader is referred to the consensus statement mentioned earlier for specific therapeutic intervention recommendations for each stone type in cats and dogs. Oftentimes, this requires an experienced operator and referral when ureteral obstruction is present.

The clinical signs associated with ureterolithiasis are variable and are often related to the rate at which ureteral obstruction develops; acute obstruction and rapid renal capsular distention in dogs and cats are often more painful compared with animals with more insidious obstructions. Nonspecific signs can include decreased appetite, weight loss, lethargy, and hiding. Cats may also present with hematuria, without concurrent lower urinary tract signs, such as stranguria, pollakiuria, and dysuria. When hematuria alone is noted in a cat without concurrent lower urinary tract signs, evaluation for renal and/or ureteroliths is warranted. Depending on the degree of renal compromise, preexisting before obstruction or secondary to obstruction, many cats have clinical signs associated with azotemia. The author routinely screens azotemic cats with some imaging modality to evaluate for the presence or absence of nephron- or ureterolithiasis.

Some cats with ureteral obstruction may not exhibit any clinical signs, and it is therefore relatively common to diagnose a chronic ureteral obstruction as an incidental finding. One example of this is the so-called big kidney, little kidney syndrome noted most commonly in cats (Fig. 43.6). This is a phrase used to describe cats with bilateral ureteral obstruction, whereby one kidney had a prior obstruction that led to a nonfunctional or minimally functional small kidney caused by a previous ureteral obstruction and the other kidney becomes hydronephrotic because of an acute ureteral obstruction. In many cases the initial obstructing event goes unnoticed by the owner because clinical signs are not evident until the cat develops azotemia, an elevation of blood urea nitrogen (BUN) and serum creatinine concentrations.



FIG 43.6
Struvite uroliths that were removed from a dog.

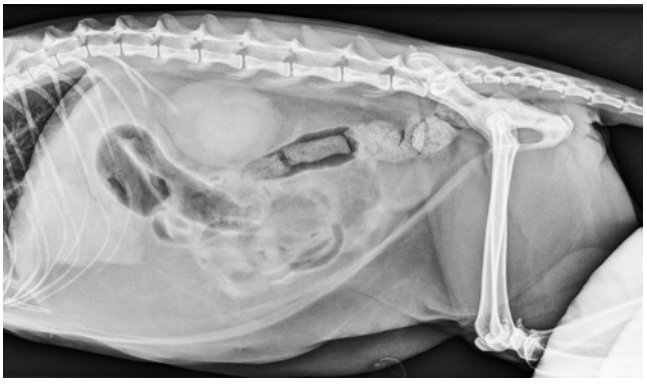


FIG 43.7
Lateral radiograph of a cat that illustrates the so-called big kidney, little kidney syndrome. The smaller kidney is superimposed over the larger kidney in this projection.

DIAGNOSTIC IMAGING

Diagnostic imaging of the abdomen should be performed in all dogs and cats with azotemia. CaOx- and struvite-containing calculi are radiopaque and, if present, can often be visualized on plain abdominal radiography (Fig. 43.7). In dogs, struvite calculi may have a staghorn appearance as the mineral dissects into the renal calices.

The sensitivity of survey abdominal radiography for the diagnosis of ureterolithiasis in cats is 81%. CaOx-containing ureteral calculi are most readily identified in the retroperitoneal area on the lateral radiographic projection; however, visibility on lateral radiographs alone can lead to difficulty in determining which ureter is involved or whether one or both ureters are affected. Therefore abdominal ultrasonography is recommended for cats suspected of having ureteroliths; it has a sensitivity of 77%. Although this is lower than

plain radiography, ultrasonography can help delineate which ureter is obstructed and the severity of hydronephrosis and hydroureter that may be present. A combination of survey radiography and ultrasonography has a sensitivity of 90% for the diagnosis of ureterolithiasis, so it is the preferred approach. In subacute ureteral obstructions, ureteral and pelvic dilation may have not yet developed, so it is critical to consider ureteral obstruction as a differential diagnosis in appropriate cases, even when dilation is not present. Additional imaging modalities, such as antegrade pyelography or computed tomography (CT), are usually not necessary, and interventional procedures are recommended if obstruction is present.

MEDICAL TREATMENT

As mentioned previously, dissolution of suspected struvite, urate, and cystine calculi can be attempted in stable animals (as mentioned previously, these mineral types can occur in the upper tract of dogs) without complete ureteral obstruction. There is no dissolution protocol for CaOx calculi, which is the most common calculi identified in the upper urinary tract of cats and can certainly occur in dogs. Conservative medical management for cats with minimal or no renal compromise can be attempted. Although there are no studies to evaluate the efficacy of any of the treatments mentioned in cats and dogs, most experienced clinicians agree that expulsive therapy may play a role in the management of this disease in stable patients. Suggested therapies can include intravenous fluid diuresis with the administration of the diuretic mannitol, with or without other drug therapies.

In humans with ureterolithiasis, the α-adrenergic antagonist tamsulosin is often used, with favorable outcome, particularly when calculi are in the distal third of the ureter. This and other α-antagonists, such as phenoxybenzamine and prazosin, have been anecdotally used in cats with variable responses. In one report, amitriptyline, a tricyclic antidepressant, was shown to facilitate the passage of urethral plugs in cats. Further studies evaluating ureteral tissue from rats, pigs, and humans found that amitriptyline inhibits smooth muscle contractions, suggesting it might be a useful therapy for ureteral obstruction in cats. Analgesic therapy such as buprenorphine should also be used to prevent ureteral "spasm," which could prevent ureterolith movement.

During conservative management, it is crucial to critically evaluate the cat's stability and fluid status. Animals should be monitored by serial measurements of serum creatinine (and possibly SDMA) because this is often the best clinicopathologic indicator currently available that the obstruction has improved or progressed. Body weight should be assessed at least twice daily to be certain the animal is not becoming overhydrated. It is important to remember that, if significant intrinsic renal damage has occurred, passage of ureteral obstruction does not always lead to immediate improvement in azotemia. In cats with severe kidney disease before obstruction, azotemia may persist. Serial radiography and ultrasonography can be useful for monitoring the success of medical management for ureterolithiasis.

The 12-month survival rate after medical treatment of 52 cats with ureteral obstruction was 66%. However, 32% of these cats did not respond to medical therapy and were euthanized or died within 1 month of diagnosis. Large case series evaluating dogs with ureteral obstructions are not published, likely because this disease is more common in the cat. If azotemia or pyelonephritis is present, surgery or minimally invasive techniques (e.g., ureteral stents) for the restoration of urine flow should be considered. Cats with marked hyperkalemia or fluid overload at the time of initial examination may benefit from aggressive medical management, such as hemodialysis.

SURGICAL INTERVENTION FOR TREATMENT OF URETERAL CALCULI

In cats and dogs, the optimal time for medical management before making a decision to pursue surgery has not been determined, and the improvement in renal function after stone removal is variable. However, early intervention with surgical or minimally invasive procedures is likely indicated in an effort to maintain functional kidneys. Surgical removal of ureteral calculi can be considered when there is evidence of partial or complete ureteral obstruction. The number of stones, degree of obstruction, operator experience, and availability of appropriate equipment should all be considered when deciding whether to proceed with ureterotomy, stent, or subcutaneous ureteral bypass (SUB). Ureterotomy may be preferred when only a single calculus is identified, but the latter two minimally invasive procedures are more often performed for a variety of reasons. Major factors determining the recovery of renal function after reestablishing ureteral patency include the degree of renal dysfunction before the development of the obstruction and the duration and extent of the obstruction. Ureteral strictures secondary to scar tissue formation can also form at the ureterotomy site, leading to reobstruction; these complications are much less likely to occur when ureteral stenting or SUBs is performed. When a subset of cats with ureteral obstruction was followed after surgical intervention, 14 of 35 (40%) had recurrent episodes of ureterolithiasis.

Ureteral stents and subcutaneous ureteral bypass

Placement of ureteral stents or SUB is being performed as the treatment of choice for ureteral obstruction in cats, particularly if there are multiple ureteroliths. Evidence suggests that these less invasive procedures have lower morbidity and mortality rate for ureteral obstruction than do traditional surgical approaches in cats. A lower re-obstruction rate and decreased severity of azotemia have been associated with stent placement. A skilled operator is necessary for these referral procedures. Attempts to place these stents using a retrograde cystoscopic approach have been made but have been largely unsuccessful in cats; however, this technique can be used for many dogs. In cats, a relatively minimally invasive surgical placement is used (Video 43.4), whereby the surgeon performs a laparotomy and places the stent from the kidney and into the bladder using a coaxial

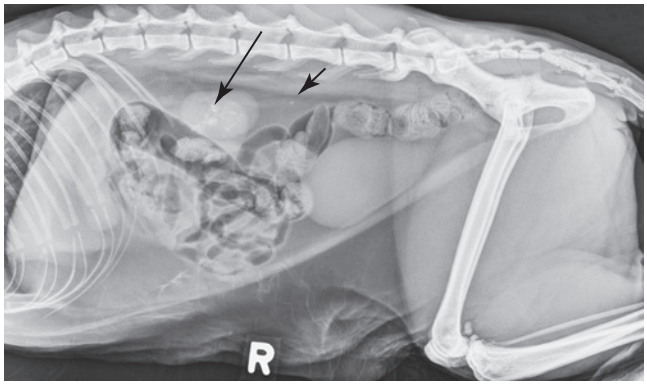


FIG 43.8
Lateral radiograph of a 5-year-old female spayed cat illustrating the multiple renal *(large arrow)* and ureteral calculi *(small arrow)* that are present. Ultrasound is often complimentary to ascertain which ureter is obstructed and to define the degree of obstruction. Ideally, subsequent radiographs should be taken after the pet has defecated in order to fully visualize the retroperitoneal area.

technique. In most cases a needle puncture in the kidney and the cystotomy are the only incisions in the urinary system. After initial placement, urine should flow through the stent lumen, and over time, ureteral dilation develops passively around the stent, allowing further passage of urine, crystals, and possibly stones around the stent (Fig. 43.8). Stents are typically left in place long term unless it becomes contraindicated because of infection or patient discomfort.

SUB was developed an alternative to ureteral stent placement and is preferred by some operators. With this technique, the placement of a nephrostomy and cystotomy tubes that sit subcutaneously are connected at a subcutaneous access port so the system can be flushed if needed. Urine can then bypass the obstructed ureter and be excreted in the bladder in a normal fashion.

Long-term management of cats with ureteral and renal CaOx calculi are similar to those with lower urinary tract CaOx calculi, except that the degree of kidney disease also needs to be considered when choosing dietary and drug therapies. High-sodium diets should be avoided in cats with renal compromise and in those with hypertension. If animals have stage II chronic kidney disease or higher, "renal diets" (i.e., those lower in phosphorus and protein) are recommended.

Prevention of Calcium Oxalate Urolithiasis

Prevention of CaOx-containing calculi is similar for cats and dogs. An outline for the management of CaOx uroliths is presented in Box 43.1.

Dietary modifications

Once a urolith has been removed, it is recommended to increase the moisture content in the diet by feeding a canned diet, if possible, to decrease the urine concentration of stone mineral precursors. See Box 43.2 for recommendations on increasing dietary moisture intake. There is no dissolution protocol for CaOx uroliths, so removal and quantitative mineral analysis of the stones should be performed if they are growing or causing clinical disease. Patient-related factors should be addressed on presentation to ascertain that no potential predisposing factors are present (e.g., hypercalcemia, obesity, other systemic disorders) and

BOX 43.1

Calcium Oxalate Stone Management for Lower Urinary Urolithiasis

1. Remove all uroliths; obtain radiographs to be certain all uroliths have been removed.
2. Submit all uroliths for quantitative crystallographic analysis.
3. Evaluate a serum calcium concentration.
   - If high, pursue further diagnostics, such as an ionized calcium and parathyroid hormone (PTH) panel.
4. Consider evaluating serum triglyceride concentrations.
   - This is particularly important in predisposed breeds, such as Miniature Schnauzers, because it may influence selection of the diet for management.
5. Obtain thorough history, document physical examination, and record body weight and body condition score.
6. Select a diet.
   - Consider all comorbidities of the patient when selecting the diet.
   - High-moisture diets are best (i.e., canned food).
7. Evaluate the following approximately 1 month after the pet is consuming the selected diet well:
   - Radiographs and/or ultrasonography
   - Urinalysis
     - This should be evaluated in-house, because in vitro crystalluria can occur within hours of collection. Refrigeration will exacerbate this artifact.
     - As a guideline, keep the urine specific gravity (USG) consistent, <1.020 in a dog and <1.025 in a cat. USG can be monitored using samples collected from the pet in the home environment.
     - Adjust moisture content or diet selected, depending on urine USG.
     - *Note:* Do not add salt or choose a higher-sodium diet if the dog or cat has kidney disease, is hypertensive, has congestive heart failure, or is hypernatremic.
     - Urine pH—CaOx solubility varies little in ranges of physiologic pH, but acidification may be a risk factor.
8. For animals with recurrent CaOx urolithiasis, consider the addition of hydrochlorothiazide, 2 mg/kg PO q12h for dogs and 1 mg/kg PO q12h for cats.
   - Evaluate serum calcium concentration 1 week after therapy to ensure hypercalcemia is not present.
   - Review and alter dietary strategy as needed.
9. For recurrent CaOx urolithiasis, potassium citrate may also be used, 50-75 mg/kg PO q12h (adjust dosage based on clinical response), which will help chelate calcium and alkalinize the urine.

BOX 43.2

Guidelines for Increasing Dietary Moisture

1. Try feeding the canned formulation of the desired diet if possible.
   - Feeding a high-moisture diet (>75% moisture) is ideal. Canned formulations of diets are the easiest way to achieve this in some animals.
   - Providing a choice of canned and dry foods for cats is recommended because an abrupt change in diet is usually not well tolerated.
2. If this is not practical, begin adding water to the dry diet:
   - Begin with 1 cup of water/cup of dry food.
   - Gradually increase the water content over 3-4 weeks.
   - Ideally, 3-4 cups of water/cup of dry food is recommended (≈70% moisture).
   - Evaluate the urine specific gravity (USG) and urine sediment periodically; free-catch urine collected in the home environment is ideal for this.
3. Adjust moisture intake or consider the addition of salt if necessary.

need to be addressed concurrently. After using strategies to increase the moisture content of the diet, if the urine is still too concentrated or the urine sediment findings remain abnormal, one can try the addition of sodium chloride (table salt) to the diet to increase the urine volume produced daily, unless the patients are hypertensive or have cardiovascular problems or renal disease. Feeding higher-sodium diets (>375 mg/100 kcal) dry foods should not a substitute for feeding a high moisture food but can be considered in dogs and cats where urine dilution is not achieved and recurrence of CaOx is of concern.

There are several diets marketed for CaOx prevention in cats and dogs, but studies on their efficacy are limited. Home-cooked diets can also be an option for some dogs and cats, particularly those with multiple comorbid conditions that need to be managed concurrently. A consultation with a veterinary nutritionist is recommend in these cases, and the readers are encouraged to consult with nutritionists for the most up-to-date marketed diets for stone prevention. Diets for CaOx prevention should not be restricted in calcium, because this could increase the absorption of intestinal oxalate. Excess calcium and oxalate intake should also be avoided. High-moisture, lower-calorie, low-oxalate treats can also be a good option for owners who wish to provide treats for their pet (see www.ohf.org/docs/Oxalate2008.pdf for approximate oxalate contents of many human foods). The list can be reviewed with the client, and foods such as raisins, grapes, and other toxic foods listed that are contraindicated for pets should be discussed with the owner.

Other nutrients to consider in the dietary management of CaOx urolithiasis include magnesium and phosphorus. Urinary magnesium, phosphate, and citrate are thought to act as inhibitors of CaOx urolith formation and therefore should not be restricted in the diet. Dietary phosphorus should not be excessively restricted because it could lead to increased activation of vitamin D_3 to calcitriol by 1α-hydroxylase in the kidney under the action of parathyroid hormone (PTH) and result in increased intestinal absorption of calcium. Finally, dietary fats have been speculated to be involved in CaOx stone formation in rats and humans. Although the pathogenesis of spontaneous CaOx stone formation in animals may differ, it may be prudent to feed animals with hypertriglyceridemia a diet restricted in fat (<2 g/100-kcal diet). When choosing a diet, the animal's entire history, physical examination (including body condition score), and medical conditions need to be considered.

Drug therapy

If dietary manipulations alone are unsuccessful in preventing CaOx urolith recurrence, drug therapy may provide additional benefit. The administration of hydrochlorothiazide (2 mg/kg orally [PO] q12h for dogs; 1 mg/kg PO q12h for cats) can be attempted because this may decrease urinary calcium excretion. Serum calcium concentration should be evaluated shortly after beginning this agent to ensure that hypercalcemia does not occur. Although there are no studies about the efficacy of hydrochlorothiazide in cats with CaOx stones, reports have suggested that this dosage is well tolerated and reduces the relative supersaturation of CaOx in healthy cats. Also, citrate as potassium citrate (50-75 mg/kg PO q12h for cats or dogs) may be helpful because the citrate can complex with calcium, thereby decreasing the urinary concentration of CaOx and alkalinizing the urine.

Struvite Stone Management

For dogs

Struvite uroliths occur more commonly in female dogs compared with male dogs. They are usually larger than CaOx and often smooth in shape (Fig. 43.9). In dogs, unlike cats, almost all struvite calculi are infection-induced, usually by *Staphylococcus intermedius* or, less commonly, by *Proteus mirabilis*. These bacteria have the ability to hydrolyze urea to form ammonia and carbon dioxide. This reaction increases the urine pH and makes ammonium available to form magnesium ammonium phosphate crystals. Occasionally the urine can be supersaturated with the minerals that comprise struvite uroliths, and stone formation can occur without an infection present. If a urine culture is negative in a dog with struvite uroliths, the stone and/or bladder mucosa can also be cultured to be certain that a bacterial pathogen is not present. Dissolution of canine struvite uroliths can be done in the same manner as described for cats (see later), but proper antimicrobials, based on minimum inhibitory concentration (MIC) testing results, should also be administered. By convention, these antimicrobials have been administered throughout the duration of the dissolution protocol. No studies have been performed to see if this duration of antimicrobial therapy is warranted, and shorter courses may be considered. Three diets are currently marketed for struvite dissolution in dogs (Royal Canin Canine



FIG 43.9
Ventrodorsal radiograph of a 7-year-old female spayed cat that required ureteral stent placement for ureteral obstruction. The stent is placed so the coils of the stent are in the renal pelvis and the urinary bladder.

Veterinary S/O, Royal Canin USA, St. Charles, MO; Hill's Prescription Veterinary Diet Canine s/d, Hill's Pet Nutrition, Topeka, KS; and Purina UR Veterinary St/Ox). Struvite dissolution can be attempted so long as the cystic calculi is not so large it is causing urethral obstruction or it encompasses the entire urinary bladder and therefore the "medicated" urine cannot adequately bathe the stone for proper dissolution. Furthermore, if the dog's clinical signs cannot be adequately controlled with diet and antimicrobials, dissolution should be discontinued. The dog should be rechecked in 3 to 4 weeks; if the uroliths have not decreased in size at that time, and owner compliance with the diet trial is good, the stone may have layers of calcium phosphate in the form of apatite or may not contain struvite. However, if clinical signs are well controlled and the stones appear diminished in size, it is advised to continue dissolution, as some larger stones can take longer (months) for dissolution. No published studies in dogs regarding struvite dissolution have currently been published, but some are underway at the time of this writing.

To prevent the recurrence of infection-induced struvite stones in dogs, treatment should be focused on preventing future urinary tract infections (UTIs). No dietary changes are indicated, but urine cultures and periodic radiographs should be assessed as clinically indicated. The dog should be treated with the proper antimicrobial; long-term therapy is usually not required in dogs with uncomplicated infections. For management of recurrent UTIs in dogs, see Chapter 45.

For cats

Determining whether a cat has a struvite urolith is more difficult than in dogs because the uroliths are not caused by bacterial infections. Struvite uroliths are usually larger and can occur as a single, often elliptical calculus, whereas CaOx are often smaller, multiple calculi. Although radiodense, they are often not as "bright" as CaOx on plain radiography. The clinician can attempt to dissolve the urolith(s) by feeding a calculolytic diet (e.g., Royal Canin Feline Veterinary S/O or Hill's Prescription Veterinary Diet s/d, Purina UR St/ox) and monitoring the urolith size with radiography. Because calculolysis usually occurs within 1 month (and can be as soon as 8-10 days based on published data), abdominal radiographs should be evaluated 2 to 3 weeks after the cat has fully adjusted to the dissolution diet. If the urolith(s) appears smaller, the urine is dilute (specific gravity < 1.016), and the pH appropriate (at least <6.5), the diet can be continued and the cat reevaluated in 3 to 4 weeks. If the urolith is not smaller with dietary intervention, the owner should be questioned regarding other food and treats the cat is receiving. If the urine pH and specific gravity are not in the desired range with the calculolytic diet chosen, owner compliance should be questioned. If compliance was good, then the stone likely contains other minerals. For both cats and dogs, contraindications to attempting dissolution for suspected struvite urolithiasis include urethroliths that are causing obstruction, or if the animals' clinical signs are severe, immediate removal may be necessary. In many cases, analgesic therapy can be provided initially to improve the animal's comfort as the dissolution protocol is started.

To help prevent the recurrence of struvite urolithiasis in cats, a high-moisture diet that produces a urine pH less than 6.8 is advised; veterinary diets are marketed for struvite prevention, which in many cases are the same as those marketed for CaOx prevention. Many of these diets are formulated to produce a urine pH that is below the relative supersaturation level for struvite, but they are not highly acidifying. The moisture intake of the cat can be evaluated by periodically assessing the urine specific gravity. Abdominal radiographs, including the entire urinary tract, should be performed to assess for new urolith formation. If no uroliths are present, radiography should be repeated periodically (every 2-3 months initially, then less often as the disease is managed). If small uroliths recur, VUH may be an option for stone removal.

URATE UROLITHIASIS IN DOGS

Etiology

Urate-containing calculi have comprised approximately 25% of the stones analyzed at our laboratory each year from dogs; other data show that 6.4% of canine uroliths were classified as purines when at least 70% of the stone consisted of purine mineral. Unlike most other breeds of dogs, Dalmatian dogs have a well-described alteration in purine metabolism

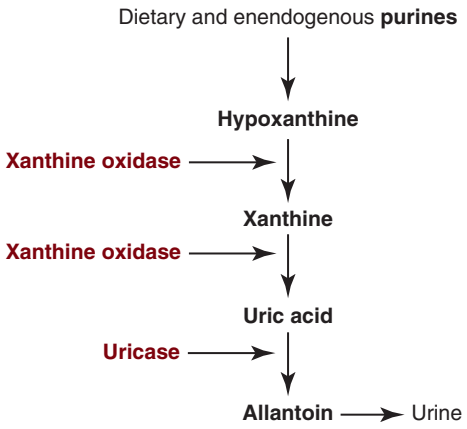


FIG 43.10
Purine metabolism in animals. Most dogs excrete the soluble product, allantoin, in the urine. Because of genetic abnormalities, Dalmatians and other breeds with the *SLC2A9* genetic mutation have larger of amounts of uric acid excreted in the urine, which may predispose them to form urate uroliths.

that leads to the excretion of uric acid in the urine rather than excretion of the more soluble metabolite, allantoin (Fig. 43.10). All Dalmatians excrete relatively high amounts of uric acid (400-600 mg of uric acid/day compared with 10-60 mg/day in non–Dalmatian dogs); however, not all Dalmatians form urate uroliths. Genetic studies have reported that the mode of inheritance is not X-linked, and the prevalence of the clinical disease in male Dalmatians ranges from 26% to 34%. Bannasch et al. (2008) identified the SLC2A9 transporter as the cause of the change in uric acid handling by Dalmatians by positional cloning using an interbreed backcross. Other breeds such as the English Bulldog and Black Russian Terrier were also homozygous for the same mutation. For a list of other predisposed breeds and information on DNA testing to help owners and breeders identify affected and carrier dogs, see http://www.vgl.ucdavis.edu/services/Hyperuricosuria.php.

Urate Urolithiasis Management

Dissolution of urate urolithiasis has been described in a small case series; a low-protein diet and allopurinol (15 mg/kg PO q 12 hr) were administered. This can be considered in dogs if obstruction is not evident. Success rates are quite variable. The prevention of urate urolithiasis in dogs with genetic hyperurocosuria such as the Dalmatian is shown in Box 43.3. A diet low in purines is recommended. This can be accomplished by feeding a diet low in protein; however, diets higher in protein and low in purines are another alternative. A recent pilot study suggested that a diet higher in protein (with added water) but low in purines was beneficial in maintaining a low urinary uric acid excretion in dogs with a history of urate urolithiasis and genetic hyperuricosuria. Vegetarian diets have also been described for use in these breeds for the management of urate urolithiasis recurrence. Ammonium urate is more soluble in alkaline urine, and these diets described should produce a urine pH higher than 7.0. Potassium citrate can be added to help alkalinize the urine in dogs with recurrent urate uroliths if the desired urinary pH is not achieved with dietary therapy alone. As with any animal that forms uroliths, the diet should be high in moisture.

If dietary strategies are not successful, allopurinol (5-7 mg/kg q12-24h), a xanthine oxidase inhibitor, can be considered. This drug will decrease the amount of uric acid formed in the urine. The exact dosage is variable, and studies have shown that the metabolism of this drug varies from dog to dog. Ideally, the amount given should be titrated based on 24-hour urine uric acid excretions, but this is rarely done in practice. Side effects of allopurinol can include

BOX 43.3

Management of Canine Urate Urolithiasis for Dogs With Genetic Hyperuricosuria

1. Can attempt urate urolith dissolution if urinary obstruction not present with a low-protein or low-purine diet and allopurinol. If unsuccessful, remove all uroliths and confirm via ultrasonography or contrast radiography.
2. Submit all uroliths for quantitative analysis as well as infrared spectroscopy, which are required to differentiate uric acid from its metabolites.
3. Select a diet appropriate for the dog, and consider all comorbid conditions that may be present. Diets marketed for urate prevention include the following:
   - Royal Canin Veterinary Diet Urinary U/C
   - Hill's Canine u/d
   - Vegetarian diets may also be acceptable
4. Evaluate the following approximately 1 month after the diet has been implemented:
   - Abdominal ultrasonography (urate uroliths have a low radiographic density)
   - Urinalysis
     - Aim for a target urine pH > 7.0, USG < 1.020, and inactive sediment.
     - If urine pH is not ideal, consider the addition of potassium citrate.
5. If recurrence is a problem, consider using allopurinol.
   - Do not use unless the animal is consuming a low-purine diet.
   - Begin a dosage of 5-7 mg/kg q12-24h
   - Ideally, the dosage should be titrated based on 24-hour urinary uric acid (UA) excretion.
     - If urinary UA < 300 mg/day, lower the allopurinol dose. If stones recur, analyze to be certain they are not xanthine. If xanthine formation occurs, stop or significantly lower dose of allopurinol
   - Adverse effects include xanthine stone formation and hepatotoxicity.
6. Monitor the dogs periodically with imaging and adjust the protocol as needed.

xanthine stone formation (particularly if the animal is not being fed a purine-restricted diet), gastrointestinal upset, and hepatotoxicity.

If urate-containing calculi are found in non–hyperuricosuric breeds, a search for an underlying portovascular anomaly, such as a portosystemic shunt (PSS), should be pursued. Urate uroliths have also rarely been reported from dogs with portal venous hypoplasia (PVH; also referred to as microvascular dysplasia). Dogs with underlying liver disorders are likely predisposed to urate urolith formation because of hyperammonuria and hyperuricosuria, which result from the reduced ability to convert ammonia to urea and uric acid to allantoin. Correction of the vascular disorder should be addressed, if possible, to help prevent urate recurrence. In patients with inoperable PSS or PVH, diets marketed for liver disease may be used to help decrease the urinary ammonium urate and help control any signs of hepatic encephalopathy. If a portovascular anomaly cannot be found, DNA testing for the hyperuricosuric genetic abnormality should be considered.

URATE UROLITHIASIS IN CATS

Etiology

After CaOx- and struvite-containing uroliths, urate uroliths are the third most common mineral type submitted to most stone laboratories from cats. There is no gender predilection for cats with urate urolithiasis; recurrence rates are variable. Specific breeds such as the Egyptian Mau and Siamese have been reported to be at higher risk. The pathophysiology of feline urate urolithiasis is largely unknown. Unlike dogs, genetic studies have not been published, and it is thought that most cats do not have underlying hepatic dysfunction such as a PSS. However, in one study, most cats seen by primary care veterinarians with urate urolithiasis did not have advanced diagnostic studies to investigate the presence of a PSS fully, but a normal physical examination, clinicopathologic findings, and no clinical signs (e.g., ptyalism, neurologic signs, lethargy) suggestive for a hepatopathy were present.

Urate Urolithiasis Management

In any cat that has been diagnosed with urate urolithiasis, a full complete blood count (CBC) and serum biochemical profile are warranted. If clinical signs and/or clinicopathologic abnormalities (e.g., microcytosis, high liver enzyme activities, abnormal liver function parameters) are suggestive for a hepatopathy or vascular anomaly, further diagnostic studies such as abdominal ultrasonography and measuring serum bile acid concentrations are recommended. If urate uroliths are diagnosed in a cat with no history, clinical signs, and clinicopathologic abnormalities suggestive for a hepatopathy, the costs of further tests can be discussed with the owner, because not all cats will require further evaluation. In older cats, further testing may not be necessary.

To prevent recurrence of urate uroliths in otherwise healthy cats, a high moisture diet that is restricted in protein is often recommended, such as those diets marketed for kidney disease (e.g., Hill's k/d; Royal Canin Renal LP; Purina NF Kidney Function, Purina, Vevey, Switzerland). Anecdotally, a commercially available hydrolyzed soy protein diet has been fed to these cats in hopes of providing an adequate protein intake with low purine content (Royal Canin Feline Hypoallergenic Hydrolyzed Adult HP). No evidence of the effectiveness of any of these approaches has been evaluated in controlled trials in cats with urate urolithiasis. As with all cases of urolithiasis, feeding a high-moisture diet is the cornerstone of urolith prevention management. Periodic imaging using ultrasonography—because urate can be difficult to see on plain radiography—is also important to monitor for recurrence.

CALCIUM PHOSPHATE CALCULI IN CATS AND DOGS

Apatite (calcium hydroxyl phosphate)-containing calculi in dogs is usually found as a so-called "tag-along mineral" because it usually is associated with struvite uroliths, either mixed throughout or as single layers. Apatite-containing uroliths are not very common in cats but can be seen in association with struvite, CaOx, or by themselves. Unlike brushite, apatite is generally less soluble in alkaline urine. Brushite (calcium hydrogen phosphate dihydrate) is another form of calcium phosphate that is much less common in dogs and very rare in cats. Brushite tends to occur as multiple small uroliths. Prevention measures for these uroliths in cats and dogs are unknown. Similar to CaOx management, a search for predisposing disorders that could result in hypercalcemia is recommended. Often it is recommended that the dog or cat be evaluated and managed similarly to those patients with CaOx uroliths. A high moisture diet that produces a neutral urinary pH is advised.

CYSTINE AND SILICA UROLITHIASIS IN CATS AND DOGS

Etiology and Management

Cystine- and silica-containing uroliths are uncommon in dogs and very rare in cats. They represented 1.3% and 6.6%, respectively, of all the canine uroliths we analyzed. Cystine urolithiasis is much more common in dogs compared with cats. Cystinuria in dogs results from a mutation in 1 of 2 genes, SLC3A1 (type I-A; autosomal recessive inheritance, and II-A; autosomal dominant inheritance) and SLC7A9 (type II-B; autosomal dominant inheritance), which encode subunits required for the dibasic amino acid transporter system that enables cystine reabsorption form the glomerular filtrate. Furthermore, an androgen dependent type III cystinuria has been reported in several breeds of intact male dogs. Cystine urolithiasis has also been reported more commonly in intact male dogs. Recently, a mutation in the SLC3A1 gene has also been reported in the cat.

Dietary management includes feeding a diet high in moisture and low in protein (e.g., Hill's Prescription Diet u/d®, Royal Canin Veterinary Diet® Urinary U/C™); or feeding

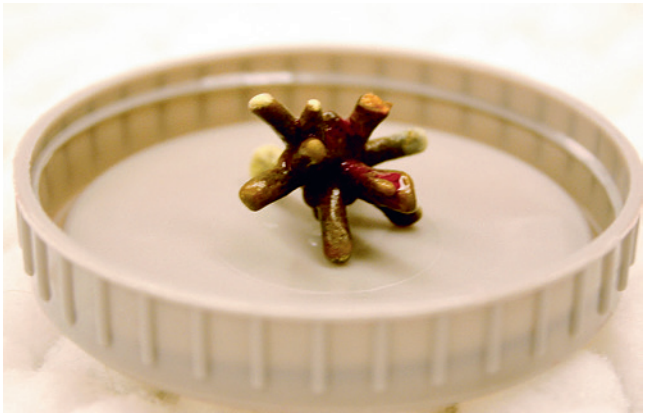


FIG 43.11
Silica urolith that was removed from a dog; note the characteristic "jack-like" appearance.



FIG 43.12
Characteristic appearance of dried solidified blood calculi that were removed from a cat.

a vegetarian-based diet. Cystine is more soluble in alkaline urine, and the recommended dietary therapy should result in a urine pH > 6.5 to 7.0. If the optimal urinary pH is not achieved in this manner, potassium citrate (starting dose of 50-75 mg/kg q12h) can be added to alkalinize the urine, because citrate salts serve as a source of bicarbonate. The drug, tiopronin (Thiola®, 2-MPG; 15-20 mg/kg PO q12h), can also be administered to help prevent (or possibly dissolve) cystine stones; however, this sulfhydryl compound can be cost prohibitive and limited in its availability. When using this medication, gastrointestinal and hematologic adverse effects can occur. Dogs and cats should be monitored with appropriate imaging studies to evaluate the effectiveness of the therapeutic approach. Due to the possible androgen-dependent cystinuria, if male intact dogs are diagnosed with cystine uroliths, castration is recommended.

Dogs with silica-containing uroliths are usually older, and most affected dogs are male. Most silica uroliths have a so-called jack stone appearance (Fig. 43.11), giving them a characteristic look on plain radiography. The recurrence rate of silica is not well known, but these uroliths are generally slow-growing. Dietary prevention strategies focus on providing a high-moisture diet that is higher in animal proteins and lower in plant origins, particularly rice, soybean hulls, and corn gluten feed.

DRIED SOLIDIFIED BLOOD CALCULI IN CATS

We have reported another urolith type called DSB calculi that we have only identified in cats. Although we have rarely noted small amounts of DSB on the surface of various canine stones, none of them was ever composed of 100% DSB, as in cats. DSB calculi can occur in various places in the upper and lower urinary tract. DSB calculi are very firm and "stone-like" but usually do not contain crystalline material (Fig. 43.12). Although these uroliths are not common, they can be a diagnostic challenge. They are generally radiolucent unless they contain a significant portion of CaOx, calcium phosphate, or other radiodense mineral. Furthermore, they can be difficult to identify on ultrasonographic examination. Management for the prevention of DSB includes evaluating the patient for underlying evidence of renal or lower urinary hematuria and increasing the moisture content of the diet.

XANTHINE UROLITHS

Xanthine uroliths are very rare in cats and dogs. The most common cause of xanthine urolithiasis in dogs is iatrogenic because of the administration of the xanthine oxidase inhibitor allopurinol, primarily in Dalmatians and those breeds genetically predisposed to urate urolithiasis. Higher levels of urinary xanthine and hypoxanthine will occur if the dosage of this drug is too high, and/or the dog is not receiving a purine-restricted diet. Xanthine uroliths have also been described in Cavalier King Charles Spaniels, caused by an autosomal recessive trait that results in increased urinary hypoxanthine and xanthine excretion. This is likely because of a deficiency in the enzyme xanthine oxidase. Secondary renal failure is relatively common when this occurs in the Cavaliers. Diets similar to those used for urate prevention, which are restricted in protein and high in moisture, are generally recommended for this condition in this breed.

CONCLUSIONS

Whenever a urolith is obtained from a dog or cat (surgically, catheter-assisted, voided, or by lithotripsy), it is important that it be submitted for crystallographic analysis to identify the minerals present. Evaluating trends in feline and canine urolithiasis is important because it may assist clinicians in determining what, if any, effect current stone prevention strategies, including dietary modifications and drug therapy, are having in cats and dogs with urolithiasis. Diets high in moisture are the cornerstone of therapy for preventing

urolithiasis recurrence in patients. Serial monitoring of urine specific gravity from samples collected in the home environment can be an easy, cost-effective method to monitor dietary moisture intake. Animals should be monitored with imaging studies appropriate for the urolith type.

Suggested Readings

Achar E, et al. Amitriptyline eliminates calculi through urinary tract smooth muscle relaxation. *Kidney Int*. 2003;64:1356.

Adams LG, et al. Use of laser lithotripsy for fragmentation of uroliths in dogs: 73 cases (2005-2006). *J Am Vet Med Assoc*. 2008;232:1680.

Bannasch D, et al. Mutations in the SLC2A9 gene cause hyperuricosuria and hyperuricemia in the dog. *PLoS Genet*. 2008;4:e1000246.

Bannasch D, Henthorn PS. Changing paradigms in diagnosis of inherited defects associated with urolithiasis. *Vet Clin North Am Small Anim Pract*. 2009;39:111.

Bannasch DL, et al. Inheritance of urinary calculi in the Dalmatian. *J Vet Intern Med*. 2004;18:483.

Bishop J, et al. Influence of hydrochlorothiazide and diet on urinary calcium oxalate relative supersaturation in healthy adult cats. *J Vet Intern Med*. 2007;21:599.

Cannon AB, et al. Evaluation of trends in urolith composition in cats: 5,230 cases (1985-2004). *J Am Vet Med Assoc*. 2007;231:570.

Dear JD, et al. Feline urate urolithiasis: a retrospective study of 159 cases. *J Feline Med Surg*. 2011;13:725.

Gatoria IS, et al. Comparison of three techniques for the diagnosis of urinary tract infections in dogs with urolithiasis. *J Small Anim Pract*. 2006;47:727.

Henthorn PS, et al. Canine cystinuria: polymorphism in the canine SLC3A1 gene and identification of a nonsense mutation in cystinuric Newfoundland dogs. *Hum Genet*. 2000;107:295.

Kyles AE, et al. Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in cats with ureteral calculi: 163 cases (1984-2002). *J Am Vet Med Assoc*. 2005;226:932.

Kyles AE, et al. Management and outcome of cats with ureteral calculi: 153 cases (1984-2002). *J Am Vet Med Assoc*. 2005;226:937.

Low WW, et al. Evaluation of trends in urolith composition and characteristics of dogs with urolithiasis: 25,499 cases (1985-2006). *J Am Vet Med Assoc*. 2010;236:193.

Lulich JP, et al. ACVIM small animal consensus recommendation on the treatment and prevention of uroliths in dogs and cats. *J Vet Intern Med*. 2016;30:1564–1574.

Lulich JP, et al. Nonsurgical removal of urocystoliths in dogs and cats by voiding urohydropropulsion. *J Am Vet Med Assoc*. 1993;203:660.

Ruland K, et al. Sensitivity and specificity of fasting ammonia and serum bile acids in the diagnosis of portosystemic shunts in dogs and cats. *Vet Clin Pathol*. 2010;39:57.

Westropp JL, et al. Dried solidified blood calculi in cats. *J Vet Intern Med*. 2006;20:828.

Westropp JL, et al. Evaluation of dogs with genetic hyperuricosuria and urate urolithiasis consuming a purine restricted diet: a pilot study. *BMC Vet Res*. 2017;13:45.

CHAPTER 44

Obstructive and Nonobstructive Feline Idiopathic Cystitis



INTRODUCTION

Feline lower urinary tract disease (FLUTD) is an inclusive term used to describe any disorder affecting the urinary bladder or urethra of cats. Signs of LUTD in cats can include variable combinations of pollakiuria, stranguria, periuria, dysuria, and hematuria. These lower urinary tract signs (LUTS) are not specific for any one particular disease; they can be seen in cats with cystic calculi, bacterial urinary tract infections, or neoplasia. The prevalence of LUTS in pet cats in the United Kingdom and the United States have been reported at 0.6% (veterinary data) up to 6.4% (owner-reported data). Up to two-thirds of young (<10 years of age) cats that present with LUTS will be diagnosed with feline idiopathic cystitis (FIC). However, cats with recurrent episodes of FLUTD have been reported to present with different causes at different times. Although FIC can be obstructive or nonobstructive in its presentation, urethral obstruction is far more common in male cats. In published studies, excessive body weight, decreased activity, multiple cats in the household, cats using nonclumping litter, and indoor housing have been associated with increased risk for FIC. Environmental stressors such as conflict with another cat in the household have also been identified as risk factors.

PATHOPHYSIOLOGY

HISTOPATHOLOGY

Histologically, FIC can be classified in two different forms, nonulcerative (type I) and ulcerative (type II). Cats with FIC almost always present with the nonulcerative form; however, the classic Hunner's ulcers seen in humans (type II) have been described rarely in cats. It is possible that the etiopathogenesis of these two forms of FIC is different. The type II form appears to be more inflammatory, whereas type I might be associated with neuroendocrine abnormalities. Furthermore, various proinflammatory serum cytokine profiles have been identified in some cats with FIC compared with healthy cats.

In cats with chronic nonulcerative FIC, histopathologic changes in the bladder wall are generally nonspecific and may include an intact or damaged urothelium with submucosal edema, dilation of submucosal blood vessels with marginated neutrophils, submucosal hemorrhage, and sometimes increased mast cell density. Histopathologic abnormalities are usually not specific for FIC and do not correlate well with clinical signs.

BLADDER ABNORMALITIES

Because cats with FIC present primarily for LUTS, many research studies have been published describing various bladder abnormalities. Although a decrease in bladder compliance has been found in cats with FIC, no evidence of spontaneous bladder contractions (overactive bladder) was noted in *female* cats with FIC when cystometrograms were evaluated. It has been proposed that the urothelial cells themselves can be targets of various stimuli, including adenosine triphosphate (ATP) and nitric oxide, which could potentiate inflammation and exacerbate clinical signs. The bladder afferent neurons in cats with FIC exhibit an increased excitability to physical and chemical stimuli as compared with unaffected cats. An increase in the release of nitrous oxide and subsequent increase in urothelial permeability suggest that the sympathetic nervous system may mediate these alterations by norepinephrine via this mechanism.

INFECTIOUS AGENTS

The role of viruses has been evaluated in cats with FIC. The feline caliciviruses, FCV-U1 and FCV-U2, have been the most studied. Feline calicivirus (FCV) viruria was detected in cats with FIC and in cats with upper respiratory infections; however, its etiologic significance was not ascertained. Serologic results suggest increased FCV exposure in FIC cats compared with controls. A weak association between seropositivity for *Bartonella* spp. and FIC has also been reported. What, if any, relationship these infectious agents play in the etiopathogenesis of LUTS in FIC thus remains unknown at this time, and to the authors' knowledge their role(s) in the

systemic manifestations of the syndrome have not been investigated.

SYSTEMIC ABNORMALITIES

Clinical signs of FIC can wax and wane, and appear to be exacerbated by internal and external stressors. Elevations in catecholamines and a decrease in serum cortisol concentrations in cats with FIC compared with healthy cats during times of acute and chronic stress have been reported, suggesting an uncoupling of these two parameters of the stress response. Therefore it appears that, although the sympathoneural system is fully activated in this disorder, the hypothalamic-pituitary-adrenal axis is not. The increased concentrations of catecholamines that were observed in cats with FIC may provide a clue to the observation that clinical signs of FIC follow a waxing and waning course and can be exacerbated by environmental stressors. Unfortunately, providing corticosteroid administration does not prevent or cure this disease.

Research in other species (e.g., rats) suggests that events experienced during development may affect visceral sensory systems and result in chronic idiopathic disorders. Although the cause of FIC has not been determined, it appears that some cats have a disorder that affects the LUT, and because systemic abnormalities have been documented in some cats, FIC should not be considered solely a bladder disease. A recent study of healthy cats and cats with FIC found that environmental stressors resulted in increased number of sickness behaviors (e.g., vomiting, lethargy, anorexia) in cats with FIC when the results were controlled for other factors. Cats with FIC have a variable combination of comorbid disorders such as behavioral, endocrine, cardiovascular, and gastrointestinal (GI) problems, and it is imperative that a detailed environmental history and complete physical examination be performed in these cats and that the focus be not just on the bladder. This will alter the therapeutic approach to management of the disease.

PATHOPHYSIOLOGY OF THE BLOCKED CAT

Urethral plugs are the most common cause of urinary tract obstruction in male cats; however, urethrolithiasis, strictures, and, rarely, neoplasia or a foreign body can result in a urethral obstruction. It is unlikely for the urethra of female cats to become obstructed, but male cats have a narrow penile urethral lumen and are predisposed to obstruction with a urolith or urethral plug. Oftentimes, the cause of the obstruction is not found, and it is thought the urethral pressure may be elevated or "spasm," although to the author's knowledge data to support urethral spasms have not been published. Many urethral plugs are composed of struvite with a proteinaceous matrix, and this composition has not changed over time (Fig. 44.1). The cause(s) of urethral plugs is still unknown; it is hypothesized that vasodilation and leakage of plasma proteins from the suburothelial capillary plexus and secondary urethritis, which can be seen cystoscopically in cats with FIC, may trap crystals and other debris in the urine within the lumen of the male cat and result in obstruction. It is likely that oozing of plasma proteins into the urine during active inflammation increases the urinary pH, which further contributes to the precipitation of struvite crystals that participate in urethral plug formation. Once the cat is unblocked and stabilized, management for obstructive FIC is very similar to that for nonobstructive FIC.

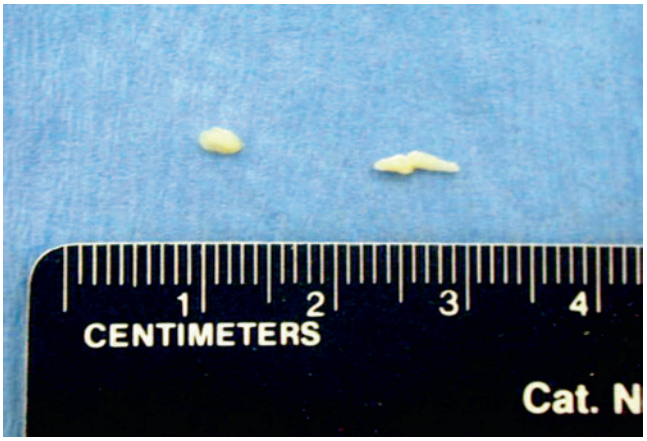


FIG 44.1
Urethral plug removed from an obstructed male cat. These plugs generally contain albumin and albumin breakdown products, as well as struvite crystals.

DIAGNOSTIC TESTS FOR CATS WITH LOWER URINARY TRACT SIGNS

When choosing the appropriate diagnostic tests for a cat that presents with LUTS, several factors need to be taken into consideration, including the number of episodes the cat has had, the severity of the cat's clinical signs, and how much the owner is willing to spend. No well-accepted diagnostic test for FIC currently exists, although research in urinary biomarkers for this disease continues. In humans, various markers such as antiproliferative factor and heparin-binding epidermal growth factor have been investigated but are not clinically available. In humans and cats, a candidate serum biomarker has been reported, and findings suggest the potential usefulness of infrared microspectroscopy to diagnose FIC (Rubio-Diaz et al., 2009). However, FIC currently remains a diagnosis of exclusion.

Because approximately 20% of cats that present with LUTS have cystic calculi, abdominal radiography is recommended. Abdominal ultrasonographic findings in cats with urethral obstruction are generally not as helpful because the urethra cannot be imaged. If a cat presents with a urethral obstruction, obtain an abdominal radiograph before a decompressive cystocentesis as long as the cat is stable. A urinalysis and urine bacterial culture should be evaluated at least once in cats with LUTS, but most young, otherwise healthy cats do not have a true bacterial cystitis. Advanced

diagnostic tests such as contrast cystourethrography, abdominal ultrasonography, and even cystoscopy (Figs. 44.2 and 44.3; Video 44.1, cystoscopy of FIC cat) can be performed in recurrent cases to be certain no other disease could account for the present clinical signs.

TREATMENT OPTIONS

ACUTE EPISODES

Obstructive Feline Idiopathic Cystitis

Once the diagnosis of a urethral obstruction is made, the cat should be assessed and stabilized with intravenous (IV) fluids. A serum biochemical panel should be submitted to evaluate for postrenal azotemia, possible hyperkalemia, and other electrolyte and acid–base disturbances such as hypocalcemia and acidosis. If hyperkalemia is present, IV treatment with fluids, regular insulin (0.25-0.5 U/kg, slow bolus), and 50% dextrose should be administered. An electrocardiogram should be evaluated and, in more severe cases, 10% IV calcium gluconate may be warranted to counteract the effects of the hyperkalemia on cardiac conduction. Acidosis is usually corrected with fluid therapy, but IV sodium bicarbonate (1-2 mEq/kg) can also be considered for cats with severe hyperkalemia. Care should be taken with bicarbonate infusions because exacerbation of hypocalcemia can occur when the acidosis is corrected.

Once the cat is stabilized, an abdominal radiograph should be obtained to evaluate for the most common calculi reported in cats (struvite and calcium oxalate [CaOx]). To provide an immediate reservoir for urine flow, a decompressive cystocentesis should then be performed. Usually a 22-gauge 1- or 1.5-inch needle is inserted into the bladder, with the bevel aimed at the trigone. The needle is connected to an extension set, three-way stopcock, and 20- or 35-mL syringe (Fig. 44.4). By doing this, all the urine can be drained without repeated needle insertions into the bladder. Analgesics should be provided (e.g., buprenorphine, 0.01 mg/kg intravenously q8-12h initially) and once the cat is anesthetized (e.g., with isoflurane, sevoflurane, or propofol), the urethral obstruction can be removed.

In rare cases, one can remove a urethral plug by massaging the distal penis. In most cases, urethral catheterization with an open-ended nonmetal catheter provides the easiest, safest means to alleviate the obstruction. The penile urethra should be clipped and scrubbed; using sterile technique, the catheter is then inserted into the distal urethra. The catheter should also be attached to an extension set and three-way stopcock. This may help lessen the trauma to the urethra during catheter insertion by allowing the assistant more room to flush the urethra with sterile saline, which is usually required to dislodge the obstruction; a smaller syringe provides a more forceful flow, which can be helpful in some cases.

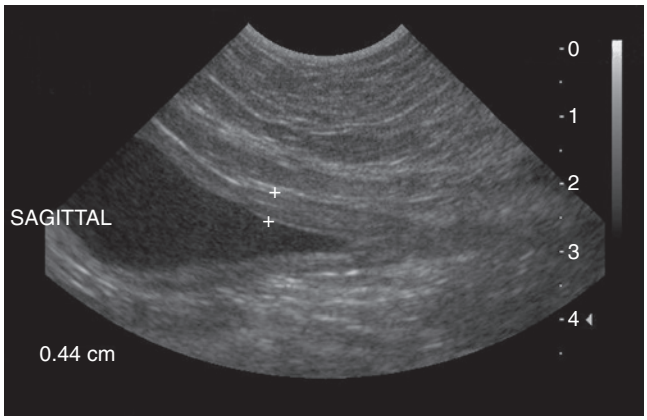


FIG 44.2
Abdominal ultrasonogram from a cat with a urethral obstruction. The findings are generally nonspecific and include a thickened bladder wall. This imaging modality is not ideal for evaluating the urethra of cats.



FIG 44.3
Cystoscopic view of a bladder from a female cat with FIC. The cat has severe edema and increased bladder friability. These findings do not appear to correlate well with the clinical signs.



FIG 44.4
Decompressive cystocentesis in a cat with urethral obstruction.

Indwelling urinary catheters are not mandatory for every urethral obstruction. An indwelling catheter might be irritating to the urethra and potentiate urethral irritation and subsequent reobstructions once the catheter is removed. However, an indwelling catheter should be placed in cats with severe azotemia, an abundance of debris and hemorrhage noted in the urine, or the presence of detrusor atony, or in cats with urethral obstructions caused by calculi (until surgery can be performed). A soft 3.5F or 5F catheter (e.g., red rubber or Slippery Sam catheter) can be left in place; strict aseptic technique should be followed. A closed collection system should be used to aid in sterility as well as to monitor urine output (Fig. 44.5). Azotemic cats can have a pronounced postobstructive diuresis, and it is imperative to provide adequate IV fluid therapy for these patients. Urine output should be recorded every 4 hours initially, and the amount recorded. The rate of IV fluids administered can then be adjusted based on the recorded urine output. Renal parameters and potassium concentration should be monitored; hypokalemia can develop during the diuresis phase. A urine culture can be considered after the urinary catheter is removed; there is no indication to culture the catheter tip.

In addition to analgesics, α_1-antagonists such as phenoxybenzamine (2.5 mg/cat orally [PO] q12h) or prazosin (0.5 mg/cat PO q12h) is often administered to cats with urethral obstruction to decrease urethral "spasms" and hopefully prevent reobstruction. Anecdotally, veterinarians have also used the more selective α_1-antagonist, tamsulosin (Flomax; anecdotal doses are 0.004-0.006 mg/kg PO q24h or q12h), with variable success. Because hypotension could develop with the administration of these drugs, they should not be given until the cat is stable and alert; blood pressure should be monitored if clinically indicated. In one study, prazosin had no effect on the incidence of urethral reobstruction in cats with naturally occurring obstructive FIC; however the authors were concerned their study was underpowered. No other medications, including oral meloxicam administered for 5 days, intravesical lidocaine infusion, or intravesical glycosaminoglycans, have been reported to have a beneficial effect in preventing urethral reobstruction in FIC cats. If bladder atony is suspected, the parasympathomimetic bethanechol can also be administered (2.5 mg/cat PO q12h). Adverse effects with this class of drugs are primarily GI (vomiting and diarrhea). Once the diuresis is complete, the IV fluids can be tapered and the catheter removed. Once the catheter is removed, chronic management is the same as for nonobstructive FIC.



FIG 44.5
Closed collection system used for a cat with significant hematuria postobstruction. By doing this, the clinician can also record the amount of urine produced by the cat to guide intravenous fluid therapy.

Nonobstructive Feline Idiopathic Cystitis

FIC has a variable outcome; clinical signs resolve in as many as 85% of cats within 2 to 3 days, with or without treatment. When a cat is diagnosed with FIC, analgesic therapy for acute management of the disease should be provided. Providing analgesia for cats with FIC seems prudent given the clinical manifestation. Nonsteroidal antiinflammatory drugs (NSAIDs) have been described for this disease, with variable results. Because of the risk for dehydration-associated reductions in blood flow to the kidneys and the potential for acute kidney injury, these medications might increase the risk for adverse outcomes. It is important the cat is eating and drinking well when NSAIDs are administered.

CHRONIC MANAGEMENT

Environmental Alterations

No cure is currently available for FIC; treatment options are aimed at clinical recovery, keeping the cat's clinical signs to a minimum, and increasing the disease-free interval. After the diagnosis of FIC is made, a thorough environmental history, as well as notation of all other comorbidities present, needs to be obtained so the clinician can establish that all the environmental needs of the cat have been met. A technician-based program, in which a staff member works with these patients as often as necessary to be sure the cat's problems are thoroughly explained to the owners so they can understand the disease process enough to feel comfortable with managing their cat's disease, can also be of great benefit.

Following a staged approach to therapy that begins with client education and multimodal environmental modifications (MEMO) seems beneficial in many cats with FIC. MEMO therapy involves obtaining a thorough environmental history, including but not limited to the topics presented in Box 44.1. The client should answer these questions for all cats in the household, and the clinician can then review the list and identify issues that may be contributing to the cat's clinical signs. After the questionnaire is completed, it should

BOX 44.1

Suggested Environmental Questionnaire for Cat Owners

1. Where did the owner obtain the cat—shelter, abandoned, breeder?
2. Number of cats in the household
   - Is intercat conflict an issue?
3. Number and type of other pets
4. Number of family members
5. Size and type of the household dwelling
6. Litter pans
   - Number?
   - How often are they cleaned?
   - How often are they changed?
   - Location in the house?
   - Type of litter used?
   - Depth of litter preferred by the cat?
7. Feeding
   - Type of food (including brand, canned versus dry)?
   - Location of bowls?
   - Food preferences?
   - Is competition for food present in the household?
8. Play and rest activity
   - Preferred toys?
   - Space in house available for play?
   - Preferred type of play?
9. Indoor or outdoor status?
10. Resting or hiding areas preferred?
    - Number of beds for the cat(s)?
11. Changes in household
12. Behavioral concerns
    - Aggression
    - Fear
    - Nervousness
    - Separation anxiety
13. Other sickness behaviors or comorbid diseases present?

be reviewed and modifications recommended. Recommend only one or two changes initially to the client so as not to overwhelm them or the cat. The goal is to optimize the environment for the cat and decrease external stressors. Based on previous findings, in which catecholamine concentrations decreased and clinical signs improved after environmental modifications, MEMO therapy was found to be successful in most cats with FIC followed over a 1-year period.

As a part of the MEMO therapy, dietary modifications may be warranted and should be discussed with clients. Increasing water intake by feeding canned food—or other methods, such as broths or automatic water dispensers—may be beneficial for cats with FIC. Efforts to acidify the urine using dry foods have no proven value in the treatment of cats with FIC; however, if pronounced struvite crystalluria is present in an obstructed male cat, a diet formulated for struvite dissolution may be warranted. Finally, obesity may be a risk factor for FIC, and implementing a weight loss program may be of benefit. Diets that have additives that

BOX 44.2

Drug Therapy for Chronic Feline Idiopathic Cystitis*

Amitriptyline—tricyclic antidepressant; 2.5-5 mg/cat PO q12-24h; adverse effects can include sedation, lethargy, urine retention.

Clomipramine—tricyclic antidepressant; 0.25-0.5 mg/kg PO q24h; adverse effects can include sedation, lethargy, and urine retention.

Fluoxetine—serotonin reuptake inhibitor; 1 mg/kg PO q24h; adverse effects can include gastrointestinal upset.

Buspirone—nonbenzodiazepine anxiolytic; 2.5-5 mg/cat PO q12h; adverse effects can include sedation.

Pentosan polysulfate sodium†—semi-synthetic carbohydrate derivative similar to glycosaminoglycans; used to help manage chronic feline idiopathic cystitis; doses vary depending on product; adverse effects are rare, but can include prolonged prothrombin time, bleeding problems, and diarrhea.

*Controlled studies are limited regarding these drugs.
†Studies in cats reported no significant differences when comparing pentosan polysulfate sodium to placebo. All groups had a clinical benefit, suggesting a strong "placebo" effect.

reportedly decrease anxiety in the cat (e.g., alpha casozepine and L-tryptophan) have also been anecdotally provided for cats with FIC. In fearful cats, feeding this diet reduced the cat's anxiety response "to placement in an unfamiliar location." All the cat's needs must be taken into consideration when making dietary and environmental recommendations.

Pheromones

Pheromones are fatty acids that transmit highly specific information among animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in the limbic system and hypothalamus that alter the emotional state of the animal. Feliway (Ceva Animal Health, St. Louis) is the synthetic F3 fraction of the naturally occurring feline facial pheromone. Treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful for FIC cats and others that experience anxiety-related problems. Feliway can be purchased as a spray formulation or a room diffuser. The spray can be used in areas such as where the litter pan is kept or sprayed in carriers 10 to 15 minutes before car transport. Room diffusers can be placed in designated rooms for cats and may help decrease anxiety and clinical signs of FIC.

Drug Therapy

A variety of drugs have been tried in cats with FIC, but placebo-controlled studies are lacking to confirm their clinical efficacy. If MEMO and pheromone therapy have failed, the medications listed in Box 44.2 can be considered. These drugs should not be used for cats with acute FIC, should be

considered only for cats if their environmental needs have been addressed, and should not be stopped abruptly. It can take longer than 1 week to see beneficial effects from many of these drugs; if no improvement in the cat's clinical signs is noted, these drugs should be tapered over 1 to 2 weeks.

CONCLUSIONS

FIC is a complex disease process that is not fully understood at this time. It is clear that the clinician and client must understand that this disease is not limited to abnormalities related solely to the bladder. Because FIC can be a chronic, frustrating disease, excellent client communication in conjunction with MEMO therapy, analgesics, and possibly other pharmacologic agents can be of benefit in treating acute and chronic cases.

Suggested Readings

Buffington CA, et al. Clinical evaluation of multimodal environmental modification (MEMO) in the management of cats with idiopathic cystitis. *J Feline Med Surg*. 2006;8:261.

Chew DJ, et al. Amitriptyline treatment for severe recurrent idiopathic cystitis in cats. *J Am Vet Med Assoc*. 1998;213:1282.

Chew DJ, et al. Randomized, placebo-controlled clinical trial of pentosan polysulfate sodium for treatment of feline interstitial (idiopathic) cystitis. *J Vet Intern Med*. 2009;23:690.

Gunn-Moore DA, Cameron ME. A pilot study using synthetic feline facial pheromone for the management of feline idiopathic cystitis. *J Feline Med Surg*. 2004;6:133.

Gunn-Moore DA, Shenoy CM. Oral glucosamine and the management of feline idiopathic cystitis. *J Feline Med Surg*. 2004;6:219.

Kruger JM, et al. Changing paradigms of feline idiopathic cystitis. *Vet Clin North Am Small Anim Pract*. 2009;39:15.

Landsberg G, et al. Therapeutic effects of an alpha-casozepine and L-tryptophan supplemented diet on fear and anxiety in the cat. *J Feline Med Surg*. 2017;19(6):596–602.

Larson J, et al. Nested case control study of feline calicivirus viruria, oral carriage, and serum neutralizing antibodies in cats with idiopathic cystitis. *J Vet Intern Med*. 2011;25:199.

Longstaff L, et al. Owner-reported lower urinary tract signs in a cohort of young cats. *J Feline Med Surg*. 2017;19(6):609–618.

Reche AJ, Buffington CA. Increased tyrosine hydroxylase immunoreactivity in the locus coeruleus of cats with interstitial cystitis. *J Urol*. 1998;159:1045.

Reineke EL, et al. The effect of prazosin on outcome in feline urethral obstruction. *J Vet Emerg Crit Care*. 2017;4:387–398.

Rubio-Diaz DE, et al. A candidate serum biomarker for bladder pain syndrome/interstitial cystitis. *Analyst*. 2009;134:1133.

Straeter-Knowlen IM, et al. Urethral pressure response to smooth and skeletal muscle relaxants in anesthetized, adult male cats with naturally acquired urethral obstruction. *Am J Vet Res*. 1995;56(7):919–923.

Welk KA, Buffington CA: Effect of interstitial cystitis on central neuropeptide and receptor immunoreactivity in cats. Presented at Research Insights into Interstitial Cystitis: A Basic and Clinical Science Symposium, Alexandria, VA, Oct. 30-Nov. 1, 2003.

Westropp JL, et al. Evaluation of the effects of stress in cats with idiopathic cystitis. *Am J Vet Res*. 2006;67:731.

Westropp JL, et al. Small adrenal glands in cats with feline interstitial cystitis. *J Urol*. 2003;170:2494.

CHAPTER 45

Disorders of Micturition



ANATOMY AND PHYSIOLOGY

Micturition depends on the coordinated actions among the sympathetic, parasympathetic (PS), and somatic nervous systems and central control centers (Fig. 45.1). The coordination among these systems in animals takes place in the pontine micturition center (PMC), also known as Barrington's nucleus, which is located in the dorsomedial pontine tegmentum in the brainstem. The PMC receives input from other sensory stimuli to determine the onset of micturition.

The thoracolumbar sympathetic pathway provides excitatory input to the bladder neck and urethra, and inhibitory input to the PS ganglia. Sympathetic preganglionic fibers exit the lumbar spinal cord (L1-L4 in dogs and L2-L5 in cats) and synapse in the caudal mesenteric ganglia. Postganglionic fibers (hypogastric nerve) release norepinephrine (NE) to activate β-receptors in the urinary bladder and α-receptors in the smooth muscle of the proximal urethra. This allows the bladder to relax and fill continuously, with little increase in intravesical pressure (via β-receptors), and provides tone to the smooth muscle near the trigone of the proximal urethra of female dogs, which is traditionally known as *the internal urethral sphincter* (via α-receptors). In male dogs the sphincter mechanism is likely associated with the striated muscle in the prostatic and postprostatic urethra.

The PS preganglionic motor neurons arise from the sacral spinal cord segments S1 to S3. Preganglionic fibers travel in the pelvic nerve and synapse in the peripheral ganglia in the wall of the bladder. Short postganglionic fibers provide excitatory input to the bladder through ACh acting on cholinergic (muscarinic) receptors in the bladder and also provide inhibitory input to the urethra, thus facilitating voiding.

Somatic innervation, supplied via the pudendal nerve, also arises from the sacral spinal cord segments S1 to S3 and provides stimulation (via ACh on nicotinic receptors) to the *external urethral sphincter*, an area of striated muscle. Cell bodies of this nerve are located in the ventrolateral nucleus of Onuf.

DEFINITIONS AND TYPES OF URINARY INCONTINENCE

Often owners will present their pet for evaluation of urinary incontinence (UI); however, there are several types of UI that a clinician must consider. Usually veterinarians use the term *UI* when referring to a dog or cat that unconsciously voids urine. Incontinence is usually due to failure of urine storage during filling, although multiple etiologies may contribute to UI. UI is more common in spayed bitches but can be seen in intact female dogs as well as male dogs and occasionally cats. Disorders associated with UI can be caused by anatomic problems as well as by alterations in urethral closure pressure. Animals may also consciously void small amounts of urine in inappropriate locations (pollakiuria), and this is what is commonly referred to as *urge incontinence.* Furthermore, it is important to evaluate if the dog is polyuric and/or polydipsic (PU-PD). An animal can also present with multiple problems, such as UI and PU or for behavioral causes of abnormal voiding. Obtaining a detailed history and ascertaining whether the animal is aware of micturition are essential to help formulate proper differential diagnoses and an appropriate diagnostic plan.

ECTOPIC URETERS

Ectopic ureters (EUs) are the most common cause of UI in young dogs. An EU is defined as a ureteral opening in an area other than the normal position in the trigone of the bladder (Fig. 45.2). UI is the most common clinical sign in dogs with EUs, and this disorder is usually diagnosed in dogs younger than 1 year of age; however, EUs should be considered in any dog with UI, particularly when the history is unknown. The severity of UI is variable, and some dogs may only be incontinent when at rest or at night (i.e., nocturia). Breeds that appear over-represented include: Golden Retriever, Labrador Retriever, Siberian Husky, Newfoundland, and English Bulldog. EUs are uncommon in male dogs and, if present, affected dogs may have few or no clinical signs or present with clinical signs at an older age. EUs are extremely rare in cats.

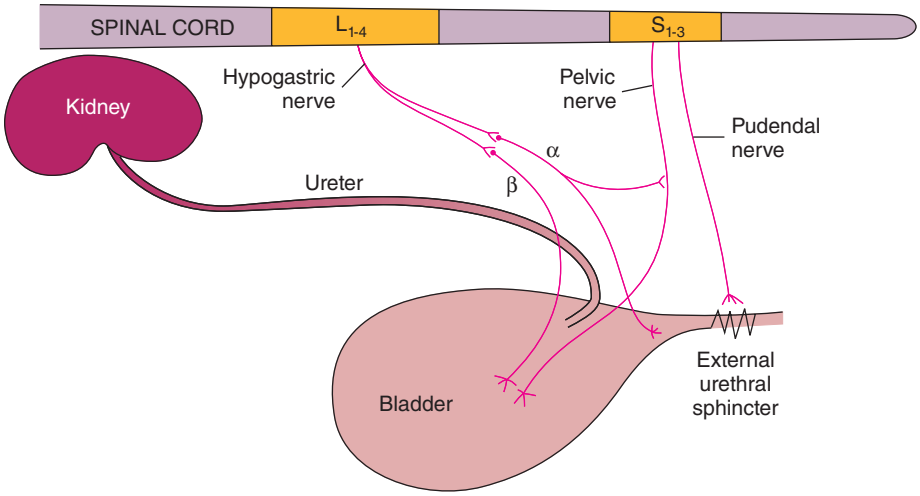


FIG 45.1
Schematic diagram of the sympathetic, parasympathetic, and somatic innervation to the lower urinary tract. The micturition pathway is much more complex than what is pictured here; the sensory pathways and higher centers are not depicted in this diagram.

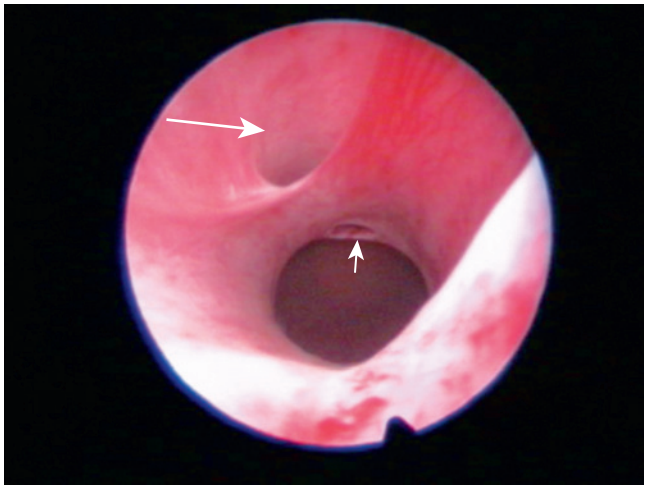


FIG 45.2
Cystoscopic view of a left unilateral ectopic ureter *(large arrow)* in a young Labradoodle. The smaller right ureter can be seen entering in the trigone region *(small arrow)*.

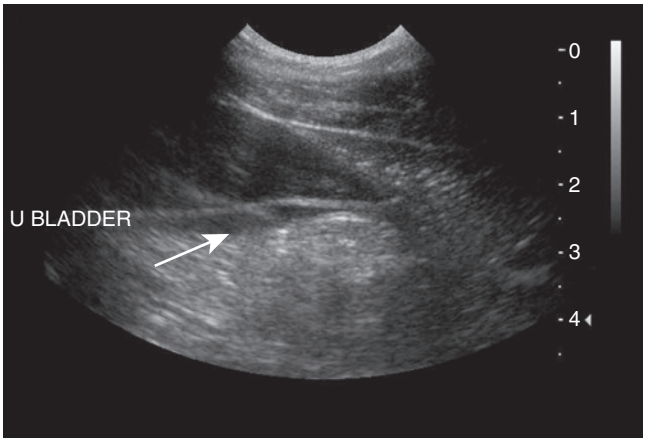


FIG 45.3
Transverse ultrasonographic image from a young Golden Retriever that presented with persistent urinary incontinence. A dilated ureter can be seen ventral to the bladder and entering the lower urinary tract distal to the trigone *(arrow)*. Hydronephrosis and hydroureter were also present on that side. Cystoscopy confirmed an ectopic ureter, and the ureter was corrected with cystoscopy-guided laser ablation.

A diagnosis of EUs can be made by excretory urography, fluoroscopic urethrography or ureterography, abdominal ultrasonography (Fig. 45.3) (Video 45.1), cystoscopy (Video 45.2), helical computed tomography (CT), or a combination of these diagnostic procedures. The latter two are reported to be the most sensitive diagnostics for confirming the presence of EUs. Furthermore, when using cystoscopy to diagnose EU, laser ablation can be done to correct the anomaly (see later). Other congenital abnormalities (e.g., renal agenesis, severe hydronephrosis) can also occur in dogs with EUs; therefore it is essential to evaluate the entire urinary system with other imaging modalities such as abdominal ultrasonography prior to correcting the EU to evaluate the upper urinary tract. Urine cultures should always be performed in dogs with suspected EUs as secondary UI can be a risk factor for bacterial cystitis. Treatment with proper antimicrobials for urinary tract infection (UTI) is clinically indicated before laser ablation or surgical correction of EUs.

EUs can be corrected via surgery, but laser ablation of EU has become the standard of care at most referral institutions. Complete continence is achieved after surgical correction in approximately 65% of cases. It has been reported that dogs weighing less than 20 kg have a better outcome postoperatively. Only intramural EUs can be corrected via cystoscopic laser ablation (Video 45.3); approximately 85% of dogs with EU have this type of anomaly. In 30 female dogs that had laser ablation to correct an EU, 47% were completely continent at a median follow-up of 2.7 years; an additional 20% were continent with additional medical management; others needed urethral bulking agents or a static hydraulic urethral occlude (see later). The variable success rate is likely due to concurrent urethral sphincter mechanism incompetence

(USMI) or other concurrent anatomic abnormalities that may have been present in the dog.

URETHRAL SPHINCTER MECHANISM INCOMPETENCE

Decreased urethral closure pressure can occur because of lumbosacral disorders such as intervertebral disk disease, degenerative myelopathy, trauma, malformations of the spinal vertebrae (e.g., in Manx cats), and rare disorders such as dysautonomia. A thorough neurologic examination should be performed on all dogs and cats that present for UI. USMI is a diagnosis of exclusion once all other disorders have been ruled out and can usually be made based on a compatible signalment and history, and absence of abnormalities on the physical examination.

USMI is similar to stress incontinence that occurs in women. USMI is primarily a disease of dogs; all cats suspected of having USMI should be tested for feline leukemia virus (FeLV) because associations between these two problems have been suggested. USMI usually occurs in spayed bitches but can occur in intact females and male dogs as well. In spayed females, the onset of clinical signs can vary from immediately after spaying to 10 years after the surgery. Nocturia appears to be the most common complaint from owners. UI can be daily or episodic and can range from mild to very severe. There appears to be a higher risk for USMI in larger-breed dogs after spaying as compared with small breeds. Although male dogs can develop USMI, it is critical to ascertain a residual urine volume because voiding disorders associated with urinary retention and paradoxical UI is more often seen in male dogs.

The exact cause of USMI is unclear. Estrogen deficiency is unlikely to be the sole cause of the UI because estrogen concentrations are similar between continent anestrous dogs and incontinent spayed dogs. Estrogen has been shown to increase urethral sphincter closure pressure in sexually intact and spayed female dogs without UI, but the urodynamic effects of estradiol are still not completely understood. Other risk factors for USMI have been reported to include larger-breed dogs (>20 kg), tail docking, obesity, and neutered status. Timing of spay with regards to USMI risk is still controversial, and the literature is variable. There is some weak evidence that "early" spay ("early" has not been well defined in studies) may increase the risk of acquiring USMI, particularly if dogs are >25 kg.

Although a urethral pressure profile (UPP) is the gold standard to document decreased urethral closure pressure (Box 45.1), the diagnosis of USMI can often be made based on signalment, history, and the absence of any other cause(s) for the UI. Response to drug therapy (see later) provides further evidence for USMI. Urodynamic tests can be performed in cats and dogs, are usually performed with propofol sedation, and provide data related to bladder and urethral function. A UPP evaluates the pressure along the entire length of the urethra; a cystometrogram evaluates the detrusor reflex, bladder fill volumes, and compliance.

BOX 45.1

Considerations for Referral for Urethral Pressure Profile and Cystometrography

Before ectopic ureter correction
If drug therapy with phenylpropanolamine (PPA) for urethral sphincter mechanism incompetence (USMI) was not effective
If drug therapy with diethylstilbestrol (DES) for USMI was not effective
If the patient with suspected USMI has a higher risk of side effects with medical management for USMI, then confirming the diagnosis is advised.

A list of drugs and suggested dosages for managing various micturition disorders is presented in Table 45.1. Medical management of USMI includes the use of drugs aimed at improving urethral pressures via the α_1-adrenoceptors (α_1-ARs), such as phenylpropanolamine (PPA). Rarely pseudoephedrine is used, but PPA is usually is more effective than PSE and has fewer adverse effects. The therapeutic benefit with α-agonists is usually seen within 2 to 3 days. If no benefit is seen after 1 week, the dosage can be increased up to 1.5 mg/kg orally (PO) q12h; if clinical signs are still present or side effects exist, another agent, such as an estrogen compound, should be considered. Adverse effects in dogs receiving α-agonists can include restlessness, anxiety, hyporexia, and possibly hypertension. A reflex bradycardia has also been reported. In a study, hypertension was not reported in healthy dogs at dosages typically used for USMI. α_1-AR agonists are not recommended for animals with cardiac disease, hypertension, or kidney disease, and PPA has not been studied in these groups of dogs. If required for dogs with kidney disease, lower dosages should be administered and the dog's blood pressure should be monitored regularly, ideally 2 to 4 hours post–PPA administration.

Estrogens may also be administered for treatment of USMI because these hormones are thought to sensitize the α_1-AR to NE and indirectly result in an improvement in the closure pressure, but the exact mechanism of action of these drugs is unclear. A U.S. Food and Drug Administration (FDA)-approved estrogen compound, estriol (Incurin, Merck Animal Health, Summit, NJ) is available (see Table 45.1). The same dosage is provided to every dog regardless of body weight (2 mg PO q24h per dog) and is initially administered daily for 2 weeks and then titrated down to the lowest effective dose. However, the author had success administering only 1 mg daily as a loading dosage to smaller-breed dogs (to avoid the potential side effect of vulvar hyperplasia). The therapeutic effect is often noted within the first week. If no benefit is seen this time, other therapeutic options should be considered. In some cases of USMI, a beneficial effect is noted when combining PPA and estrogen therapy. Older estrogen compounds such as diethylstilbestrol (DES) are also usually available and can often be administered

TABLE 45.1

Commonly Used Drugs for Micturition Disorders in Small Animal Patients

DRUG (TRADE NAME)	CLASS	MECHANISM OF ACTION	CLINICAL INDICATION(S) FOR USE	DOSAGE	POTENTIAL ADVERSE EFFECTS
Phenylpropanolamine (PPA)	α_1-agonist	Indirectly stimulates α- and β-receptors by causing release of norepinephrine (NE)	To increase urethral closure pressure for urethral sphincter mechanism incompetence (USMI)	1-1.5 mg/kg PO q12-24h	Restlessness, anxiety, tachycardia, hypertension
Diethylstilbestrol (DES)	Synthetic estrogen	May sensitize α_1-adrenergic receptors to NE	To increase urethral closure pressure for USMI	0.5-1 mg/dog PO; give total dose daily for 3-5 days, then titrate down to lowest effective dose to maintain continence (once or twice/wk)	Blood dyscrasias (rare when used at very low doses); mammary neoplasia
Estriol (Incurin)	Natural estrogen	May sensitize α_1-adrenergic receptors to NE	To increase urethral closure pressure for USMI	Begin loading dose of 2 mg/dog PO q24h; titrate down every 2 wk to lowest effect dose	Alopecia, blood dyscrasia
Acepromazine (PromAce)	Phenothiazine derivative	Varying degrees of antispasmodic and α-adrenergic blocking capabilities	To decrease urethral closure pressure for functional urethral outflow tract obstruction	0.01-0.05 mg/kg SC q8-12h	Sedation, hypotension
Prazosin (Minipress)	α-adrenergic antagonist	Inhibits α_1-receptors	To decrease urethral closure pressure for functional urethral outflow tract obstruction	1 mg/15 kg BW PO q8-12h (dog); 0.5 mg/cat PO q12h	Sedation, hypotension

Continued

TABLE 45.1

Commonly Used Drugs for Micturition Disorders in Small Animal Patients—cont'd

DRUG (TRADE NAME)	CLASS	MECHANISM OF ACTION	CLINICAL INDICATION(S) FOR USE	DOSAGE	POTENTIAL ADVERSE EFFECTS
Phenoxybenzamine (Dibenzyline)	α-adrenergic antagonist	Inhibits α_1-receptors	To decrease urethral closure pressure for functional urethral outflow tract obstruction	2.5 mg/cat PO q12h (cat); 0.25 mg/kg PO q12h (dog)	Sedation, hypotension
Tamsulosin (Flomax)	α_1-adrenergic antagonist	Inhibits α_1-receptors	To decrease urethral closure pressure for functional urethral outflow tract obstruction; anecdotal use for ureteral obstructions	Anecdotal: 0.1-0.2 mg/10 kg BW/day PO (dog); 0.004-0.006 mg/kg PO q12-24h (cat)	Sedation, hypotension
Bethanechol (Urecholine)	Parasympathomimetic	Stimulates primarily muscarinic receptors	To improve bladder contractility (i.e., detrusor atony)	2.5 mg/cat PO q12h; 5-15 mg/dog PO q12h	Vomiting, diarrhea, salivation
Amitriptyline (Elavil)	Tricyclic antidepressant	NE reuptake inhibition; central and peripheral anticholinergic activity; antagonism of the H_1 receptor; 5-HT reuptake inhibition; glutamate and sodium channel receptor antagonist	Idiopathic overactive bladder (OAB); refractory chronic feline idiopathic cystitis; submissive urinations (only in conjunction with behavior modification)	2.5-5 mg/cat PO q12h; 1-2 mg/kg PO q12h (dog)	Weight gain, lethargy, urine retention
Oxybutynin (Ditropan)	Anticholinergic	Antimuscarinic	Idiopathic OAB	0.2 mg/kg PO q8-12h (dog), no more than 5 mg total dose; 0.5-1 mg/cat PO q8-12h	Constipation, diarrhea, sedation, vomiting

tapered to a twice-weekly dose; however, this drug is considered off-label use in dogs.

Bone marrow suppression has been described in dogs receiving older-generation depot estrogens and in those receiving much higher doses of DES than those recommended for USMI. However, a complete blood count (CBC) should be monitored periodically in all dogs receiving estrogen therapy. Estriol differs from other estrogen compounds because it occupies the nuclear-bound receptors for a shorter period of time. Although it is reported to be safer than DES, a CBC can be monitored once to twice a year because leukopenia, anemia, and thrombocytopenia have also been rarely reported with its use. Other side effects reported include local and generalized alopecia and vulvar hyperplasia, particularly in small-breed dogs (in the author's opinion).

Submucosal urethral bulking agents such as polydimethylsiloxane (PDMS-Macroplastique), calcium hydroxylapetite (Coaptite), carbon-coated beads (Durasphere), and a newly available cross-linked bovine collagen material (ReGain) are commercially available in the United States and can be considered for those dogs that are refractory to medications or for owners who do not wish to medicate their pet continually. To perform this procedure, dogs are anesthetized, and three to four deposits of the bulking agent are injected in a circular fashion approximately 1.5 cm distal to the trigone via the cystoscope (Video 45.4). Some dogs still require medications after this procedure, but greater continence is usually gained following the implants. Response rates to collagen in 40 dogs were variable, and these dogs were continent for a mean of 17 months (range 1-64 months). Interestingly, the duration of effectiveness of collagen varied among dogs; this procedure often needs to be repeated several times, particularly in younger dogs. In older dogs, this treatment may be more appealing because no surgery is required and the duration of response may be adequate. A short-term study evaluating Macroplastique had positive results 3 months after the injections were administered to dogs; however, no long-term studies are currently available.

If dogs are nonresponsive to medical therapy, urethral occluders can also be considered. The occluders can be surgically placed around the proximal third of the urethra; they act as an external occluder to maintain continence. If the occluder alone is not enough, these devices are attached to an access port (Fig. 45.4) and saline can be infused into the occluder to increase their effectiveness. In one study evaluating 27 dogs (24 females, 3 males) with urethral occluder placement, continence scores were significantly improved postsurgery, and 22/27 (81%) of owners were very satisfied with the procedure. Two dogs developed partial urethral obstructions.

URINARY INCONTINENCE

Increased Urethral Closure Pressure

A persistent increase in urethral closure pressure from a mechanical or functional obstruction can lead to secondary bladder dysfunction (atony) and overflow incontinence. Mechanical causes for urinary retention can include urethroliths, bladder and/or urethral neoplasia, proliferative urethritis, urethral strictures and foreign bodies, urethral plugs, prostatic diseases (e.g., abscess, paraprostatic cyst, benign prostatic hypertrophy), and extraluminal urethral compressions. Functional obstructions can be seen with suprasacral or brainstem disease (upper motor neuron bladders), urethritis or a mechanical obstruction, and idiopathic functional urethral outflow tract obstruction, also known as detrusor-urethral dyssynergia (reflex dyssynergia).

The diagnosis of overflow incontinence is made based on history, thorough physical and neurologic examination, and complete imaging of the urinary tract. Most animals will have a history of intermittent to persistent stranguria before the UI. Watching the animal void and assessing the residual urine volume is also helpful. Normal animals will have less than 0.5 to 1 mL/kg of urine remaining in the bladder after voiding. Plain radiography, cystourethrography, and cystoscopy can all be beneficial to evaluate the dog or cat for mechanical obstructions. An enema should be given before radiographic studies to evaluate the proximal urethra. Cystoscopy is useful to evaluate the urethral mucosa, obtain samples for biopsy and culture, and aid in the placement of

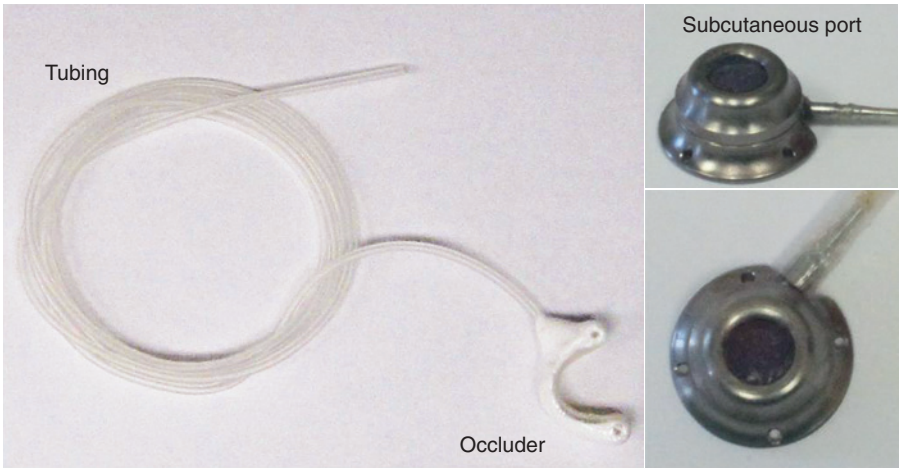


FIG 45.4
Urethral occluder. These occluders can be placed around the proximal urethra to increase the urethral closure pressure and improve or resolve urinary incontinence. The results appear to last longer than those achieved with urethral bulking agents. If the occluder is not sufficient to maintain continence, the subcutaneous port can be injected with saline to increase the pressure in the silicone occluder. (Courtesy Dr. William Culp, University of California, Davis.)

urethral stents if needed (Video 45.5). If no mechanical obstructions are present, urodynamic studies may help provide insight for functional obstructions, but oftentimes the increased urethral pressure may only occur during the act of micturition. The diagnosis of idiopathic functional urethral outflow tract obstruction (detrusor-urethral dyssynergia [DUD]) is usually made when all other causes for the increased urethral closure pressure have been excluded. This disease usually occurs in large-breed male dogs, both castrated or intact.

Treatment for mechanical obstructions is to remove the obstruction, if possible. Urethral stones can be removed via surgery or holmium:YAG laser lithotripsy. Bladder and urethral neoplasia, usually transitional cell carcinoma (TCC; Fig. 45.5), should be treated with piroxicam or another nonsteroidal antiinflammatory drug (NSAID); other chemotherapeutics such as mitoxantrone or platinum compounds may improve survival. Proliferative urethritis is usually seen in female dogs and may result from chronic UTIs. More recent unpublished data suggests that deep-seated UTIs may be associated with some of these cases, and fluorescent in situ hybridization (FISH) studies can be submitted if urethral biopsies are obtained. Cystoscopically, proliferative urethritis appears as multiple frond-like pieces of tissue in the urethral lumen that can be very dense and cause urethral obstruction. A biopsy is necessary to differentiate this from TCC. In addition to proper antimicrobials, NSAID therapy has been reported to help manage this disease. In one case study, azathioprine was also reported to be effective. If urethral obstruction occurs, urethral stenting should be considered.

For idiopathic, functional, urethral outflow tract obstruction, α_1-adrenoceptor antagonists such as prazosin can be used to help decreased the closure pressure of the internal urethral sphincter. Prazosin is much more cost-effective that phenoxybenzamine, another α-antagonist, particularly when used in larger-breed dogs. More selective α_1-antagonists, such as tamsulosin (Flomax), have been used anecdotally for functional urethral outflow obstructions, with variable and better results for DUD. In some cases, a skeletal muscle relaxant such as diazepam is also beneficial. Once these drugs have taken effect, or a urinary catheter is in place, parasympathomimetics can be started if secondary bladder atony is also present. Bethanechol, a muscarinic agent, might help restore bladder tone and facilitate bladder emptying. In severe cases, a tube cystotomy, indwelling urinary catheter, or urethral stent (Fig. 45.6) may be needed for urine evacuation.

Overactive Bladder

Animals that present with pollakiuria may have an overactive bladder (OAB), which results in urge incontinence. Usually animals with OAB have underlying cystitis caused by bacteria, cystic calculi, neoplasia, polyps, or drugs (e.g., cyclophosphamide). A detailed history is necessary to document whether other lower urinary tract signs are present. Physical examination of animals with pollakiuria is generally unremarkable; the bladder is usually small on palpation. In some dogs and cats, masses or numerous cystic calculi may be palpable, if present. A urinalysis should be performed and a urine culture should be evaluated. If the culture is negative and clinical signs persist, further diagnostic studies such as abdominal ultrasonography and radiography are indicated. If an underlying cause for the clinical signs is not found, referral for a cystometrogram and advanced imaging may be considered.

Occasionally idiopathic OAB (iOAB) is thought to occur and medical treatment may be beneficial for controlling

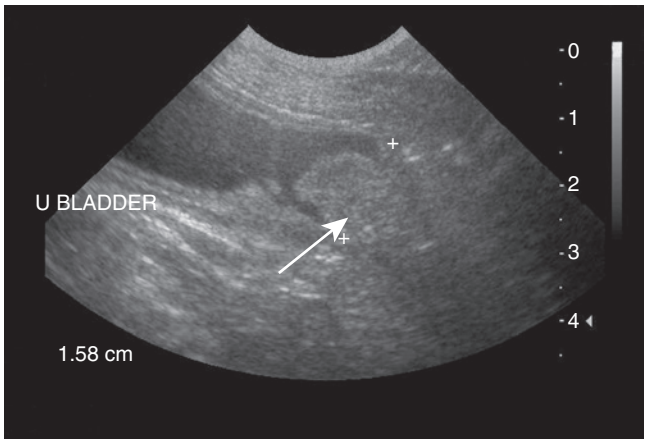


FIG 45.5
An ultrasonographic image from an 11-year-old female spayed Brittany Spaniel Mix that presented for stranguria and urinary incontinence. A urethral mass is noted that extends into the bladder lumen *(arrow)*. Fine-needle aspiration confirmed this mass to be a transitional cell carcinoma. In addition to piroxicam therapy, a urethral stent was placed in this dog.

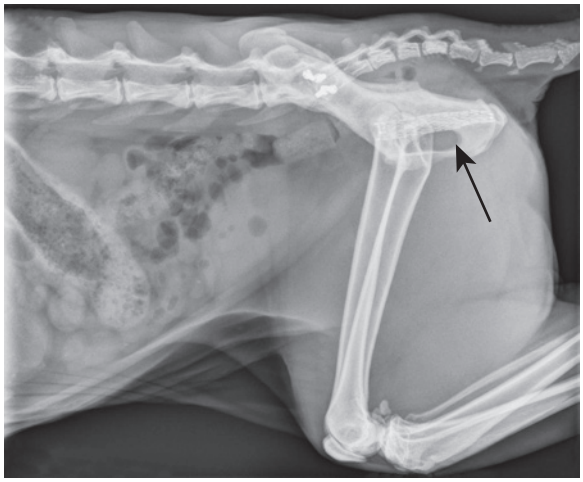


FIG 45.6
Later radiograph of a 1.5-year-old male, castrated domestic shorthair that presented for a urethral stricture secondary to trauma. After the stricture was ballooned, a urethral stent *(arrow)* was placed. Because of concern for bladder atony, the parasympathomimetic bethanechol was also administered.

clinical signs. Idiopathic OAB may occur with USMI, and the dog can have mixed UI as the reason for the clinical signs. Oxybutynin and tolterodine are anticholinergics that may help stop iOAB and promote urine retention. The tricyclic antidepressants—amitriptyline, imipramine, clomipramine—have anticholinergic properties, which can be considered for the treatment of dogs suspected of having iOAB. This class of drugs can also be considered for dogs that have urge incontinence secondary to behavioral problems as well. However, they should only be used when behavioral modifications have been unsuccessful, and discontinued when clinical signs improve.

Suggested Readings

Berent A, et al. Evaluation of cystoscopic-guided laser ablation of intramural ectopic ureters in female dogs. *J Am Vet Med Assoc*. 2012;240(6):716–725.

Blok BF, Holstege G. The central nervous system control of micturition in cats and humans. *Behav Brain Res*. 1998;92:119.

Byron JK, et al. Effect of phenylpropanolamine and pseudoephedrine on the urethral pressure profile and continence scores of incontinent female dogs. *J Vet Intern Med*. 2007;21:47.

Byron JK, et al. Urethral sphincter mechanism incompetence in 13 neutered female dogs: diagnosis, treatment, and relationship of weight and age at neuter to development of disease. *J Vet Intern Med*. 2017;31(2):442–448.

Cannizzo KL, et al. Evaluation of transurethral cystoscopy and excretory urography for diagnosis of ectopic ureters in female dogs: 25 cases (1992-2000). *J Am Vet Med Assoc*. 2003;223:475.

Carofiglio F, et al. Evaluation of the urodynamic and hemodynamic effects of orally administered phenylpropanolamine and ephedrine in female dogs. *Am J Vet Res*. 2006;67:723.

de Groat WC, et al. Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA, eds. *Nervous Control of the Urogenital System: the Autonomic Nervous System*. Chur, Switzerland: Harwood Academic Publishers; 1993:227.

Hamaide AJ, et al. Urodynamic and morphologic changes in the lower portion of the urogenital tract after administration of estriol alone and in combination with phenylpropanolamine in sexually intact and spayed female dogs. *Am J Vet Res*. 2006;67:901.

Hostutler RA, et al. Cystoscopic appearance of proliferative urethritis in 2 dogs before and after treatment. *J Vet Intern Med*. 2004;18:113.

Lautzenhiser SJ, Bjorling DE. Urinary incontinence in a dog with an ectopic ureterocele. *J Am Anim Hosp Assoc*. 2002;38:29.

Reeves L, et al. Outcome after placement of an artificial urethral sphincter in 27 dogs. *Vet Surg*. 2013;42(1):12–18.

Reichler IM, et al. Changes in plasma gonadotropin concentrations and urethral closure pressure in the bitch during the 12 months following ovariectomy. *Theriogenology*. 2004;62:1391.

Samii VF, et al. Digital fluoroscopic excretory urography, digital fluoroscopic urethrography, helical computed tomography, and cystoscopy in 24 dogs with suspected ureteral ectopia. *J Vet Intern Med*. 2004;18:271.

Drugs Used in Dogs and Cats With Urinary Tract Disorders

DRUG	TRADE NAME	ACTION	DOSAGE
Allopurinol	Zyloprim	Xanthine oxidase inhibitor	5-10 mg/kg PO q12h (dog)
Aluminum carbonate, aluminum hydroxide	Basaljel, Amphojel	Enteric phosphate binders	10-30 mg/kg PO q8h, with or immediately after meals
Amitriptyline	Elavil	Norepinephrine (NE) reuptake inhibition	2.5-5 mg/cat PO q12h; 1-2 mg/kg PO q12h (dog)
Amlodipine	Norvasc	Calcium antagonist	0.1-0.2 mg/kg PO q12-24h (dog); 0.625-1.25 mg PO q24h (cat)
Ammonium chloride		Urinary acidifier	100 mg/kg PO q12h (dog); 800 mg mixed with food daily (≈ ¼ tsp, cat)
Aspirin		Antiplatelet, antiinflammatory	0.5-5 mg/kg PO q12h (dog); 0.5-5 mg/kg PO q48-72h (cat)
Azathioprine	Imuran	Immunosuppressant	1-2 mg/kg PO q24h initially, then 0.5-1 mg/kg PO q48h (dogs only)
Benazepril	Lotensin	Angiotensin-converting enzyme inhibitor	0.25-0.5 mg/kg PO q24h
Bethanechol	Urecholine	Parasympathomimetic	5-15 mg total dose PO q8h (dog); 2.5 mg/cat PO q12h (cat)
Calcium acetate	PhosLo	Enteric phosphate binder	5-25 mg/kg PO q8h, immediately after meals

Continued

Drugs Used in Dogs and Cats With Urinary Tract Disorders—cont'd

DRUG	TRADE NAME	ACTION	DOSAGE
Chlorpromazine	Thorazine	Antiemetic	0.25-0.5 mg/kg IM, SC, PO q6-8h (after dehydration only)
Colchicine	Generic	Antiinflammatory, antifibrotic, inhibition of serum amyloid A synthesis and secretion	0.03 mg/kg/day PO (dog)
Cyclophosphamide	Cytoxan, Neosar	Immunosuppressant	50 mg/m^2 PO q48h (dogs); 200-300 mg/m^2 PO q3wk (cats)
Cyclosporine	Neoral, Sandimmune	Immunosuppressant	3-7 mg/kg PO q12-24h, adjust dose via monitoring
Darbepoetin alfa	Aranesp	Stimulates erythropoiesis	0.25-0.5 µg/kg SC once/wk adjusted according to PCV
Diazepam	Valium	Skeletal muscle relaxant for functional urethral outflow tract obstruction	2-5 mg total dose PO q8h (dog); give 30 min before urination
Diethylstilbestrol (DES)		Increases urethral closure pressure	0.5-1 mg/dog PO; give total dose daily for 3-5 days, then titrate down to lowest effective dose to maintain continence (once or twice/wk)
Dimethylsulfoxide	Domoso	Antiinflammatory	90 mg/kg/wk SC (dogs)
Dopamine	Inotropin	Adrenergic (α and β_1) and dopaminergic agent; positive inotropic effect; may increase renal blood flow and urine output	2-5 µg/kg/min CRI (dogs)
Estriol (Incurin)	Natural estrogen	Increases urethral closure pressure	Begin loading dose of 2 mg/dog PO q24h; titrate down every 2 wk to lowest effect dose
1,25-Dihydroxycholecalciferol, calcitriol	Rocaltrol	Active vitamin D_3, decreases parathyroid hormone	2.5-3.5 ng/kg PO q24h
Enalapril	Enacard	Angiotensin-converting enzyme inhibitor	0.5 mg/kg PO q12-24h (dog); 0.25-0.5 mg/kg PO q12-24h (cat)
Erythropoietin (r-Hu-EPO), epoetin alfa	Epogen	Stimulates erythropoiesis	35-50 U/kg IV, SC three times/wk or 400 U/kg IV, SC weekly; adjust dose to PCV of 30%-35%
Famotidine	Pepcid	H_2 blocker	0.5 mg/kg IM, SC, PO q12-24h
Furosemide	Lasix	Loop diuretic	2-4 mg/kg IV, PO q8-12h
Hydralazine	Apresoline	Arterial vasodilator	0.5-2 mg/kg PO q12h (dog); 2.5 mg PO q24h-q12h (cat)
Imipramine	Tofranil	Tricyclic antidepressant, antimuscarinic, mild α-agonist activity	5-15 mg/dog PO q12h; 2.5-5 mg/cat PO q12h
Lanthanum carbonate	Fosrenol, Renalzin	Enteric phosphate binder	20-30 mg/kg/day PO given immediately after meals
Lisinopril	Prinivil, Zestril	Angiotensin-converting enzyme inhibitor	0.5 mg/kg PO q24h (dog)
Mannitol	Osmitrol	Osmotic diuretic	0.5-1 g/kg as 20%-25% solution, slow IV bolus over 5-10 min



Drugs Used in Dogs and Cats With Urinary Tract Disorders—cont'd

DRUG	TRADE NAME	ACTION	DOSAGE
Maropitant citrate	Cerenia	Antiemetic	1-2 mg/kg, SC or PO (dog); 1 mg/kg SC (cat)
Tiopronin 2-MPG	Thiola	Promotes disulfide bond formation with cysteine for prevention of cystine urolithiasis	10-20 mg/kg PO q12h (dog); higher end of dose range used for attempting cystine dissolution
Metoclopramide	Reglan	Antiemetic; promotility	0.2-0.5 mg/kg PO, SC q8h
Ondansetron	Zofran	Antiemetic	0.6-1 mg/kg PO q12h
Oxybutynin	Ditropan	Anticholinergic	0.2 mg/kg PO q8-12h (dog), no more than 5 mg total dose; 0.5-1 mg/cat PO q8-12h
Phenoxybenzamine	Dibenzyline	α-antagonist, decreases urethral closure pressure	0.25 mg/kg PO q12h (dog); 2.5 mg total dose PO q12h (cat)
Phenylpropanolamine	Proin	α-adrenergic, increases urethral closure pressure	1-1.5 mg/kg PO q12-24h
Prazosin	Minipress	α-blocker	1 mg/15 kg BW PO q8-12h (dog); 0.5 mg total dose PO q12h (cat)
Propantheline bromide	Pro-Banthine	Anticholinergic, decreases detrusor contractility	0.25-0.5 mg/kg PO q8-12h (dog)
DL-Methionine	Uroeze, Methio-Form	Urinary acidifier	100 mg/kg PO q12h (dog); 1-1.5 g/day PO (cat)
Ranitidine	Zantac	H_2 blocker	2 mg/kg PO, IV q8h (dog); 2.5 mg/kg IV q12h, 3.5 mg/kg PO q12h (cat)
Sevelamer HCl	Renagel	Enteric phosphate binder	10-20 mg/kg PO q8h given with food
Sucralfate	Carafate	Gastrointestinal protectant	0.5-1 g PO q8-12h

PCV, Packed cell volume.

PART SIX ▪ Endocrine Disorders

Richard W. Nelson and Ann-Marie Della Maggiore

CHAPTER 46

Disorders of the Hypothalamus and Pituitary Gland



POLYURIA AND POLYDIPSIA

Water consumption and urine production are controlled by complex interactions between plasma osmolality, fluid volume in the vascular compartment, the thirst center, the kidney, the pituitary gland, and the hypothalamus. Dysfunction in any of these areas results in the clinical signs of polyuria (PU) and polydipsia (PD). In dogs normal water intake is usually less than 80 mL/kg of body weight/24 h. Water intake between 80 and 100 mL/kg/24 h is suggestive of PD but may be normal in some dogs. Water intake greater than 100 mL/kg/24 h confirms PD. Similar values are used for cats, although most cats drink considerably less than these amounts. Normal urine output ranges between 20 and 45 mL/kg/24 h (1-2 mL/kg/h). PU in the dog and cat has been defined as urine production greater than 50 mL/kg/24 h, although it is possible for urine production to be abnormal within the limits of these normal values in individual dogs and cats.

A variety of metabolic disturbances can cause PU-PD. Primary polyuric disorders can be classified on the basis of the underlying pathophysiology into primary pituitary (central) and nephrogenic diabetes insipidus (NDI), secondary NDI, osmotic diuresis-induced PU, and interference with the hypothalamic-pituitary secretion of arginine vasopressin (AVP). The most common form of diabetes insipidus is acquired secondary NDI. This form includes a variety of renal and metabolic disorders in which the renal tubules lose the ability to respond adequately to AVP. Most of these acquired forms are potentially reversible after elimination of the underlying illness.

Secondary NDI results from interference with the normal interaction of AVP and renal tubular AVP receptors, problems with the generation of intracellular cyclic adenosine monophosphate (cAMP), problems with renal tubular cell function, or loss of the renal medullary interstitial concentration gradient. Primary polydipsic disorders occur in dogs and usually have a psychogenic or behavioral basis for the compulsive water consumption (see the discussion of psychogenic PD, p. 7). A complete discussion of the diagnostic approach to PU-PD is presented in Chapter 38. An index of suspicion for most of the endocrinopathies that cause PU-PD can be raised after a review of the history, physical examination findings, and results of a complete blood count (CBC), serum biochemistry panel, serum thyroxine (T_4) concentration (cat), urinalysis, and urine culture. Specific tests may be necessary to confirm the diagnosis (Table 46.1). See the appropriate chapters in this section for a more complete discussion of the diagnosis and treatment of each of these endocrinopathies.

Occasionally, physical examination findings and initial blood and urine test results are normal in dogs and cats with PU and PD. Differential diagnoses in these dogs and cats include diabetes insipidus, psychogenic PD, hyperadrenocorticism, mild renal insufficiency without azotemia, mild hepatic insufficiency (most notably with portosystemic shunts), and the early stages of hypoadrenocorticism. Hyperadrenocorticism, hypoadrenocorticism, renal insufficiency, and hepatic insufficiency should be ruled out before diagnostic tests for diabetes insipidus or psychogenic PD are performed. Diagnostic tests to consider include evaluation of the range of urine specific gravities obtained from several urine samples (discussed in the next paragraph), tests for hyperadrenocorticism (e.g., urine cortisol/creatinine ratio, low-dose dexamethasone suppression test), hypoadrenocorticism (e.g., baseline serum cortisol concentration), liver function tests (e.g., measurement of preprandial and postprandial bile acid concentrations), determination of the urine protein/creatinine (P:C) ratio, and abdominal ultrasonography. Ideally, all realistic causes of secondary acquired NDI should be ruled out before tests for primary pituitary and NDI and psychogenic PD are performed.

Critical evaluation of urine specific gravity measured from several urine samples obtained by the client at different

times of the day and night for 2 to 3 days may provide clues to the underlying disorder (Table 46.2). Urine samples should be stored in the refrigerator until they can be brought to the veterinary hospital for determination of urine specific gravity. Urine specific gravity varies widely among healthy dogs and can range from less than 1.006 to greater than 1.040 within a 24-hour period. Wide fluctuations in urine specific gravity have not been reported in healthy cats.

TABLE 46.1

Endocrine Disorders Causing Polyuria and Polydipsia in the Dog and Cat

DISORDER	TESTS TO ESTABLISH THE DIAGNOSIS
Diabetes mellitus	Fasting blood glucose, urinalysis
Hyperadrenocorticism	Urine C:C ratio, low-dose dexamethasone suppression test
Hypoadrenocorticism	Blood electrolytes, ACTH stimulation test
Primary hyperparathyroidism	Blood calcium/phosphorus, cervical ultrasound, serum PTH concentration
Hyperthyroidism	Serum T_4, free T_4, and TSH concentrations
Diabetes insipidus Pituitary Nephrogenic	Modified water deprivation test, response to DDAVP therapy
Acromegaly	Baseline GH or IGF-1 concentration, CT or MR scan
Primary hyperaldosteronism	Blood electrolytes, plasma aldosterone concentration

ACTH, Adrenocorticotropic hormone; *C:C,* cortisol/creatinine; *CT,* computed tomographic; *DDAVP,* desmopressin; *GH,* growth hormone; *IGF-1,* insulin-like growth factor 1; *MR,* magnetic resonance; *PTH,* parathyroid hormone; *T_4,* tetraiodothyronine (thyroxine); *TSH,* thyroid-stimulating hormone.

Urine specific gravities measured from multiple urine samples that are consistently less than 1.020 support the presence of PU and PD and the need for a diagnostic evaluation to determine the cause; the lower the urine specific gravities, the stronger the support for the existence of a PU-PD disorder. Identification of one or more urine specific gravities greater than 1.030 supports normal urine concentrating ability and an intact, functioning pituitary vasopressin-renal tubular cell axis. Dogs and cats may still have PU and PD despite identification of concentrated urine; possible differentials include disorders causing an osmotic diuresis (e.g., diabetes mellitus), psychogenic PD, and disorders in the regulation of AVP secretion.

If the urine specific gravity is consistently in the isosthenuric range (1.008-1.015), renal insufficiency should be considered the primary differential diagnosis, especially if the blood urea nitrogen and serum creatinine concentration are at the upper end of the reference range or increased (i.e., ≥25 mg/dL and 1.6 mg/dL, respectively). Although isosthenuria is relatively common in dogs with hyperadrenocorticism, psychogenic water consumption, hepatic insufficiency, pyelonephritis, and partial central diabetes insipidus (CDI) with concurrent water restriction, urine specific gravities tend to fluctuate above and/or below the isosthenuric range with these disorders. In contrast, if the urine specific gravity is consistently less than 1.006, renal insufficiency is ruled out and central and primary NDI, psychogenic water consumption, hyperadrenocorticism, and hepatic insufficiency should be considered the primary differential diagnoses. CDI and primary NDI are ruled out if the urine specific gravity exceeds 1.025. Urine specific gravities that range from less than 1.005 to greater than 1.030 are suggestive of psychogenic PD.

DIABETES INSIPIDUS

Etiology

AVP plays a key role in the control of renal water resorption, urine production and concentration, and water balance.

TABLE 46.2

Results of Urinalysis in Dogs With Selected Disorders Causing Polyuria and Polydipsia

DISORDER	NO. OF DOGS	URINE SPECIFIC GRAVITY		PROTEINURIA	WBC (>5/HPF)	BACTERIURIA
		MEAN	RANGE			
Central diabetes insipidus	20	1.005	1.001-1.012	5%	0%	0%
Psychogenic polydipsia	18	1.011	1.003-1.023	0%	0%	0%
Hyperadrenocorticism	20	1.012	1.001-1.027	48%	0%	12%
Renal insufficiency	20	1.011	1.008-1.016	90%	25%	15%
Pyelonephritis	20	1.019	1.007-1.045	70%	75%	80%

HPF, High-power field; *WBC,* white blood cells.

AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus, is stored in and secreted from the posterior pituitary gland in response to an increase in plasma osmolality or a decrease in extracellular fluid volume, and interacts with distal tubular and collecting duct cells of the kidney to promote water resorption and the formation of concentrated urine. The defective synthesis or secretion of AVP or an inability of the renal tubules to respond to AVP causes diabetes insipidus.

CENTRAL DIABETES INSIPIDUS

CDI is a polyuric syndrome that results from insufficient secretion of AVP to concentrate urine for water conservation. This deficiency may be absolute or partial. An absolute deficiency of AVP, referred to as *complete CDI,* causes persistent hyposthenuria and severe diuresis. The urine specific gravity in dogs and cats with complete CDI remains hyposthenuric (i.e., ≤1.005), even with severe dehydration. A partial deficiency of AVP, referred to as *partial CDI,* also causes persistent hyposthenuria and marked diuresis as long as the dog or cat has unlimited access to water. During periods of water restriction, the urine specific gravity can increase into the isosthenuric range (i.e., 1.008-1.015), but typically the urine cannot be concentrated to more than 1.015 to 1.020 even when the animal is severely dehydrated. In any dog or cat with partial CDI, maximum urine-concentrating ability during dehydration is inversely related to the severity of the deficiency in AVP secretion—that is, the more severe the AVP deficiency, the less concentrated is the urine specific gravity during dehydration.

CDI may result from any condition that damages the neurohypophyseal system (Box 46.1). Idiopathic CDI is the most common form, appearing at any age in any breed, and affecting animals of either sex. Necropsies performed in dogs and cats with idiopathic CDI fail to identify an underlying reason for the AVP deficiency. Although CDI is well documented in kittens and puppies, a hereditary form of CDI has not yet been documented. The most common identifiable causes of CDI in dogs and cats are head trauma (accidental or neurosurgical), neoplasia, and hypothalamic-pituitary malformations (e.g., cystic structures). Head trauma may cause transient (typically lasting 1-3 weeks) or permanent CDI, depending on the viability of the cells in the supraoptic and paraventricular nuclei.

Primary intracranial tumors associated with diabetes insipidus in dogs and cats include craniopharyngioma, pituitary chromophobe adenoma, and pituitary chromophobe adenocarcinoma. Metastatic mammary carcinoma, lymphoma, malignant melanoma, and pancreatic carcinoma have been reported to cause CDI in dogs through their presence in the pituitary gland or hypothalamus. Metastatic neoplasia has not yet been reported to be a cause of CDI in cats.

BOX 46.1

Recognized Causes of Diabetes Insipidus in Dogs and Cats

CENTRAL DIABETES INSIPIDUS	NEPHROGENIC DIABETES INSIPIDUS
Idiopathic	Primary idiopathic
Trauma to the head	Primary familial history (Huskies)
Neoplasia	Secondary acquired (see Table 41.1)
Craniopharyngioma	
Meningioma	
Chromophobe adenoma	
Chromophobe adenocarcinoma	
Metastasis	
Hypothalamic and pituitary malformations	
Cysts	
Lymphocytic hypophysitis	
Parasitic migration	
Hypophysectomy	
Familial history (?)	

NEPHROGENIC DIABETES INSIPIDUS

NDI is a polyuric disorder that results from impaired responsiveness of the nephron to AVP. Plasma AVP concentrations are normal or increased in animals with this disorder. NDI may be classified as primary (familial) or secondary (acquired). Secondary or acquired NDI is common in dogs and cats and is discussed in an earlier section (Polyuria and Polydipsia) and in Chapter 38. Primary NDI is a rare congenital disorder in dogs and cats, with only a few reports in the literature. The etiology of primary NDI in dogs and cats is unknown, although decreased binding affinity of AVP receptors was identified in a family of Siberian Huskies. Affected puppies showed antidiuretic responses to high doses of synthetic vasopressin (desmopressin [DDAVP]).

Clinical Features

SIGNALMENT

No breed-, sex-, or age-related predilection for CDI is apparent. The age at the time of diagnosis of CDI in dogs ranges from 7 weeks to 14 years, with a median age of 5 years. Most cats with CDI are domestic short- and long-haired cats, although the disorder has been documented in Persians and Abyssinians. The age at the time of diagnosis of CDI in cats ranges from 8 weeks to 6 years, with a mean of 1.5 years. Primary NDI has been identified only in puppies, kittens, and young adult dogs and cats younger than 18 months of age. PU and PD have been present since the clients acquired these pets.

CLINICAL SIGNS

PU and PD are the hallmark signs of diabetes insipidus and are typically the only signs seen in dogs and cats with congenital and idiopathic CDI and in those with primary NDI. PU and PD can be quite severe with 24-hour water intake exceeding 200 mL/kg. Clients may believe that affected animals are incontinent because of the frequency of urination and the loss of normal housebroken behavior or because

of observed problems with urine dribbling, especially when resting or asleep. Owners of cats with diabetes insipidus often complain that they need to change the kitty litter more frequently than expected. Additional clinical signs may be found in dogs and cats with secondary causes of diabetes insipidus. The most worrisome are neurologic signs and inappetence, which may indicate the presence of an expanding hypothalamic or pituitary tumor in the adult dog or cat that has not had head trauma.

PHYSICAL EXAMINATION

The physical examination findings are usually unremarkable in animals with CDI, although some dogs and cats are thin, presumably because the pet's strong desire for water overrides its normal appetite. As long as access to water is not restricted, the animal's hydration status, mucous membrane color, and capillary refill time remain normal. The presence of neurologic abnormalities is variable in dogs and cats with trauma-induced CDI or neoplastic destruction of the hypothalamus or pituitary gland. When present, neurologic signs may include stupor, disorientation, ataxia, circling, pacing, and convulsions. Severe hypernatremia may also cause neurologic signs in the traumatized dog or cat with undiagnosed CDI given inadequate fluid therapy (see Chapter 53) and the dog or cat with undiagnosed CDI that has prolonged restricted access to water. Hyposthenuria in the presence of persistent hypernatremia should raise suspicion for diabetes insipidus.

Diagnosis

The diagnostic workup for PU and PD should initially rule out causes of acquired secondary NDI (see Chapter 38). Recommended initial diagnostic studies include CBC; a serum biochemistry panel; serum T_4 concentration (older cat); urinalysis with bacterial culture; abdominal ultrasonography; and in dogs, a urine cortisol/creatinine ratio or low-dose dexamethasone suppression test, or both; a baseline serum cortisol concentration if hypoadrenocorticism is suspected; and pre- and postprandial bile acids if hepatic insufficiency is suspected.

Results of these screening tests are normal in dogs and cats with CDI, primary NDI, and psychogenic water consumption, although a low-normal serum urea nitrogen concentration (5-10 mg/dL), and mild hyponatremia and hypokalemia may be found. Random urine specific gravity is usually less than 1.006 and is often as low as 1.001 if the dog or cat has unlimited access to water. The urine osmolality is less than 300 mOsm/kg. A urine specific gravity in the isosthenuric range (i.e., 1.008-1.015) does not rule out diabetes insipidus (Fig. 46.1), especially if the urine has been obtained after water is knowingly or inadvertently withheld (e.g., after a long car ride and wait in the veterinary office). The urine of dogs and cats with partial diabetes insipidus can be concentrated into the isosthenuric range if they become dehydrated. Erythrocytosis (packed cell volume of 50%-60%), hyperproteinemia, hypernatremia, and azotemia may be found in animals whose access to water has been restricted.

Diagnostic tests to confirm and differentiate among CDI, primary NDI, and psychogenic water consumption include the modified water deprivation test, random plasma osmolality determination, and the response to AVP supplementation. Results of these tests can be interpreted only after known causes for acquired secondary NDI have been ruled out, most notably hyperadrenocorticism. Pituitary-dependent hyperadrenocorticism can mimic CDI in the adult dog. Pituitary-dependent hyperadrenocorticism commonly causes severe PU and PD, and occasionally dogs have no other clinical signs, do not have the typical abnormalities (e.g., increased serum alkaline phosphatase activity, hypercholesterolemia) associated with the disease, and adrenal gland size is in the reference interval with ultrasonography. Results of the modified water deprivation test in dogs with hyperadrenocorticism are similar to results in dogs with partial CDI and, sometimes, dogs with psychogenic PD. Severity of PU and PD may improve noticeably to the owner after initiating treatment with DDAVP in these dogs, but improvement tends to be transient, lasting only a few months, and the dog typically presents to the hospital with owner concerns that the DDAVP is no longer working. For these reasons, we always perform screening tests for hyperadrenocorticism in

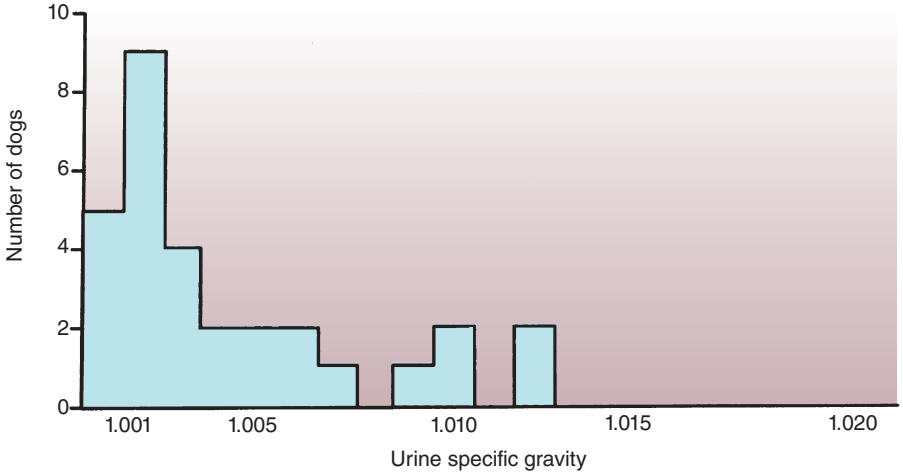


FIG 46.1
Urine specific gravity measured in 30 dogs with central diabetes insipidus at the time of initial presentation to the veterinarian. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

an adult dog in which CDI and psychogenic PD have risen to the top of the differentials and always before initiating DDAVP treatment.

RESPONSE TO TRIAL THERAPY WITH DESMOPRESSIN ACETATE

CDI, primary NDI, and psychogenic PD are uncommon to rare causes of PU and PD in dogs and cats, and of these three differentials, partial CDI and psychogenic PD are the most common. Because CDI is treated with DDAVP, a viable approach to establishing the diagnosis is to evaluate the animal's response to trial therapy with DDAVP (Desmopressin acetate®, Aventis Pharmaceuticals). Oral DDAVP tablets or conjunctival drops of DDAVP nasal spray (see Treatment section) should be administered every 12 hours for 7 days. The effect of DDAVP should not be critically evaluated until after 5 to 7 days of therapy because renal medullary washout may prevent the dog or cat with CDI from concentrating its urine and decreasing water intake after only 1 or 2 days of DDAVP treatment. Clients should notice a definite improvement in the severity of PU and PD by the end of the treatment period if the PU and PD are caused by CDI. Urine specific gravity should be measured on several urine samples collected by the client on the last couple of days of trial therapy. An increase in urine specific gravity by 50% or more, compared with pretreatment specific gravities, supports the diagnosis of CDI, especially if the urine specific gravity exceeds 1.030. There should be only minimal improvement in dogs and cats with primary NDI, although a response may be observed with very high doses of DDAVP. Dogs and cats with psychogenic water consumption may exhibit a mild decline in urine output and water intake because the chronically low serum osmolality tends to depress AVP production. Theoretically, dogs with psychogenic PD could develop clinical signs of hyponatremia during DDAVP therapy, but we have only identified this complication with excess DDAVAP administered by SC injection. This approach to diagnosis requires that all other causes of PU and PD, except CDI, primary NDI, and psychogenic PD, must be previously ruled out.

A thorough review of the diagnostic evaluation of the patient, owner compliance in treating their pet, and adjustments in the DDAVP treatment protocol should be undertaken in dogs and cats that fail to respond to DDAVP before considering the modified water deprivation test.

MODIFIED WATER DEPRIVATION TEST

The technique, interpretation, contraindications, and complications of the modified water deprivation test are described in Chapter 39. The test consists of two phases. In phase I, AVP secretory capabilities and renal distal and collecting tubule responsiveness to AVP are evaluated by assessing the effects of dehydration (i.e., water restriction until the animal loses 3%-5% of its body weight) on urine specific gravity. The normal dog and cat, as well as those with psychogenic water consumption, should be able to concentrate urine to greater than 1.030 (1.035 in the cat) if dehydrated. Dogs and cats with partial and complete CDI and primary NDI have an impaired ability to concentrate urine in the face of dehydration (Table 46.3 and Fig. 46.2). The time required to attain 3% to 5% dehydration can sometimes be helpful in establishing the diagnosis. It often takes less than 6 hours for dogs and cats with complete CDI to attain 3% to 5% dehydration, whereas it often takes longer than 8 to 10 hours for dogs and cats with partial CDI, especially those with psychogenic water consumption, to attain 3% to 5% dehydration.

Phase II of the water deprivation test is indicated for dogs and cats that do not concentrate urine to greater than 1.030 during phase I of the test. Phase II determines the effect, if any, that exogenous AVP has on the renal tubular ability to concentrate urine in the face of dehydration (see Fig. 46.2). This phase differentiates impaired AVP secretion from impaired renal tubular responsiveness to AVP (see Table 46.3).

RANDOM PLASMA OSMOLALITY

Measurement of random plasma osmolality may help identify primary or psychogenic PD. Plasma osmolality in normal dogs and cats is approximately 280 to 300 mOsm/kg. Diabetes insipidus is a primary polyuric disorder, with compensatory

TABLE 46.3

Guidelines for Interpretation of the Modified Water Deprivation Test

DISORDER	URINE SPECIFIC GRAVITY			TIME TO 5% DEHYDRATION	
	INITIAL	5% DEHYDRATION	POST ADH	MEAN (h)	RANGE (h)
Central Di					
Complete	<1.006	<1.006	>1.008	4	3-7
Partial	<1.006	1.008-1.020	>1.015	8	6-11
Primary nephrogenic DI	<1.006	<1.006	<1.006	5	3-9
Primary polydipsia	1.002-1.020	>1.030	NA	13	8-20

ADH, Antidiuretic hormone; *DI,* diabetes insipidus; *NA,* not applicable.

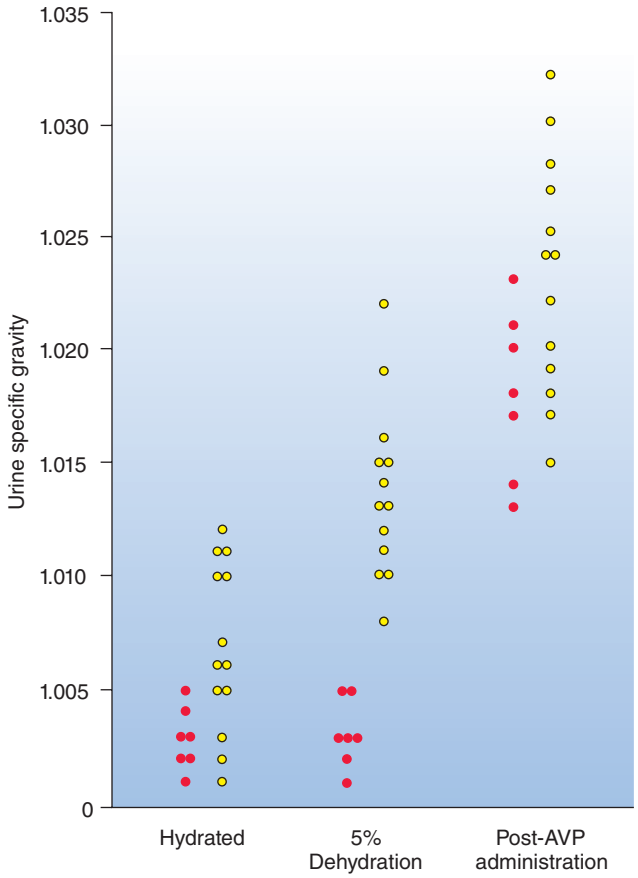


FIG 46.2
Urine specific gravity in seven dogs with complete central diabetes insipidus *(red circle)* and in 13 dogs with partial central diabetes insipidus *(yellow circle)* at the beginning (hydrated), at the end of phase I (5% hydrated), and at the end of phase II (after arginine vasopressin administration) of the modified water deprivation test. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

PD to prevent severe hyperosmolality. Random plasma osmolality should be greater than 300 mOsm/kg. Psychogenic PD is a primary polydipsic disorder, with compensatory PU to prevent hyposmolality and water intoxication. Random plasma osmolality should be less than 280 mOsm/kg. Unfortunately, considerable overlap in random plasma osmolality is seen in dogs with these disorders. A random plasma osmolality of less than 280 mOsm/kg obtained while the dog has free access to water suggests the presence of psychogenic PD, whereas a plasma osmolality of 280 mOsm/kg or greater is consistent with CDI, NDI, or psychogenic PD.

ADDITIONAL DIAGNOSTIC TESTS

Neoplasia in the region of the pituitary gland and hypothalamus should be considered in the older dog or cat in which CDI develops. A complete neurologic evaluation, including computed tomographic (CT) or magnetic resonance (MR) scan, may be warranted before idiopathic CDI is arbitrarily diagnosed, especially if the client is willing to consider radiation therapy or chemotherapy should a tumor be identified. Similarly, a more complete evaluation of the kidney (e.g., creatinine clearance studies, intravenous pyelogram, CT or MR scan, kidney biopsy) may be warranted in the older dog or cat tentatively considered to have primary NDI.

BOX 46.2

Therapies Available for Polydipsic/Polyuric Dogs and Cats With Central Diabetes Insipidus, Nephrogenic Diabetes Insipidus, or Primary (Psychogenic) Polydipsia

A. Central diabetes insipidus (severe)
  1. DDAVP (desmopressin acetate)
    a. Effective
    b. Expensive
    c. Oral tablets or drops of nasal solution in conjunctival sac
  2. LVP (lypressin [Diapid])
    a. Short duration of action; less potent than DDAVP
    b. Expensive
    c. Requires drops into nose or conjunctival sac
  3. No treatment—provide continuous source of water
B. Central diabetes insipidus (partial)
  1. DDAVP
  2. LVP
  3. Chlorpropamide
    a. 30%-70% effective
    b. Inexpensive
    c. Pill form
    d. Takes 1-2 weeks for effect of drug to be noted
    e. May cause hypoglycemia
  4. Thiazide diuretics
    a. Mildly effective
    b. Inexpensive
    c. Pill form
    d. Should be used with low-sodium diet
  5. Low-sodium diet (NaCl < 1.0 g/1000 kcal/ME)
  6. No treatment—provide continuous source of water
C. Nephrogenic diabetes insipidus
  1. Thiazide diuretics
  2. Low-sodium diet (NaCl < 1.0 g/1000 kcal/ME)
  3. No treatment—provide continuous source of water
D. Primary (psychogenic) polydipsia
  1. Water restriction at times
  2. Water limitation
  3. Change in environment or daily routine; exercise; increased contact with humans or dogs

ME, Metabolizable energy.

Treatment

Therapeutic options for dogs and cats with diabetes insipidus are listed in Box 46.2. The synthetic analog of vasopressin, DDAVP, is the standard therapy for CDI. DDAVP has almost three times the antidiuretic action of AVP, with minimal to no vasopressor or oxytocic activity. The intranasal DDAVP preparation (DDAVP nasal drops, 2.5- and 5.0-mL bottles

containing 100 μg DDAVP/mL) is used most commonly in treating CDI in dogs and cats. Administration of medication to animals via the intranasal route is possible but is not recommended. The DDAVP nasal preparation may be transferred to a sterile eye dropper bottle and drops placed into the conjunctival sac of the dog or cat. Although the solution is acidic, ocular irritation rarely occurs. One drop of DDAVP contains 1.5 to 4 μg of DDAVP, and a dosage of one to four drops administered once or twice daily controls signs of CDI in most animals.

Because of the expense of DDAVP nasal drops and loss of DDAVP drops from the conjunctival sac with head shaking, blinking, and inadvertent application of excessive amounts, our preference is to initially try oral DDAVP (DDAVP tablets, 0.1 and 0.2 mg) when using response to DDAVP to establish the diagnosis of CDI and when providing long-term treatment for CDI. Clinical response in humans is variable, in part because the bioavailability of oral DDAVP is approximately 5% to 15% of the intranasal dose in humans. Similar information is not available for dogs and cats. Our initial dose of oral DDAVP is 0.05 mg for dogs weighing less than 5 kg and for cats, 0.1 mg for dogs weighing 5 to 20 kg, and 0.2 mg for dogs weighing more than 20 kg given every 12 hours. The frequency of administration is increased to every 8 hours if unacceptable PU and PD persist 1 week after therapy is initiated. Treatment should be switched to the intranasal DDAVP preparation if minimal to no response to oral DDAVP administered three times a day is noted. Decreasing the frequency of administration, decreasing the dose of DDAVP, or both can be tried once clinical response has been documented. Periodic monitoring of serum electrolytes is also recommended and the dose of DDAVP adjusted if hyponatremia develops. To date, most dogs have required 0.1 to 0.2 mg of DDAVP two to three times a day, and most cats have required 0.025 to 0.05 mg of DDAVP two to three times a day, for control of PU and PD.

DDAVP parenteral (2 mL vials containing 4 μg/mL) can be used in lieu of the nasal formulation or oral tablets. In humans, parenteral administration of DDAVP is 5 to 20 times as potent as DDAVP nasal. The initial parenteral dosage of DDAVP is 0.5 to 1.0 μg administered SC once a day. Subsequent adjustments in the dose and frequency of administration are based on improvement in PU and PD, duration of clinical response, and changes in serum sodium concentration. Hyponatremia is more apt to develop with parenteral DDAVP than with tablets or nasal spray and can mimic the syndrome of inappropriate vasopressin secretion.

The maximal effect of DDAVP, regardless of the route of administration, occurs from 2 to 8 hours after administration, and the duration of action ranges from 8 to 24 hours. Larger doses of DDAVP appear both to increase its antidiuretic effects and to prolong its duration of action; however, expense becomes a limiting factor. The medication may be administered exclusively in the evening as insurance against nocturia.

We have had excellent results in dogs and cats receiving daily medication for longer than 5 years. Owners of dogs and cats with CDI have reported that their pets become accustomed to receiving eye drops, mentioning eye or conjunctival irritation as an infrequent complication. If PU and PD recur despite DDAVP therapy, several possibilities should be considered, including problems with owner compliance or administration technique, inadequate dose, outdated or inactivated DDAVP, or development of a concurrent disorder causing PU and PD. Hyperadrenocorticism is the primary differential when PU and PD recur despite DDAVP treatment in a dog with CDI.

Chlorpropamide, thiazide diuretics, and oral sodium chloride restriction have limited efficacy in the treatment of NDI. DDAVP may control the clinical signs if administered in massive amounts (i.e., five to ten times the amount used for the treatment of CDI), but the cost of the drug obviously detracts from the attractiveness of this therapeutic approach. Fortunately, therapy for CDI or NDI is not mandatory as long as the dog or cat has unlimited access to water and is housed in an environment that cannot be damaged by severe PU. A constant water supply is of paramount importance because relatively short periods of water restriction can have catastrophic results (i.e., the development of hypernatremic, hypertonic dehydration, and neurologic signs).

Prognosis

Dogs and cats with idiopathic or congenital CDI usually become asymptomatic with appropriate therapy, and with proper care these animals have an excellent life expectancy. Unfortunately, many owners discontinue DDAVP therapy or elect euthanasia of their pet after a few months because of the expense of DDAVP. Without therapy, these animals often lead acceptable lives as long as water is constantly provided and they are housed in an environment that cannot be damaged by severe PU. However, the untreated animal is always at risk for developing life-threatening dehydration if water is withdrawn for longer than a few hours. PU and PD frequently resolve in dogs and cats with trauma-induced CDI, often within 2 weeks of the traumatic incident. The prognosis in dogs and cats with hypothalamic and pituitary tumors is guarded to grave. Neurologic signs typically develop within 6 months after the diagnosis of CDI, and clinical response to radiation therapy and chemotherapy is variable and unpredictable.

The prognosis for animals with primary NDI is guarded to poor because of limited therapeutic options and a generally poor response to therapy. The prognosis for animals with secondary NDI depends on the prognosis of the primary problem.

PRIMARY (PSYCHOGENIC) POLYDIPSIA

Primary PD is defined as a marked increase in water intake that cannot be explained as a compensatory mechanism for excessive fluid loss. In humans, primary PD results from a defect in the thirst center or may be associated with mental illness. Primary dysfunction of the thirst center resulting in

compulsive water consumption has not been reported in the dog or the cat, although an abnormal vasopressin response to hypertonic saline infusion has been reported in dogs with suspected primary PD. A psychogenic or behavioral basis for compulsive water consumption has been described in the dog, typically in young hyperactive dogs that have been placed in exercise-restricted environments but has not been reported in the cat. Psychogenic PD may be induced by concurrent disease (e.g., hepatic insufficiency, hyperthyroidism) or may represent a learned behavior after a change in the pet's environment. PU is compensatory to prevent overhydration. Psychogenic PD can be diagnosed in dogs of any age, either gender, and numerous breeds.

Dogs (and presumably cats) with primary or psychogenic PD have an intact hypothalamic-pituitary-renal axis for controlling fluid balance and variable severity of renal medullary solute washout. Because AVP production and renal tubular response to AVP are normal, these dogs can concentrate urine in excess of 1.030. Depending on the severity of renal medullary solute washout, a period of 24 hours or longer of water deprivation may be necessary to attain concentrated urine. Urine specific gravity may vary widely over time and concentrated urine may be identified on random urine evaluation. Identification of concentrated urine implies hypothalamic AVP production, pituitary AVP secretion, and renal tubular responsiveness to AVP.

Psychogenic PD is diagnosed by exclusion of other causes of PU and PD and by demonstrating that the dog or cat can concentrate urine to a specific gravity in excess of 1.030 during water deprivation.

Treatment is aimed at gradually limiting water intake to amounts in the upper end of the normal range. The client should determine the dog's approximate water intake over a 24-hour period when free-choice water is allowed; this volume of water is then reduced by 10% per week until water volumes of 60 to 80 mL/kg/24 h are reached. The total 24-hour volume of water should be divided into several aliquots, with the last aliquot given at bedtime. Oral salt (1 g/30 kg q12h) and/or oral sodium bicarbonate (0.6 g/30 kg q12h) may also be administered for 3 to 5 days to help reestablish the renal medullary concentration gradient. Changes in the dog's environment or daily routine should be considered, such as initiating a daily exercise routine; bringing a second pet into the home; providing some distraction, such as a radio playing when the clients are not at home; or moving the dog to an area that will ensure an increased amount of contact with humans.

ENDOCRINE ALOPECIA

Symmetric alopecia without historical or clinical evidence of inflammation usually results from hair cycle arrest induced by hormonal disease or imbalance—hence the term *endocrine alopecia* (Fig. 46.3). Hair follicles are atrophic, the hairs are easily epilated, the skin is often thin and hypotonic, and hyperpigmentation is common. Other dermatologic lesions, such as scales, crusts, and papules, are absent. Seborrhea and pyoderma may develop, depending on the underlying cause.

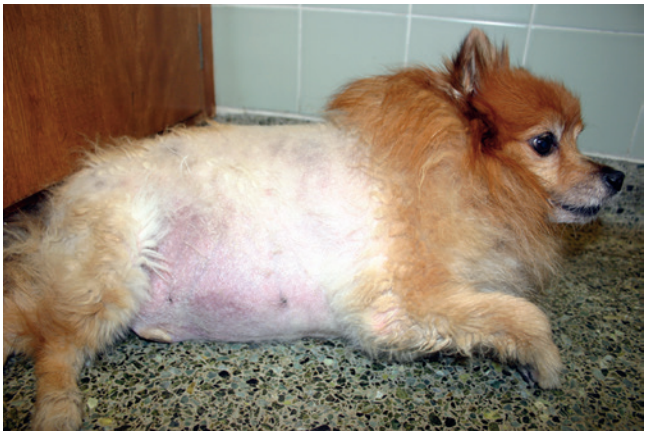


FIG 46.3
Endocrine alopecia, thin skin, and severe obesity in a 7-year-old male castrated Pomeranian with iatrogenic hyperadrenocorticism caused by long-term administration of prednisone for a seizure disorder. Note the symmetric truncal alopecia with sparing of the head and distal extremities.

Causes of endocrine alopecia are listed in Table 46.4. In dogs the most common causes are hypothyroidism and glucocorticoid excess (iatrogenic or spontaneous). Hormone-induced causes of alopecia are not common in cats. The diagnostic evaluation for endocrine alopecia begins with a complete history, physical examination, CBC, serum biochemistry panel, and urinalysis. Results of these tests often provide evidence of hypothyroidism and hyperadrenocorticism; appropriate diagnostic tests can then be performed to confirm these diagnoses (see Chapters 48 and 50, respectively).

Once hypothyroidism and hyperadrenocorticism have been ruled out, the next diagnostic step is to rule out an excess or less commonly a deficiency of one of the sex hormones, most notably estrogen and progesterone. Dermatologic manifestations are similar for most sex hormone–induced dermatoses and include endocrine alopecia that initially begins in the perineal, genital, and ventral abdominal regions and spreads cranially; dull, dry, easily epilated hair; failure of the haircoat to regrow after clipping; and variable presence of seborrhea and hyperpigmentation. Additional clinical signs of hyperestrogenism may include gynecomastia, a pendulous prepuce, the attraction of other male dogs, squatting to urinate, and unilateral testicular atrophy (contralateral to the testicular tumor) in the male dog, and vulvar enlargement and persistent proestrus or estrus in the female dog. Results of a CBC may reveal aplastic anemia. Histologic assessment of a skin biopsy specimen can be used to identify nonspecific endocrine-related alterations and to support the diagnosis of endocrine alopecia (Table 46.5). No pathognomonic histologic changes are noted for sex hormone–induced dermatoses. Identification of cornified epithelial cells on cytologic examination of vaginal or preputial smears provides a clue

TABLE 46.4

Disorders Causing Endocrine Alopecia

DISORDER	COMMON CLINICOPATHOLOGIC ABNORMALITIES	DIAGNOSTIC TESTS
Hypothyroidism	Lipemia, hypercholesterolemia, mild nonregenerative anemia	Serum T_4, free T_4, TSH concentrations
Hyperadrenocorticism	Stress leukogram, increased ALP, hypercholesterolemia, hyposthenuria, proteinuria, urinary tract infection	Urine cortisol/creatinine ratio, low-dose dexamethasone suppression test, abdominal US
Hyperestrogenism		
Functional Sertoli cell tumor in male dog	None (bone marrow depression uncommon)	Physical findings, abdominal US, cytologic or histopathologic findings, plasma estrogen concentration
Hyperestrogenism in intact female dog (follicular cyst)	None (bone marrow depression uncommon)	Vaginal cytology, abdominal US, plasma estrogen concentration, response to ovariohysterectomy
Hyperprogesteronism Luteal cyst in intact female dog Adrenocortical tumor	None	Physical findings, abdominal US, serum progesterone concentrati
Increased adrenocortical steroid hormone intermediates Occult (atypical) hyperadrenocorticism	None	Measure adrenocortical steroid hormone intermediates before and after ACTH administration
Growth hormone deficiency pituitary dwarfism	None	Signalment, physical findings
Alopecia X*	None	Measure adrenocortical steroid hormone intermediates before and after ACTH administration
Feline endocrine alopecia	None	Response to progestin therapy
Telogen defluxion (effluvium)	None	History of recent pregnancy or diestrus
Diabetes mellitus	Hyperglycemia, glycosuria	Blood and urine glucose measurement

ACTH, Adrenocorticotropic hormone; *ALP,* alkaline phosphatase; *T_4,* tetraiodothyronine; *TSH,* thyroid-stimulating hormone; *US,* ultrasonography.
*Alopecia X encompasses previously named syndromes such as growth hormone–responsive dermatosis, castration-responsive dermatosis, estrogen-responsive dermatosis, biopsy-responsive dermatosis, and congenital adrenal hyperplasia–like syndrome.

to the presence of hyperestrogenism (see Chapter 54), and documenting an increased plasma estrogen (i.e., estradiol) concentration provides further evidence for the presence of a functional Sertoli cell tumor in the dog and hyperestrogenism in the bitch (assuming that the bitch is not in proestrus or early estrus). Abdominal ultrasound may identify ovarian cysts or neoplasia in the bitch with hyperestrogenism, and abdominal and testicular ultrasound may identify testicular neoplasia in the male dog. Hyperestrogenism and endocrine alopecia should resolve after surgical removal of the ovarian cyst, ovarian tumor, or testicular tumor.

An abnormal increase in serum progesterone may result from adrenocortical neoplasia (more common in cats than dogs) or functional ovarian luteal cysts in the bitch and may serve as a component of an imbalance in adrenocortical steroid hormone intermediates. Functional luteal cysts may cause prolonged anestrus or failure to cycle in the bitch. Clinical features of progesterone-secreting adrenocortical tumors mimic hyperadrenocorticism (see Chapter 50). Documenting increased serum progesterone concentration establishes the diagnosis, especially in a male or female spayed cat or dog. Serum progesterone is normally increased in an intact female dog or cat in diestrus. A history of recent cycling behavior and examination of the ovaries and adrenal glands with abdominal ultrasound will help differentiate diestrus, functional luteal cysts, and adrenal neoplasia.

Alopecia X is a syndrome in dogs characterized by hair cycle arrest, endocrine alopecia, and hyperpigmentation. Alopecia X has been identified in many breeds, most notably Nordic Breeds, Poodles, and "plush-coated dogs" such as the Pomeranian, Chow, Samoyed, and Keeshond (Fig. 46.4). Alopecia occurs in young adult dogs and occurs equally in males and females, intact or neutered. Systemic illness is not a feature of Alopecia X. Routine blood and urine test results are typically normal. Skin biopsy specimens from affected dogs show the typical changes of endocrine alopecia (see

TABLE 46.5

Dermatohistopathologic Alterations Associated With Endocrinopathy-Induced Alopecia

ABNORMALITY	SPECIFIC ENDOCRINE DISORDER
Nonspecific Abnormalities Supporting an Endocrinopathy	
Orthokeratotic hyperkeratosis	—
Follicular keratosis	—
Follicular dilation	—
Follicular atrophy	—
Predominance of telogen hair follicles	—
Sebaceous gland atrophy	—
Epidermal atrophy	—
Epidermal melanosis	—
Thin dermis	—
Dermal collagen atrophy	—
Abnormalities Suggestive of Specific Endocrine Disorder	
Decreased amount and size of dermal elastin fibers	Hyposomatotropism
Excessive trichilemmal keratinization (flame follicles)	Alopecia X, Growth hormone– and castration-responsive dermatosis
Vacuolated and/or hypertrophied arrector pili muscles	Hypothyroidism
Increased dermal mucin content	Hypothyroidism
Thick dermis	Hypothyroidism
Comedones	Hyperadrenocorticism
Calcinosis cutis	Hyperadrenocorticism
Absence of arrector pili muscles	Hyperadrenocorticism

Table 46.5) and may also show features of follicular dysplasia. The cause is unknown and may be multifactorial or may differ between breeds. *Alopecia X* is somewhat of an umbrella term that encompasses previously named syndromes such as growth hormone (GH)–responsive dermatosis, castration-responsive dermatosis, biopsy-responsive dermatosis, and congenital adrenal hyperplasia–like syndrome. An increase in one or more of the adrenocortical steroid hormone intermediates such as progesterone, 17-hydroxyprogesterone, and androstenedione was initially proposed as the underlying cause of Alopecia X, but subsequent studies failed to confirm adrenal hormone imbalance as the cause, although steroid hormone intermediates may play a role in some dogs. The diagnosis of Alopecia X is based on ruling out other endocrine diseases known to cause endocrine alopecia.

Melatonin is perhaps the least innocuous nonspecific treatment option for dogs with suspected Alopecia X. Melatonin, a neurohormone produced by the pineal gland, controls the circadian and seasonal reproductive and hair growth cycles. One reported treatment protocol for dogs with Alopecia X is 3 mg of melatonin for dogs weighing 15 kg or less and 6 mg for dogs weighing more than 15 kg administered every 12 hours initially for 6 to 8 weeks, with subsequent adjustments based on clinical response (i.e., regrowth of hair). Partial to complete hair regrowth occurred in 62% of 29 dogs treated with melatonin. Trilostane and mitotane have also been used to treat Alopecia X and occult (atypical) hyperadrenocorticism in dogs (see Chapter 50, Occult [Atypical] Hyperadrenocorticism section). Response to melatonin, trilostane, and mitotane treatment has not been uniform or predictable.

Many clients elect not to treat their dog once hypothyroidism, hyperadrenocorticism, ovarian cysts, and neoplasia of the adrenal gland, ovary, and testis have been ruled out. For these dogs, the long-term prognosis is good, even without treatment. Dogs remain healthy, aside from the alopecia and hyperpigmentation.

FELINE ACROMEGALY

Etiology

Chronic excessive secretion of GH in adult cats results in acromegaly, a disease characterized by overgrowth of connective tissue, bone, and viscera. In cats acromegaly is caused by a functional adenoma of the somatotropic cells of the pituitary pars distalis that secretes excess GH (Fig. 46.5). In most cats, the pituitary tumor is a macroadenoma that extends dorsally above the sella turcica. Progestogen-induced acromegaly has not been documented in the cat. Progestogens, including megestrol acetate, do not appear to increase serum GH or insulin-like growth factor 1 (IGF-1) concentrations in the cat. In contrast, acromegaly in the dog is seen most commonly after prolonged exposure to progestogens, administered either exogenously (e.g., medroxyprogesterone acetate) or late in life after years of endogenous progesterone secretion during the diestrual phase of the estrous cycle in the intact bitch. Acromegaly caused by a pituitary somatotroph adenoma and by GH-producing mammary tumors has been reported in the dog but is rare.

Chronic excessive secretion of GH has catabolic and anabolic effects. The anabolic effects are caused by increased concentrations of IGF-1. The growth-promoting effects of IGF-1 result in proliferation of bone, cartilage, and soft tissues, and in organomegaly, most notably of the kidney and heart. These anabolic effects are responsible for producing the classic clinical manifestations of acromegaly (Box 46.3). The catabolic effects of GH are a direct result of GH-induced insulin resistance, which ultimately leads to carbohydrate intolerance, hyperglycemia, and the development of diabetes mellitus that quickly becomes resistant to insulin treatment. Most but not all cats with acromegaly have



FIG 46.4
(A) and **(B)** Endocrine alopecia in a 6-year-old Pomeranian with suspected adult-onset, growth hormone (GH)-responsive dermatosis; this is a presumptive diagnosis that is now included in the syndrome called *Alopecia X*. Note the symmetric truncal alopecia with lesser involvement of the extremities and sparing of the head.

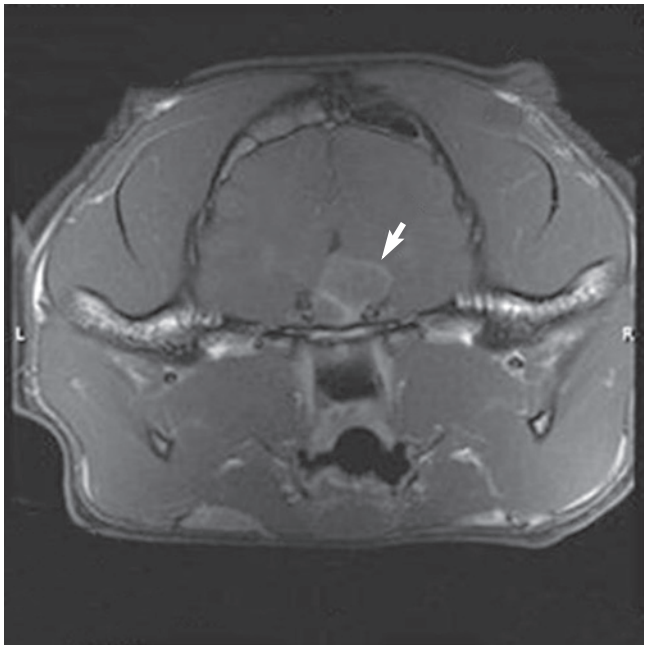


FIG 46.5
Magnetic resonance image of the pituitary region of a 6-year-old male, castrated domestic short-haired cat with insulin-resistant diabetes mellitus and acromegaly (see Fig. 46.6, *A*). A mass is evident in the hypothalamic-pituitary region *(arrow)*.

BOX 46.3

Clinical Signs Associated With Acromegaly in Cats

Anabolic, IGF-1–Induced

Respiratory*
- Inspiratory stridor, stertor

Conformational*
- Increased size
- Increased soft tissue in oropharyngeal/laryngeal area

Enlargement of:
- Abdomen
- Head*
- Feet
- Viscera*

Broad face*
Prognathia inferior*
Increased interdental space*
Degenerative polyarthropathy

Catabolic, GH-Induced

Polyuria, polydipsia*
Polyphagia*

Neoplasia-Induced

Lethargy, stupor

GH, Growth hormone; *IGF-1,* insulin-like growth factor 1.
*Common findings.

diabetes mellitus at the time acromegaly is diagnosed, and most eventually develop severe resistance to exogenously administered insulin.

Clinical Features

Acromegaly typically occurs in male, mixed-breed cats that are 8 years of age or older (range, 4-17 years). Clinical signs result from the catabolic and diabetogenic effects of GH, the anabolic actions of chronic IGF-1 secretion by the liver, and the growth of the pituitary macroadenoma (see Box 46.3). The earliest clinical signs are usually PU, PD, and polyphagia resulting from concurrent diabetes mellitus. Polyphagia can become quite intense. Weight loss varies and depends in part on whether the anabolic effects of IGF-1

or the catabolic effects of uncontrolled diabetes predominate. Most cats initially lose weight and then experience a period of stabilization, followed by a slow, progressive gain in body weight as the anabolic effects of IGF-1 begin to dominate the clinical picture. Severe insulin resistance eventually develops. Insulin dosages in cats with acromegaly frequently exceed 2 to 3 U/kg of body weight twice a day, with minimal to no apparent decline in the blood glucose concentration.

Clinical signs related to the anabolic actions of excessive GH secretion (see Box 46.3) may be evident before or at the time diabetes mellitus is diagnosed. More commonly, however, they become apparent several months after diabetes has been diagnosed, often in conjunction with the realization that hyperglycemia is difficult to control with exogenous insulin therapy. Because of the insidious onset and slowly progressive nature of the anabolic clinical signs, clients are often not aware of subtle changes in the appearance of their cat until the clinical signs are quite obvious. Anabolic changes in acromegalic cats include an increase in body size; enlargement of the abdomen, head, and paws; development of prognathia inferior; widening of the interdental spaces; and weight gain (Fig. 46.6). Weight gain in a cat with poorly regulated diabetes mellitus is an important diagnostic clue to acromegaly. Over time, organomegaly, especially of the heart, kidney, liver, and adrenal gland, may develop. Cardiac abnormalities are common and include concentric left ventricular hypertrophy, diastolic functional abnormalities, and left atrial enlargement. Systemic hypertension may also be present. Cardiomegaly may lead to congestive heart failure. Diffuse thickening of soft tissues in the pharyngeal region can lead to extrathoracic upper airway obstruction and respiratory distress.

Neurologic signs may develop as a result of pituitary tumor growth and resultant invasion and compression of the hypothalamus and thalamus. Signs include altered mentation, adipsia, anorexia, temperature deregulation, circling, seizures, and changes in behavior. Blindness is not common because the optic chiasm is located anterior to the pituitary gland. Papilledema may be evident during an ophthalmic examination. Peripheral neuropathy causing weakness, ataxia, and a plantigrade stance may develop as a result of poorly controlled diabetes mellitus. Other endocrine and metabolic abnormalities resulting from the compressive effects of the tumor on the pituitary are uncommon.

Clinical Pathology

Concurrent, poorly controlled diabetes mellitus is responsible for causing most of the abnormalities identified on a serum biochemistry panel and urinalysis, including hyperglycemia, glycosuria, hypercholesterolemia, and a mild increase in alanine transaminase and alkaline phosphatase activities. Ketonuria is an infrequent finding. Mild erythrocytosis, persistent mild hyperphosphatemia without concurrent azotemia, and persistent hyperproteinemia (total serum protein concentration of 8.2-9.7 mg/dL) with a normal pattern of distribution on protein electrophoretic studies



FIG 46.6
(A) A 6-year-old male, castrated domestic short-haired cat with insulin-resistant diabetes mellitus and acromegaly. Note the broad face and the mildly protruding mandible (prognathia inferior). **(B)** and **(C)** An 8-year-old male, castrated domestic short-haired cat with insulin-resistant diabetes mellitus and acromegaly. Note the broad head, the mildly protruding mandible, and the prognathia inferior with displacement of the lower canine teeth. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

may also be found. Renal failure is a potential sequela of acromegaly and, if present, will be associated with azotemia, isosthenuria, and proteinuria.

Diagnosis

Clinical suspicion for acromegaly is based on the identification of conformational alterations (e.g., increased body size, large head, prognathia inferior, organomegaly) associated with acromegaly and a stable or progressive increase in body weight in a cat with insulin-resistant diabetes mellitus. Measurement of serum IGF-1 concentrations provides further evidence for the diagnosis of acromegaly. Measurement of serum IGF-1 is commercially available (e.g., the Diagnostic Center for Population and Animal Health, Michigan State University, East Lansing, Mich; www.dcpah.msu.edu). Concentrations are usually increased in acromegalic cats, but values may be in the reference range in the early stages of the disease (Fig. 46.7). Repeat measurements performed 3 to 6 months later usually reveal an increase in serum IGF-1 if acromegaly is present. This increase in serum IGF-1 typically coincides with development and growth of the pituitary somatotropic adenoma. Serum IGF-1 concentrations are lower in newly diagnosed untreated diabetic cats, compared with healthy cats, and serum IGF-1 concentrations increase after initiation of insulin treatment. Fortunately, most cats are diabetic and being treated with insulin at the time acromegaly is diagnosed. Increased serum IGF-1 concentrations have been identified in a small number of poorly controlled diabetic cats in which the poor control was not caused by acromegaly and in cats with acromegaly that do not have concurrent diabetes mellitus. In the nondiabetic cats, acromegaly is usually suspected based on the presence of a large cat with prognathia inferior, organomegaly, and cardiac abnormalities.

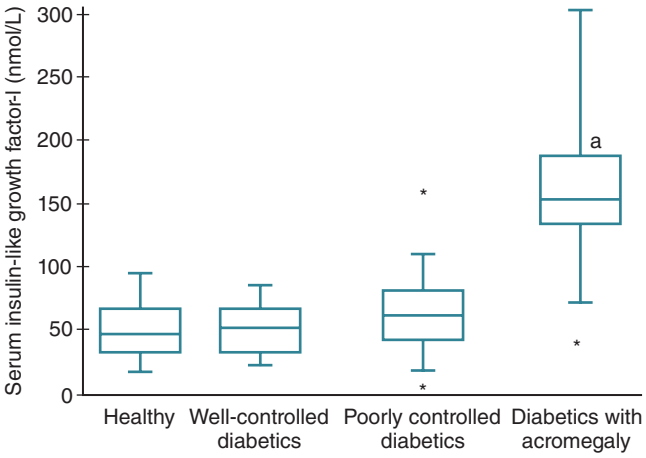


FIG 46.7
Box plots of serum concentrations of insulin-like growth factor 1 (IGF-1) in 38 healthy cats, 15 well-controlled diabetic cats, 40 poorly controlled diabetic cats, and 19 poorly controlled diabetic cats with acromegaly. For each box plot, T-bars represent the main body of data, which in most instances is equal to the range. Each box represents the interquartile range (twenty-fifth to seventy-fifth percentile). The horizontal bar in each box is the median. Asterisks represent outlying data points. a, $P < 0.0001$, compared with healthy cats and well-controlled and poorly controlled diabetic cats. (From Berg RIM, et al.: Serum insulin-like growth factor-I concentration in cats with diabetes mellitus and acromegaly, *J Vet Intern Med* 21:892, 2007.)

Interpretation of serum IGF-1 test results should always take into consideration the status of control of the diabetic state, the presence and severity of insulin resistance, and the index of suspicion for acromegaly based on review of the history, physical examination, and results of routine blood and urine tests and diagnostic imaging. Identification of an increased serum IGF-1 concentration in a poorly controlled diabetic cat with insulin resistance and clinical features suggestive of acromegaly supports the diagnosis and provides justification for CT or MR imaging of the pituitary gland. A pituitary mass documented by CT or MR scanning (see Fig. 46.5) adds further evidence for the diagnosis and is indicated whenever the client is considering radiation treatment. It is usually necessary to administer a positive contrast agent for visualization of a pituitary mass when CT or MR imaging is used.

A definitive diagnosis of acromegaly requires documentation of an increased baseline serum GH concentration. Baseline serum GH concentration in cats with acromegaly typically exceeds 10 ng/mL (reference range varies with the laboratory but is typically < 7.2-7.9 ng/mL in cats). Unfortunately, a commercial GH assay is not currently available for cats in the United States.

ACROMEGALY VERSUS HYPERADRENOCORTICISM

Hyperadrenocorticism and acromegaly are uncommon disorders that occur in older cats, have a strong association with diabetes mellitus, can cause severe insulin resistance, and are often caused by a functional pituitary macrotumor. Clinical signs related to poorly controlled diabetes mellitus are common in cats with hyperadrenocorticism and acromegaly. Additional clinical signs differ dramatically between the two disorders. Hyperadrenocorticism is a debilitating disease that results in progressive weight loss leading to cachexia and dermal and epidermal atrophy causing extremely fragile, thin, and easily torn and ulcerated skin (i.e., feline fragile skin syndrome). In contrast, conformational changes caused by the anabolic actions of chronic IGF-1 secretion dominate the clinical picture in acromegaly, most notably an increase in body size, prognathia inferior, and weight gain despite poorly regulated diabetes mellitus. Feline fragile skin syndrome does not occur with acromegaly. With both disorders most of the abnormalities identified on routine blood and urine tests are caused by concurrent poorly controlled diabetes mellitus. Abdominal ultrasound may reveal mild bilateral adrenomegaly with both disorders. Ultimately, differentiation between the two diseases is based on results of tests of the pituitary-adrenocortical axis (see Chapter 50) and serum GH and/or IGF-1 concentrations.

Treatment

Radiation therapy is currently considered the most viable treatment option for acromegaly in cats. Types and techniques of radiation, treatment protocols, and follow-up schedules vary widely between institutions. Radiation therapy is effective in improving insulin resistance and clinical signs of diabetes mellitus, and in decreasing tumor size, in 50% or more of treated acromegalic cats. However, the clinical response to radiation therapy is unpredictable and ranges from no response to a dramatic response, characterized by shrinkage of the tumor; elimination of hypersomatotropism; resolution of insulin resistance; and reversion to a subclinical diabetic state. Typically, tumor size and plasma GH and, and less reliably, serum IGF-1 concentrations are decreased and insulin responsiveness improves after radiation therapy, although this improvement is difficult to predict and may occur within a few weeks or not for several months after radiation treatment is finished. Treated cats that respond to radiation therapy are at risk for developing potentially severe hypoglycemia. Close monitoring of blood glucose concentrations, preferably by the owner at home, is highly recommended (see Chapter 49). In most treated cats that respond to radiation therapy, diabetes mellitus and/or insulin resistance recurs 6 months or longer after treatment, although growth of the pituitary mass is often not evident on CT or MR imaging.

Successful use of both microsurgical transsphenoidal hypophysectomy and transsphenoidal cryotherapy of a pituitary tumor has been described in a cat with acromegaly. Although preliminary studies evaluating newer somatostatin analogs (e.g., pasireotide are promising, a cost-effective medical treatment for acromegaly in cats has yet to be identified.

MANAGING INSULIN-RESISTANT DIABETES

Diabetes mellitus is difficult to control in an acromegalic cat, even with the administration of large doses of insulin (≥20 U/injection) twice daily. Cats typically have blood glucose concentrations that remain in excess of 400 mg/dL regardless of the dosage or type of insulin administered. In our experience, control of hyperglycemia is difficult to attain in most acromegalic cats. The goal of insulin treatment is to avoid severe hyperglycemia (blood glucose concentrations >500 mg/dL) and hypoglycemia—not to attain control of the diabetic state per se. Increases in the insulin dose should not be based on the severity of PU, PD, or polyphagia, or persistent hyperglycemia and glycosuria but rather on the owner's perception of how the cat is doing in terms of activity, ambulation, grooming behavior, and interactions with family members. Severe hyperglycemia causes lethargy, obtundation, and the perception that the cat is "not feeling well." We consider increasing the insulin dose if owners report these problems, especially if the blood glucose concentration is consistently greater than 500 mg/dL. We are cautious when increasing the insulin dose because of concerns for the development of severe life-threatening hypoglycemia, which can occur unexpectedly after months of severe insulin resistance, presumably as a result of sporadic reductions in GH secretion and subsequent improvement in insulin resistance. We rarely exceed 12 to 15 units of insulin per injection, and then only because of owner concerns that the cat is "not feeling well" and only after blood glucose concentrations are measured to confirm the presence of severe hyperglycemia. Home blood glucose monitoring and testing of urine for the presence of glucose by the owner should be encouraged to help prevent hypoglycemia and to identify when insulin resistance has improved (see Chapter 49).

Prognosis

The short- and long-term prognosis for cats with tumor-induced acromegaly is guarded to good and poor, respectively. In our experience, survival time has ranged from 4 to 60 months (typically, 1.5-3 years) from the time the diagnosis of acromegaly is established. The GH-secreting pituitary tumor usually grows slowly, and neurologic signs associated with an expanding tumor are uncommon until late in the disorder. Most cats with acromegaly eventually die or are euthanized because of the development of kidney failure, congestive heart failure, respiratory distress from severe thickening of soft tissues in the oropharyngeal region, coma caused by severe hypoglycemia, or neurologic signs caused by an expanding pituitary tumor.

PITUITARY DWARFISM

Etiology

Pituitary dwarfism results from a congenital deficiency of GH. Studies in German Shepherd dog dwarfs suggest that congenital GH deficiency is caused by primary failure of differentiation of the craniopharyngeal ectoderm into normal tropic hormone-secreting pituitary cells. Pituitary cysts are commonly identified through diagnostic imaging of the pituitary region using CT or MR imaging and may enlarge as the pituitary dwarf ages. However, current belief is that pituitary cysts develop secondary to primary failure of anterior pituitary formation in most pituitary dwarfs. Pituitary dwarfism is encountered most often as a simple, autosomal recessive inherited abnormality in the German Shepherd dog. A similar mode of inheritance has been reported in Karelian Bear dogs and Saarloos and Czechoslovakian Wolfdogs. Inherited pituitary dwarfism may be due to isolated GH deficiency or may be part of a combined pituitary hormone deficiency. Concurrent deficiencies in thyroid-stimulating hormone (TSH) and prolactin and impaired release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are most commonly identified in affected German Shepherd dogs; adrenocorticotropic hormone (ACTH) secretion is preserved. An LHX3 mutation is associated with pituitary dwarfism in German Shepherd dogs and Wolfdogs. Kooistra et al (2000) hypothesize that the disorder is caused by a mutation in a developmental transcription factor that precludes effective expansion of a

pituitary stem cell after differentiation of the corticotropic cells that produce ACTH. Pituitary dwarfism resulting from a mutant GH or insensitivity to GH owing to lack of or a defect in GH receptors (e.g., Laron-type dwarfism in human beings) has not been documented in dogs or cats.

Clinical Features

SIGNALMENT

Pituitary dwarfism occurs primarily in German Shepherd dogs, Karelian Bear dogs, and Saarloos and Czechoslovakian Wolfdogs, although pituitary dwarfism in other dog breeds, including the Weimaraner, Spitz, Miniature Pinscher, Golden Retreiver, and Labrador Retriever, and in cats has been observed. A sex-related predilection is not apparent.

CLINICAL SIGNS

The most common clinical manifestations of pituitary dwarfism are lack of growth (i.e., short stature), endocrine alopecia, and hyperpigmentation of the skin (Box 46.4). Affected animals are usually normal in size during the first 2 to 3 months of life but after that grow more slowly than their litter mates. By 4 to 5 months of age, affected dogs and cats are obviously runts of the litter and do not attain full adult dimensions. Dwarfs with an isolated GH deficiency typically maintain a normal body contour and body proportions as they age (i.e., proportionate dwarfism), whereas dwarfs with combined deficiencies (most notably TSH) may acquire a square or chunky contour typically associated with congenital hypothyroidism (i.e., disproportionate dwarfism; Fig. 46.8).

The most notable dermatologic sign is retention of the lanugo, or secondary hairs, with concurrent lack of the primary or guard hairs. As a result, the haircoat in a dwarf is initially soft and woolly. The lanugo hairs are easily epilated, and a bilateral symmetric alopecia gradually develops in most dwarfs. Initially, hair loss is confined to areas of wear, such as the neck (collar) and posterolateral aspects of the thighs (from sitting). Eventually, the entire trunk, neck, and proximal limbs become alopecic, with primary hairs remaining only on the face and the distal extremities. The skin is initially normal but becomes hyperpigmented, thin, wrinkled, and scaly. Comedones, papules, and secondary pyoderma frequently develop in the adult dwarf. Secondary bacterial infections are common long-term complications.

Hypogonadism may also develop, although normal reproductive function has been observed in some animals with pituitary dwarfism. In the male animal, cryptorchidism, testicular atrophy, azoospermia, and a flaccid penile sheath are typical; in the female, persistent anestrus is common with impaired secretion of pituitary gonadotropins.

Clinical Pathology

Results of CBC, a serum biochemical panel, and urinalysis are usually normal in animals with uncomplicated pituitary dwarfism and isolated GH deficiency. Concurrent deficiency of TSH may result in clinicopathologic abnormalities affiliated with hypothyroidism, such as hypercholesterolemia and anemia (see Chapter 48). Deficiency of GH, IGF-1, and TSH may also affect kidney development and function, resulting in azotemia.

BOX 46.4

Clinical Signs Associated With Pituitary Dwarfism

Musculoskeletal

Stunted growth*
Thin skeleton, immature facial features*
Square, chunky contour (adult)*
Bone deformities
Delayed closure of growth plates
Delayed dental eruption
Muscle atrophy

Dermatologic

Soft, woolly haircoat*
Retention of lanugo hairs*
Lack of guard hairs*
Alopecia*
  Bilaterally symmetric
  Trunk, neck, proximal extremities
Hyperpigmentation of the skin*
Thin, fragile skin
Wrinkles
Scales
Comedones
Papules
Pyoderma
Seborrhea sicca

Reproductive

Testicular atrophy
Flaccid penile sheath
Failure to have estrous cycles

Other Signs

Mental dullness
Shrill, puppy-like bark*
Signs of secondary hypothyroidism
Signs of secondary adrenal insufficiency (uncommon)

*Common findings.

Diagnosis

The signalment, history, and physical examination usually provide sufficient evidence for inclusion of pituitary dwarfism among the tentative diagnoses of short stature. Strong presumptive evidence can be obtained by ruling out other potential causes of small size (Box 46.5) after a thorough evaluation of the history and physical examination findings, results of routine laboratory studies (i.e., CBC, fecal examinations, serum biochemical panel, serum T_4 and TSH concentration, urinalysis), and radiographic studies (Fig. 46.9). Serum IGF-1 concentrations may be decreased or may be in the reference range in pituitary dwarfs. Because baseline



FIG 46.8
(A) A 9-month-old male domestic short-haired cat with pituitary dwarfism. The size of the pituitary dwarf cat was similar to that of an 8-week-old kitten. Note the normal body contour and the juvenile appearance. **(B)** and **(C)** A 7-month-old female German Shepherd dog with pituitary dwarfism. Note the normal body contour, puppy haircoat, and juvenile appearance. **(D)** A 2-year-old female spayed Labrador Retriever with pituitary dwarfism sitting next to an age-matched normal Labrador Retriever to illustrate the small stature and juvenile appearance of the pituitary dwarf. All of the pituitary dwarfs were presented with the primary owner complaint of failure of the pet to grow.

plasma GH concentrations may be low in healthy dogs and cats, a definitive diagnosis of hyposomatotropism has relied on documenting failure of plasma GH concentration to increase during a GH stimulation test using human GH-releasing hormone (GHRH), clonidine, or xylazine. Because a commercial GH assay is currently not available in the United States, a presumptive diagnosis of pituitary dwarfism is based on exclusion of other causes of failure to grow. A genetic test for the LHX3 gene is now available through the University of Utrecht and several other laboratories. GH testing is not necessary if a dwarf tests positive for the mutation.

Treatment

Treatment for pituitary dwarfism relies on the administration of GH. Unfortunately, an effective GH product is not available for use in dogs. Canine GH is not available for therapeutic use, GH antibody formation and legal restrictions preclude the use of biosynthetic human GH, and the concentration of biosynthetic bovine GH in commercial products for use in cattle precludes its use in dogs. The amino acid sequence of porcine GH is identical to that of canine GH, but porcine GH is difficult to find. If available, the recommended subcutaneous dose is 0.1 IU/kg three times per week for 4 to 6 weeks. Because of the synergistic

BOX 46.5

Some Potential Causes of Small Stature in Dogs and Cats

Endocrine Causes

Congenital growth hormone deficiency
Congenital hypothyroidism
Juvenile diabetes mellitus
Congenital hypoadrenocorticism
Hyperadrenocorticism
  Congenital (rare)
  Iatrogenic

Nonendocrine Causes

Malnutrition
Gastrointestinal tract disorders
  Megaesophagus
  Inflammatory diseases
  Infectious diseases
  Heavy intestinal parasitism
Exocrine pancreatic insufficiency
Hepatic disorders
  Portosystemic vascular shunt
  Glycogen storage disease
Renal disease and failure
Cardiovascular disease, anomalies
Skeletal dysplasia; chondrodystrophy
Mucopolysaccharidoses
Hydrocephalus

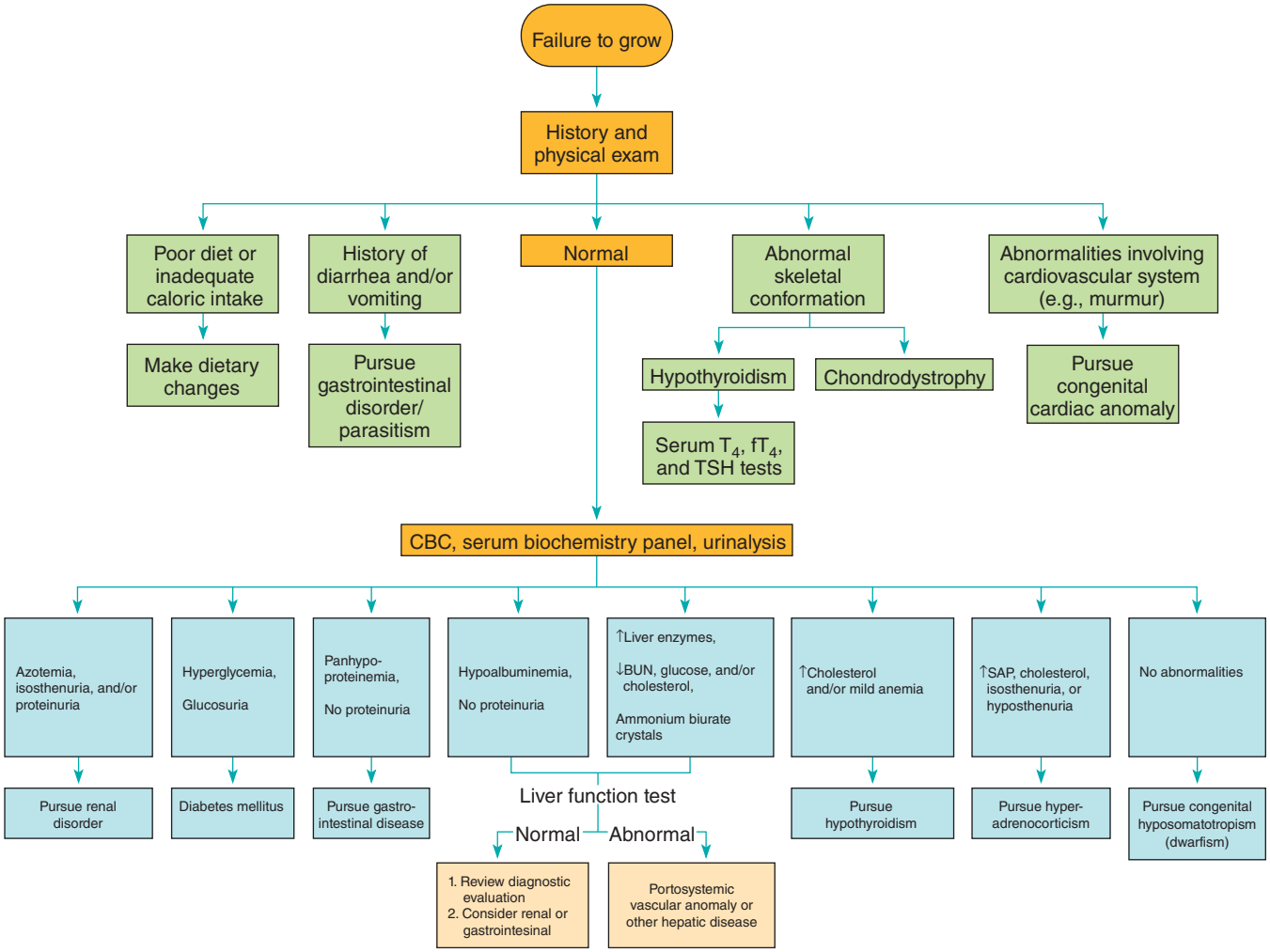


FIG 46.9
Diagnostic approach to the puppy or kitten that fails to grow. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

influence of GH and thyroid hormone on growth processes, subnormal concentrations of thyroid hormone may diminish the effectiveness of GH therapy. Dogs and cats with suspected concurrent TSH deficiency should be treated with daily thyroid hormone supplementation, as discussed in Chapter 48.

Hypersensitivity reactions and insulin resistance leading to diabetes mellitus are the primary adverse reactions associated with GH injections. An increase in height is dependent on the status of the growth plates at the time treatment is initiated. A significant increase in height may occur if the growth plates are open, and minimal to no change in height will occur if the growth plates have closed.

An increase in body size and regrowth of a complete haircoat have been reported in pituitary dwarfs treated with medroxyprogesterone acetate). Progestogens induce expression of the GH gene in the mammary gland of dogs, resulting in GH secretion from foci of hyperplastic ductular epithelial cells and increased plasma concentrations of GH and IGF-1. Adverse reactions associated with progestogen treatment include recurrent pruritic pyoderma, abnormal skeletal development, mammary tumors, diabetes mellitus, acromegaly, and cystic endometrial hyperplasia.

Prognosis

The prognosis for dogs with pituitary dwarfism is unpredictable and dependent on the severity of GH deficiency (i.e., partial or complete); the impact of GH deficiency on development of organ systems such as the skeletal, neuromuscular, and immune systems; presence and expansion of concurrent pituitary cyst; and the severity of changes to the skin that develop over time. In our experience, pituitary dwarf dogs have typically lived 3 to 6 years, with outliers living up to 10 years.

Suggested Readings

Feldman EC, et al. *Canine and feline endocrinology*. ed 4. St. Louis: Elsevier; 2015.

Diabetes Insipidus

Aroch I, et al. Central diabetes insipidus in five cats: clinical presentation, diagnosis and oral desmopressin therapy. *J Fel Med Surg*. 2005;7:333.

Meij BP, et al. Lymphocytic hypophysitis in a dog with diabetes insipidus. *J Comp Path*. 2012;147:503.

Oliveira KM, et al. Head trauma as a possible cause of central diabetes insipidus in a cat. *J Fel Med Surg*. 2012;15:155.

van Vonderen IK, et al. Disturbed vasopressin release in 4 dogs with so-called primary polydipsia. *J Vet Intern Med*. 1999;13:419.

van Vonderen IK, et al. Vasopressin response to osmotic stimulation in 18 young dogs with polyuria and polydipsia. *J Vet Intern Med*. 2004;18:800.

Endocrine Alopecia

Behrend EN, et al. Atypical Cushing's syndrome in dogs: arguments for and against. *Vet Clin N Am*. 2010;40:285.

Frank LA, et al. Adrenal steroid hormone concentrations in dogs with hair cycle arrest (Alopecia X) before and during treatment with melatonin and mitotane. *Vet Derm*. 2004;15:278.

Feline Acromegaly

Berg RIM, et al. Serum insulin-like growth factor-I concentration in cats with diabetes mellitus and acromegaly. *J Vet Intern Med*. 2007;21:892.

Dunning MD, et al. Exogenous insulin treatment after hypofractionated radiotherapy in cats with diabetes mellitus and acromegaly. *J Vet Intern Med*. 2009;23:243.

Fletcher CJ, et al. Hypersomatotropism in 3 cats without concurrent diabetes mellitus. *J Vet Intern Med*. 2016;30:2031.

Gostelow R, et al. Pasireotide long-acting release treatment for diabetic cats with underlying hypersomatotropism. *J Vet Intern Med*. 2017;31:355.

Lamb CR, et al. Computed tomographic signs of acromegaly in 68 diabetic cats with hypersomatotropism. *J Fel Med Surg*. 2014;16:99.

Lourenco ER, et al. Abdominal ultrasonographic findings in acromegalic cats. *J Fel Med Surg*. 2015;17:698.

Meij BP, et al. Successful treatment of acromegaly in a diabetic cat with transsphenoidal hypophysectomy. *J Fel Med Surg*. 2010;12:406.

Murai A, et al. GH-producing mammary tumors in two dogs with acromegaly. *J Vet Med Sci*. 2012;74:771.

Myers JA, et al. Echocardiographic findings in 11 cats with acromegaly. *J Vet Intern Med*. 2014;28:1235.

Niessen SJM, et al. Feline acromegaly: an underdiagnosed endocrinopathy? *J Vet Intern Med*. 2007;21:899.

Posch B, et al. Magnetic resonance imaging findings in 15 acromegalic cats. *Vet Radiol Ultrasound*. 2011;52:422.

Reusch CE, et al. Measurements of growth hormone and insulin-like growth factor 1 in cats with diabetes mellitus. *Vet Rec*. 2006;158:195.

Scudder CJ, et al. Pasireotide for the medical management of feline hypersomatotropism. *J Vet Intern Med*. 2015;29:1074.

Sellon RK, et al. Linear-accelerator-based modified radiosurgical treatment of pituitary tumors in cats: 11 cases (1997-2008). *J Vet Intern Med*. 2009;23:1038.

Tschuor F, et al. Evaluation of four methods used to measure plasma inulin-like growth factor 1 concentrations in healthy cats and cats with diabetes mellitus or other diseases. *Am J Vet Res*. 1925;73:2012.

Pituitary Dwarfism

Knottenbelt CM, Herrtage ME. Use of proligestone in the management of three German Shepherd dogs with pituitary dwarfism. *J Small Anim Pract*. 2002;43:164.

Kooistra HS, et al. Progestin-induced growth hormone (GH) production in the treatment of dogs with congenital GH deficiency. *Domest Anim Endocrinol*. 1998;15:93.

Kooistra HS, et al. Combined pituitary hormone deficiency in German Shepherd dogs with dwarfism. *Domest Anim Endocrinol*. 2000;19:177.

Voorbij PA, et al. Pituitary dwarfism in Saarloos and Czechoslovakian Wolfdogs is associated with a mutation n LHX3. *J Vet Intern Med*. 1770;28:2014.

CHAPTER 47

Disorders of the Parathyroid Gland



CLASSIFICATION OF HYPERPARATHYROIDISM

Hyperparathyroidism is a sustained increase in parathyroid hormone (PTH) secretion. Chief cells located within the parathyroid gland synthesize and secrete PTH—a peptide hormone that controls the minute-to-minute concentration of ionized calcium in the blood and extracellular fluid (ECF). The major regulator of PTH secretion is the concentration of ionized calcium in the blood. Decreased serum ionized calcium increases PTH secretion and vice versa. PTH stimulates calcium absorption from the intestine, stimulates calcium reabsorption and inhibits phosphate reabsorption by the kidney, stimulates synthesis of the active form of vitamin D (calcitriol) in the kidney, and stimulates bone resorption. The net effect consists of increased serum ionized and total calcium concentrations, and decreased serum phosphorus concentration.

Hyperparathyroidism can result from a normal physiologic response to decreased serum ionized calcium concentrations (renal, nutritional, and adrenal secondary hyperparathyroidism) or from a pathologic condition caused by excessive synthesis and secretion of PTH by abnormal, autonomously functioning parathyroid chief cells (i.e., primary hyperparathyroidism [PHP]). In PHP increased secretion of PTH is maintained regardless of the serum ionized calcium concentration. Hypercalcemia and hypophosphatemia develop as a result of the physiologic actions of PTH.

In *renal secondary hyperparathyroidism,* renal failure causes retention of phosphorus, which in turn stimulates secretion of the phosphaturic hormone phosphatonin (fibroblast growth factor-23). Phosphatonin inhibits renal tubular 1α-hydroxylase activity, causing a relative deficiency of calcitriol (the most active form of vitamin D) and decreased intestinal calcium absorption. Retention of phosphorus also directly stimulates PTH secretion and promotes deposition of calcium phosphorus complexes in tissues. The decrease in serum ionized calcium, in turn, stimulates PTH secretion. The net effect consists of increased serum phosphate, normal to low serum ionized calcium, increased serum PTH, and decreased calcitriol concentrations as well as diffuse parathyroid gland hyperplasia. The etiogenesis of hyperparathyroidism is similar in *nutritional secondary hyperparathyroidism,* except that the decrease in calcium results from feeding diets low in calcium and vitamin D or excessive in phosphorus, such as the exclusive feeding of liver or beef heart. Chronic dietary calcium deficiency or phosphorus excess increases PTH secretion and induces parathyroid gland hyperplasia. Depletion of skeletal calcium leads to osteoporosis and pathologic bone fractures. An increase in serum PTH has been documented in dogs with hyperadrenocorticism and is believed to be a compensatory response to increased calcium loss and/or increased serum phosphorus concentrations—hence the term *adrenal secondary hyperparathyroidism.* Serum phosphorus and PTH decrease and serum calcium increases after successful treatment of hyperadrenocorticism.

PRIMARY HYPERPARATHYROIDISM

Etiology

PHP is a disorder resulting from the excessive, relatively uncontrolled secretion of PTH by one or more abnormal parathyroid glands. The physiologic actions of PTH ultimately cause hypercalcemia and hypophosphatemia (Table 47.1). It is an uncommon disorder in the dog and rare in the cat. Parathyroid adenoma is the most common histologic finding in dogs and cats, identified in approximately 80% of dogs and 70% of cats with PHP. Parathyroid carcinoma and parathyroid hyperplasia have also been described in dogs and cats. Parathyroid adenomas are typically small, well-encapsulated, light brown to red tumors located in close apposition to the thyroid gland (Fig. 47.1). The remaining parathyroid glands are normal, atrophied, or not visible at surgery. Parathyroid carcinomas grossly appear similar to adenomas; the diagnosis of carcinoma is based on the finding of certain histologic features such as capsular or vascular invasion by the tumor. The biologic behavior of parathyroid carcinoma is not well characterized in dogs and cats. Similarly, the histologic criteria for differentiating between adenoma and hyperplasia are not well established. Although

TABLE 47.1

Biologic Actions of the Hormones That Affect Calcium and Phosphorus Metabolism

HORMONE	BONE	KIDNEY	INTESTINE	NET EFFECT	
				SERUM Ca	SERUM PO_4
Parathyroid hormone	Increased bone resorption	↑Ca absorption ↑PO_4 excretion	No direct effect	↑	↓
Calcitonin	Decreased bone resorption	↓Ca resorption ↓PO_4 resorption	No direct effect	↓	↓
Vitamin D	Maintains Ca transport system	↓Ca resorption	↑Ca absorption ↑PO_4 absorption	↑	↑

↑, Increased; ↓, decreased; *Ca*, calcium; *PO_4*, phosphorus.

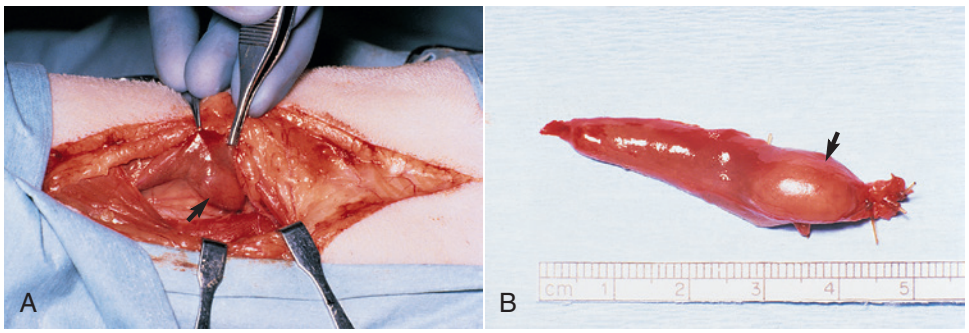


FIG 47.1
(A) Surgical site in a 12-year-old dog with primary hyperparathyroidism (PHP). A parathyroid adenoma *(arrow)* can be seen in the thyroid lobe. **(B)** Gross appearance of parathyroid adenoma *(arrow)* and thyroid lobe after removal from the dog in **A.**

involvement of multiple parathyroid glands suggests hyperplasia, adenoma involving two parathyroid glands and hyperplasia involving only one gland have been identified in dogs with PHP. In addition, hyperplasia caused by renal and nutritional secondary hyperparathyroidism may not cause uniform enlargement of the parathyroid glands even though the stimulus for enlargement is presumably the same for each gland. Differentiating hyperplasia from adenoma has important prognostic implications. The surgical removal of parathyroid adenoma(s) results in a cure, if at least one normal parathyroid gland remains to prevent hypoparathyroidism. In contrast, hypercalcemia caused by parathyroid hyperplasia may persist or recur weeks to months after surgery if the remaining grossly normal-appearing parathyroid tissue is hyperplastic at the time of surgery or becomes hyperplastic in the future.

SIGNALMENT

The age at which clinical signs of PHP appear in dogs ranges from 4 to 16 years, with a mean age of 10 years. No sex-related predilection has been noted. Any breed of dog and mixed-breeds can be affected, although PHP is most commonly diagnosed in the Keeshond and is an autosomal dominant, genetically transmitted disease in this breed. The age at the time of diagnosis of PHP in cats has ranged from 8 to 20 years, with a mean age of 13 years. Most affected cats have been mixed breed and Siamese. No apparent sex predisposition has been reported.

CLINICAL SIGNS

Clinical signs of PHP result from the physiologic actions of excessive PTH secretion rather than from the space-occupying nature of the tumor. Clinical signs are caused by hypercalcemia, which is the hallmark of this disorder, and by the presence of cystic calculi and lower urinary tract infection, which are consequences of the hypercalcemia. Clinical signs are absent in most dogs and cats with the mildest form of PHP, and hypercalcemia is discovered only after a serum biochemistry panel is performed, often for unrelated reasons. When clinical signs do develop, they initially tend to be nonspecific and insidious in onset. Clinical signs in dogs are typically renal, gastrointestinal, and neuromuscular in origin (Box 47.1). The most common clinical signs in cats with PHP are lethargy, anorexia, and vomiting. Less common clinical signs in cats include constipation, polyuria, polydipsia, and weight loss.

BOX 47.1

Clinical Signs Associated With Primary Hyperparathyroidism in Dogs

- Polyuria and polydipsia*
- Muscle weakness*
- Decreased activity*
- Lower urinary tract signs*
  - Pollakiuria
  - Hematuria
  - Stranguria
- Decreased appetite
- Urinary incontinence
- Weight loss/muscle wasting
- Vomiting
- Shivering/trembling
- Constipation

*Common signs.

PHYSICAL EXAMINATION

The physical examination is usually normal, which is an important diagnostic finding when dogs with PHP are differentiated from dogs with hypercalcemia of malignancy (see Chapter 53). Lethargy, generalized muscle atrophy, weakness, and cystic calculi (calcium phosphate, calcium oxalate, or both types) may be noted in some dogs with PHP. The severity of weakness is variable, but it is usually subtle. Cervical palpation of a parathyroid mass is rare in dogs with PHP. If a mass is palpated in the neck of a dog with hypercalcemia, then thyroid gland carcinoma, squamous cell carcinoma, lymphoma, and, least likely, parathyroid gland carcinoma should be considered. In contrast, cats with PHP often have a palpable parathyroid mass that is typically located in the region of the thyroid gland. Therefore a palpable mass in the ventral cervical region of the neck should raise suspicion for hyperthyroidism (common) as well as PHP (rare) in cats.

Diagnosis

PHP should be suspected in a dog or cat with persistent hypercalcemia and normophosphatemia to hypophosphatemia. The serum calcium concentration is typically 12 to 15 mg/dL but can exceed 16 mg/dL (reference range, 9.0-11.7 mg/dL [dog]; 8.0-10.5 mg/dL [cat]). The serum ionized calcium concentration is typically 1.4 to 1.8 mmol/L but can exceed 2.0 mmol/L (reference range, 1.1-1.4 mmol/L for dog and cat). The serum phosphorus concentration is typically less than 4 mg/dL, unless concurrent renal insufficiency is present. Although hypercalcemia in dogs and cats has several causes (Table 47.2), the primary differential diagnoses for hypercalcemia and hypophosphatemia are humoral hypercalcemia of malignancy (most notably lymphoma in dogs and carcinomas in cats) and PHP (see Chapter 53). The history, findings on physical examination, results of routine blood and urine tests, thoracic radiographs, abdominal and cervical ultrasound, and measurement of PTH and parathyroid hormone–related peptide (PTHrP) will usually establish the diagnosis. With PHP, clinical signs are usually mild to absent, the physical examination is normal, and results of routine blood tests, thoracic and abdominal radiography, and abdominal ultrasonography are unremarkable, except for hypercalcemia, hypophosphatemia, and cystic calculi. Additional tests used to identify lymphoma as the cause of hypercalcemia (i.e., cytologic evaluations of bone marrow, lymph node, liver, and splenic aspirates and PTHrP concentrations) are normal in dogs with PHP.

Renal failure in a dog with hypercalcemia can create a diagnostic dilemma. Fortunately, development of hypercalcemia-induced renal failure rarely occurs in dogs with PHP. Prolonged severe hypercalcemia may cause progressive nephrocalcinosis, renal damage, and azotemia, but most dogs with PHP have mild hypercalcemia and concurrent hypophosphatemia; the latter protects the kidney by keeping the calcium × phosphorus product less than 50.

Measurement of serum ionized calcium concentration will help reveal the cause of hypercalcemia in dogs with concurrent renal failure. Serum ionized calcium concentration is typically normal in dogs with renal failure–induced hypercalcemia and is increased in dogs with PHP and concurrent renal failure. Urine specific gravity usually is not helpful when renal function in dogs with hypercalcemia is assessed, because of the interference of calcium with the actions of vasopressin on renal tubular cells. Urine specific gravities less than 1.015 are common in dogs with PHP. Hematuria, pyuria, bacteriuria, and crystalluria may be identified if cystic calculi and secondary bacterial cystitis develop. Hypercalciuria, proximal renal tubular acidosis with impaired bicarbonate resorption, and the production of alkaline urine may predispose dogs to the development of cystic or renal calculi and bacterial cystitis. In one study, urinary tract infection was identified in 29% and cystic calculi in 31% of 210 dogs with PHP (Feldman et al., 2005). Uroliths are typically composed of calcium phosphate, calcium oxalate, or mixtures of the two salts.

Cervical ultrasound should identify one or more enlarged parathyroid glands in dogs and cats with PHP (Fig. 47.2) and (Video 47.1). The parathyroid glands of healthy dogs are typically 3 mm or less in maximum width when visualized ultrasonographically. The maximum width of the abnormal parathyroid glands ranged from 3 to 23 mm (median, 6 mm) in 130 dogs with PHP (Feldman et al., 2005). A solitary parathyroid mass was identified in 89%, and two parathyroid masses were identified in 10%, of the dogs.

Measurement of baseline serum PTH concentration is used to establish the diagnosis of PHP. The two-site immunoradiometric assay (IRMA) system is currently used by most veterinary laboratories and is considered the most reliable assay system for PTH quantification in dogs and cats. In the United States, serum PTH concentrations are usually measured at the Diagnostic Center for Population and Animal Health, Michigan State University East Lansing, Mich; www.dcpah.msu.edu, and the current PTH reference ranges for dogs and cats are 0.5 to 5.8 pmol/L and 0 to 4.0 pmol/L, respectively. The major regulator of

TABLE 47.2

Causes of Hypercalcemia in Dogs and Cats

DISORDER	TESTS TO HELP ESTABLISH THE DIAGNOSIS
Primary hyperparathyroidism*	Serum PTH concentration, cervical ultrasound, surgery
Hypercalcemia of malignancy* Humorally mediated: LSA, apocrine gland adenocarcinoma, carcinoma (nasal, mammary gland, gastric, thyroid, pancreatic, pulmonary), thymoma Locally osteolytic (multiple myeloma, LSA, squamous cell carcinoma, osteosarcoma, fibrosarcoma)	Physical examination; thoracic and abdominal radiography; abdominal ultrasonography; aspiration of lymph nodes, liver, spleen, and bone marrow; serum PTHrP
Hypervitaminosis D* Cholecalciferol rodenticides, plants *(Cestrum diurnum)* Excessive supplementation	History, serum biochemistry panel, serum vitamin D concentration
Hypoadrenocorticism*	Serum electrolytes, ACTH stimulation test
Renal failure (especially chronic)*	Serum biochemistry panel, urinalysis
Idiopathic*—cats	Rule out by exclusion
Granulomatous disease (uncommon) Systemic mycosis—blastomycosis, histoplasmosis, coccidioidomycosis Schistosomiasis, FIP	Thoracic radiography, abdominal ultrasonography, fundic examination, cytologic studies of pulmonary wash samples or intestinal biopsy specimens, serum fungal titers
Nonmalignant skeletal disorder (rare) Osteomyelitis Hypertrophic osteodystrophy	Radiography of peripheral skeleton
Iatrogenic disorder Excessive calcium supplementation Excessive oral phosphate binders Grape/raisin toxicity Anti-psoriasis cream (calcipotriol)	History
Dehydration (mild hypercalcemia)	—
Factitious disorder Lipemia Postprandial measurement Young growing animal (<6 months)	—
Laboratory error	Repeat calcium measurement

ACTH, Adrenocorticotropic hormone; *FIP,* feline infectious peritonitis; *LSA,* lymphosarcoma; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related peptide.
*Common causes.

PTH secretion is the concentration of ionized calcium in the blood. Decreased serum ionized calcium increases PTH secretion and vice versa. Serum PTH test results should always be interpreted in conjunction with serum calcium or, preferably, with serum ionized calcium measured from the same blood sample. If the parathyroid gland is functioning normally, the serum PTH concentration should be below the reference range or undetectable in the face of hypercalcemia because of the inhibitory effects of an increased serum calcium concentration on parathyroid gland function. Dogs with non–parathyroid-induced hypercalcemia should also have low to undetectable serum PTH concentrations. Serum PTH concentration within or above the reference range is inappropriate in the face of hypercalcemia and is indicative of an autonomously functioning parathyroid gland (Fig. 47.3). Among 185 dogs with PHP, none had serum PTH concentration below the reference range (2-13 pmol/L at the time of the study), 45% were in the lower half of the reference range (2.3-7.9 pmol/L), 28% were in the upper half of the reference range (8.0-13.0 pmol/L), and 27% had increased serum PTH concentrations (13-121 pmol/L; Feldman et al., 2005).

Treatment

(See Chapter 53 for details on the medical treatment of hypercalcemia in dogs and cats.)

Surgical removal of the abnormal parathyroid tissue is the treatment of choice. Johnston and Tobias (2018) have adequately described surgical techniques for the thyroparathyroid complex (see Suggested Readings). Almost all dogs

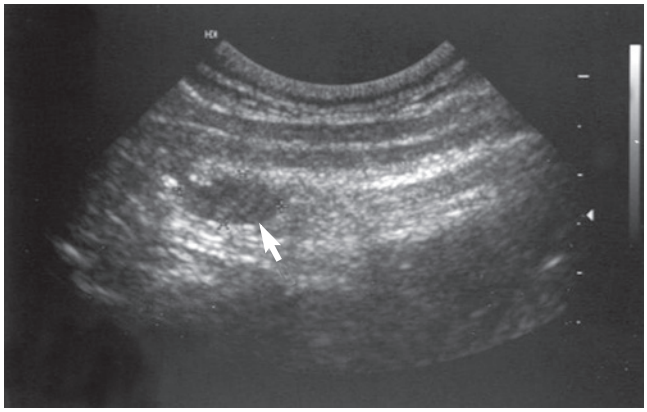


FIG 47.2
Ultrasound image of the right thyroid lobe of a 13-year-old Labrador Retriever with hypercalcemia and primary hyperparathyroidism. A hypoechoic mass is seen in the region of the parathyroid gland *(arrow)*. Hypercalcemia resolved after heat ablation of the parathyroid mass.

and cats with PHP have a solitary, easily identified parathyroid adenoma (see Fig. 47.1). Enlargement of more than one parathyroid gland indicates the presence of multiple adenomas or parathyroid hyperplasia. If none of the parathyroid glands appears enlarged, or if all appear small, the diagnosis of PHP must be questioned, and hypercalcemia stemming from occult neoplasia or PTH production by a parathyroid tumor in an ectopic site (often located in the soft tissues near the thyroid gland) or by a nonparathyroid tumor should be considered.

Chemical (i.e., ethanol) or radiofrequency heat ablation of abnormal parathyroid tissue performed under ultrasound guidance is effective treatment for PHP (Fig. 47.4). Surgery is avoided, anesthetic time is significantly reduced, and no incisions or issues related to wound healing are involved. However, management of the dog after chemical or heat ablation is identical to management after surgical removal of the parathyroid nodule. In one retrospective study, surgical removal, heat ablation, and chemical ablation of the

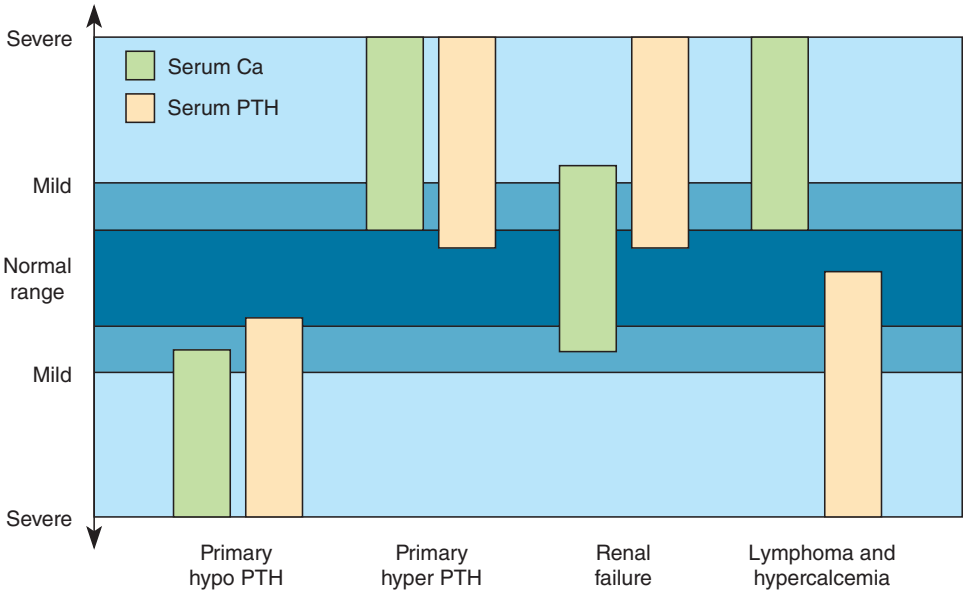


FIG 47.3
Ranges of serum calcium and parathyroid hormone concentrations in the more common disorders causing alterations in serum calcium concentration, parathyroid gland function, or both. *hyper PTH,* Hyperparathyroidism; *hypo PTH,* hypoparathyroidism; *PTH,* parathyroid hormone.

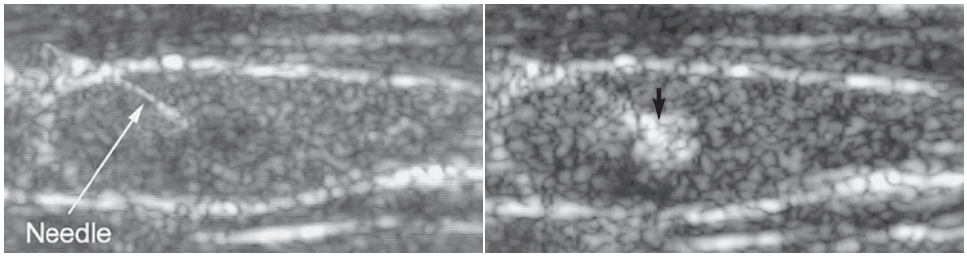


FIG 47.4
(A) Ultrasound image of the left thyroid lobe of a 12-year-old Keeshond with hypercalcemia. A mass can be seen in the region of the parathyroid gland, and a needle *(arrow)* has been inserted into the mass under ultrasound guidance before heat ablation of the mass is performed. **(B)** Heat is administered to the mass, causing hyperechogenicity of the mass *(arrow)*.

parathyroid nodule were successful in controlling hypercalcemia in 94%, 90%, and 72% of dogs treated for PHP, respectively (Rasor et al., 2007). Not all dogs are candidates for chemical or heat ablation. Surgery is indicated if more than one parathyroid nodule is identified with cervical ultrasound, the parathyroid nodule is less than 4 mm or greater than 15 mm in maximum width, a parathyroid nodule is not identified, the parathyroid nodule is too close to the carotid artery, or cystic calculi are identified with abdominal radiographs or ultrasound. Ablation of a parathyroid nodule is also difficult in dogs with concurrent hypothyroidism and loss of thyroid parenchyma that provides resistance to the movement of the parathyroid nodule.

An attempt must be made to ensure that at least one parathyroid gland remains intact to maintain calcium homeostasis and prevent permanent hypocalcemia. Removal or ablation of the parathyroid nodule results in a rapid decline in circulating PTH and a decrease in serum calcium. In the early stages of PHP, the remaining parathyroid glands may secrete PTH in response to the decrease in serum calcium, thereby preventing development of severe hypocalcemia. In dogs with more advanced PHP, atrophy of the normal parathyroid glands may prevent a response to the decrease in serum calcium, leading to severe hypocalcemia and clinical signs typically within 2 to 4 days of surgery or ablation. In these dogs intravenous and oral calcium, and oral vitamin D therapy must be initiated to correct and/or prevent hypocalcemia.

Two approaches may be used in managing the dog before and after the parathyroid nodule has been removed with surgery or ablation. One approach is to treat dogs with oral calcium and calcitriol (the most active form of vitamin D) beginning 24 hours before surgical removal or ablation of the parathyroid nodule. Another approach is to treat dogs with oral calcium while withholding calcitriol therapy until the serum calcium concentration decreases to below an arbitrarily designated concentration—typically a serum calcium or ionized calcium concentration of 9.0 mg/dL or 0.9 mmol/L, respectively—and before clinical signs of hypocalcemia develop. The hope with the latter approach is that the remaining parathyroid glands will secrete enough PTH to prevent hypocalcemia, reestablish normal serum calcium concentration, and avoid the expense of vitamin D therapy and its subsequent gradual withdrawal and monitoring over several months.

Unfortunately there are no reliable predictors for identifying which dogs do and do not need calcitriol after surgery or ablation. We rely most heavily on the severity of hypercalcemia and the duration of hypercalcemia, if known. The longer the duration of hypercalcemia and the higher the serum calcium concentration, the more likely we are to start calcitriol therapy the day before surgery or ablation. As a general rule, we do not initially treat hyperparathyroid dogs with calcitriol if the serum calcium or ionized calcium concentration before surgery or ablation is less than 14 mg/dL or 1.6 mmol/L, respectively. Serum calcium or ionized calcium concentrations greater than 14 mg/dL and 1.6 mmol/L, respectively, and hypercalcemia known to be present for longer than 3 months suggest the existence of significant atrophy of the remaining parathyroid glands and a high probability for the development of signs of hypocalcemia after surgery or ablation. In these dogs oral calcium (dairy products and supplements) and calcitriol therapy are started 24 hours before the time that treatment for PHP is provided. Regardless of which approach is taken, the diet should be supplemented with calcium-rich foods (e.g., dairy products), oral calcium tablets should be administered, exercise restricted, and serum total or ionized calcium should be monitored once or twice a day until the serum calcium concentration is stable and in the reference range.

Therapy for hypocalcemia includes the administration of intravenous calcium to control immediate clinical signs and the long-term oral administration of calcium and vitamin D supplements to maintain low-normal blood calcium concentrations while the parathyroid gland atrophy resolves. (See Chapter 53 and Box 53.7 for details about the management of hypocalcemia.) The goal of calcium and vitamin D therapy is to maintain the serum calcium concentration within the lower end of the reference range (9.5-10.5 mg/dL). Maintaining the serum calcium concentration in the lower end of the reference range prevents the development of clinical signs of hypocalcemia, minimizes the risk of hypercalcemia, and stimulates a return of function in the remaining atrophied parathyroid glands. Once the parathyroid glands regain control of calcium homeostasis and the serum calcium concentration is stable in the dog or cat in the home environment, calcium and vitamin D supplements can be gradually withdrawn over a period of 3 to 4 months. This gradual withdrawal allows time for the parathyroid glands to become fully functional, thereby preventing hypocalcemia. Vitamin D therapy is withdrawn by gradually increasing the number of days between administrations. The dosing interval should be increased by 1 day every 2 to 3 weeks, after the serum calcium concentration has been measured and found to be 9.5 mg/dL or greater. Vitamin D therapy can be discontinued once the dog or cat is clinically normal, the serum calcium concentration is stable between 9.5 and 11.5 mg/dL, and the vitamin D dosing interval is every 6 to 7 days.

Prognosis

The prognosis for dogs and cats undergoing surgical or ablation therapy for PHP is excellent, assuming severe hypocalcemia is avoided postoperatively and PHP is caused by a parathyroid adenoma. Hypercalcemia may recur weeks to months after surgery in dogs and cats with PHP caused by parathyroid hyperplasia, if one or more parathyroid glands have been left in situ.

PRIMARY HYPOPARATHYROIDISM

Etiology

Primary hypoparathyroidism develops as a result of an absolute or relative deficiency in the secretion of PTH. This

deficiency ultimately causes hypocalcemia and hyperphosphatemia resulting from loss of the effects of PTH on bone, kidney, and intestine (see Table 47.1). The major signs of hypoparathyroidism are directly attributable to the decreased concentration of ionized calcium in the blood, which leads to increased neuromuscular activity.

Spontaneous primary hypoparathyroidism is uncommon in dogs and cats. Most cases are classified as idiopathic (i.e., there is no evidence of trauma, malignant or surgical destruction, or other obvious damage to the neck or parathyroid glands). The glands are difficult to locate visually and show microscopic evidence of atrophy. Histologic evaluation of the parathyroid gland may reveal a diffuse lymphocytic, plasmacytic infiltration and fibrous connective tissue, suggesting an underlying immune-mediated cause of the disorder.

Iatrogenic hypoparathyroidism after performance of bilateral thyroidectomy for the treatment of hyperthyroidism is common in cats. The parathyroid tissue in such animals may be excised or traumatized, or its blood supply may be compromised during surgery. This form of hypoparathyroidism may be transient or permanent, depending on the viability of the parathyroid gland or glands saved at the time of surgery. Only one viable parathyroid gland is needed to maintain a normal serum calcium concentration.

Transient hypoparathyroidism may develop secondary to severe magnesium depletion (serum magnesium concentration < 1.2 mg/dL). Severe magnesium depletion may suppress PTH secretion without parathyroid destruction, increase end-organ resistance to PTH, and impair the synthesis of the active form of vitamin D (i.e., calcitriol). The end result is mild hypocalcemia and hyperphosphatemia. Magnesium repletion reverses the hypoparathyroidism. Serum magnesium concentrations in dogs and cats with spontaneous primary hypoparathyroidism usually have been normal when measured. (See Chapter 53 for more information on magnesium.)

Clinical Features

SIGNALMENT

The age at which the clinical signs of hypoparathyroidism appear in dogs ranges from 6 weeks to 13 years, with a mean of 5 years. A sex-related predisposition may be present in female dogs. No apparent breed-related predisposition has been noted, although Toy Poodles, German Shepherd dogs, Labrador Retrievers, Miniature Schnauzers, and Terriers are commonly affected. However, this increased prevalence may merely reflect the popularity of these breeds. Only a few cases of naturally acquired primary hypoparathyroidism in cats have been reported. To date, most of these cats have been young to middle-aged (range, 6 months to 11 years), of several breeds, and usually male.

CLINICAL SIGNS

Clinical signs and physical examination findings in dogs and cats with primary hypoparathyroidism are similar. The major clinical signs are directly attributable to hypocalcemia, most notably its effects on the neuromuscular system. Neuromuscular signs include muscle tremors and twitching, tetany, rear limb muscle cramping, pain, stiff gait, and generalized seizures. Additional clinical signs include nervous or anxious behavior, weakness, facial rubbing, and intense biting or licking of the paws (Box 47.2). The onset of clinical signs tends to be abrupt and severe and to occur more frequently during exercise, excitement, and stress. Clinical signs also tend to occur episodically. Episodes of clinical hypocalcemia are interspersed with relatively normal periods, lasting minutes to days. Hypocalcemia persists during these clinically "normal" periods.

PHYSICAL EXAMINATION

The most common physical examination findings are related to muscular tetany and include a stiff gait; muscle rigidity; a tense, splinted abdomen; and muscle fasciculations. Fever, panting, and nervousness are also common. Potential cardiac abnormalities include bradycardia, paroxysmal tachyarrhythmias, muffled heart sounds, and weak femoral pulses. In a few dogs and cats with primary hypoparathyroidism, cataracts were noted as small, punctate to linear, white opacities that were randomly distributed in the anterior and posterior cortical subcapsular region of the lens; no loss of vision was noted. The physical examination is occasionally normal, despite the previous history of neuromuscular disorders.

Diagnosis

Primary hypoparathyroidism should be suspected in a dog or cat with persistent hypocalcemia, hyperphosphatemia, and normal kidney function. The serum calcium concentration is usually less than 7 mg/dL, serum ionized calcium is usually less than 0.8 mmol/L, and serum phosphorus is usually greater than 6 mg/dL. Low serum calcium and high serum phosphorus concentrations can also be encountered during nutritional and renal secondary hyperparathyroidism, after phosphate-containing enema, and during tumor



BOX 47.2

Clinical Signs of Primary Hypoparathyroidism in Dogs

Seizures*
Stiff gait, muscle tetany, cramping, pain*
Focal muscle fasciculations, twitching, tremors*
Facial rubbing (intense)*
Nervousness, anxious, restless, vocalizing*
Panting, hyperventilation*
Aggressive behavior*
Ataxia
Weakness
Inappetence, vomiting
Listlessness, lethargy
Biting, licking paws (intense)

*Common signs.

lysis syndrome. (See Chapter 53 for more information on causes of hypocalcemia and hyperphosphatemia in dogs and cats.) The diagnosis of primary hypoparathyroidism is established by identifying an undetectable serum PTH concentration in the face of severe hypocalcemia in a dog or cat in which other causes of hypocalcemia have been ruled out (Table 47.3). Most causes of hypocalcemia can be identified after evaluation of the history, findings on physical examination, and results of routine blood and urine tests and review of an abdominal ultrasound. The history and physical examination findings are essentially unremarkable in dogs and cats with primary hypoparathyroidism, other than those findings caused by hypocalcemia. The only relevant abnormalities identified on routine blood and urine tests are severe hypocalcemia and, in most dogs and cats, hyperphosphatemia. Serum total protein, albumin, urea nitrogen, creatinine, and magnesium concentrations are normal. Abdominal ultrasound is also normal.

TABLE 47.3

Causes of Hypocalcemia in Dogs and Cats

DISORDER	TESTS TO HELP ESTABLISH THE DIAGNOSIS
Primary hypoparathyroidism Idiopathic Postthyroidectomy	History, serum PTH concentration, rule out other causes
Puerperal tetany	History
Renal failure Acute Chronic	Serum biochemistry panel, urinalysis
Ethylene glycol toxicity	History, urinalysis
Acute pancreatitis	Physical findings, abdominal ultrasound, serum cPLI (dog), fPLI (cat)
Sepsis, systemic inflammatory response syndrome (SIRS)	History, physical findings, CBC
Intestinal malabsorption syndromes	History, digestion and absorption tests, intestinal biopsy
Hypoproteinemia or hypoalbuminemia	Serum biochemistry panel
Hypomagnesemia	Serum total and ionized Mg
Diabetic ketoacidosis	Serum biochemistry panel, urinalysis
Nutritional secondary hyperparathyroidism	Dietary history
Hypovitaminosis D (rickets)	History
Soft tissue trauma/ rhabdomyolysis	History
Tumor lysis syndrome	History
Phosphate-containing enemas	History
Anticonvulsant medications	History
$NaHCO_3$ administration	History
Laboratory error	Repeat calcium measurement

CBC, Complete blood count; *cPLI,* canine pancreatic lipase immunoreactivity; *fPLI,* feline pancreatic lipase immunoreactivity; *Mg,* magnesium; *$NaHCO_3$,* sodium bicarbonate; *PTH,* parathyroid hormone.

Measurement of serum PTH concentration helps confirm a diagnosis of primary hypoparathyroidism. Blood for PTH determination should be obtained before the initiation of calcium and vitamin D therapy, while the animal is still hypocalcemic. The two-site IRMA system is currently used by most veterinary laboratories and is considered the most reliable assay system for PTH quantification in dogs and cats. Serum PTH concentration must be interpreted in conjunction with the serum calcium concentration. If the parathyroid gland is functioning normally, the serum PTH concentration should be increased in the face of hypocalcemia because of the stimulatory effects of a decreased serum ionized calcium concentration on parathyroid gland function. A low to undetectable serum PTH concentration in a hypocalcemic dog or cat is strongly suggestive of primary hypoparathyroidism (see Fig. 47.3). A serum PTH concentration at the lower end of the reference range is inappropriate in the presence of severe hypocalcemia and also supports primary hypoparathyroidism. Dogs and cats with non–parathyroid-induced hypocalcemia should have normal or high serum PTH concentrations; the exceptions are those with disorders causing severe hypomagnesemia (see Chapter 53 for causes of hypomagnesemia).

Treatment

Treatment for primary hypoparathyroidism involves the administration of vitamin D and calcium supplements (see Chapter 53 and Box 53.7). Therapy is typically divided into two phases. The first phase (i.e., acute therapy) should initially control hypocalcemic tetany and involves the slow administration of 10% calcium gluconate (not calcium chloride) intravenously, to effect. Once clinical signs of hypocalcemia are controlled, calcium gluconate should then be administered by continuous intravenous infusion until orally administered calcium and vitamin D therapy (i.e., second phase of therapy) becomes effective. A solution of 10% calcium gluconate contains 9.3 mg Ca/mL and is initially administered IV at an initial dose of 0.5 to 1.5 mL/kg body weight added to the infusion solution. Calcium should not be added to solutions containing lactate, bicarbonate, acetate, or phosphates because of the potential for precipitation problems. Serum calcium concentrations should be monitored frequently and the rate of infusion adjusted as needed to control clinical signs and maintain the serum calcium concentration between 8 and 10 mg/dL.

The second phase of therapy (i.e., maintenance therapy) should maintain the blood calcium concentration between 8 and 10 mg/dL through daily administration of vitamin D

and calcium. These calcium concentrations are above the level at which there is risk of clinical hypocalcemia and below the level at which hypercalciuria (risk of calculi formation) or severe hypercalcemia and hyperphosphatemia (risk of nephrocalcinosis and kidney failure) may occur. Maintenance therapy should be initiated once the hypocalcemic tetany is controlled with intravenous calcium therapy. The onset of action of vitamin D varies depending on the formulation of vitamin D that is administered. 1,25-dihydroxyvitamin D_3 (calcitriol) has the fastest onset of action and is preferred for treating hypoparathyroidism. The initial dosage of calcitriol is 20 to 30 ng/kg/day. Dogs and cats should ideally remain hospitalized until their serum calcium concentration remains between 8 and 10 mg/dL without parenteral support. Serum calcium concentrations should be monitored weekly, and the vitamin D dose should be adjusted to maintain a serum calcium concentration of 8 to 10 mg/dL. The aim of therapy is to prevent hypocalcemic tetany—not to induce hypercalcemia. Serum calcium concentrations greater than 10 mg/dL are unnecessary to prevent tetany and increase the likelihood of unwanted hypercalcemia.

Once the serum calcium concentration has stabilized, attempts can be made to slowly taper the dose of oral calcium and then vitamin D to the lowest dose that maintains the serum calcium concentration at between 8 and 10 mg/dL. Vitamin D is critical for establishing and maintaining a normal blood calcium concentration. Most dogs and cats with primary hypoparathyroidism require permanent vitamin D therapy. The calcium supplement often can be gradually tapered over a period of 2 to 4 months and then stopped once the animal's serum calcium concentration is stable at between 8 and 10 mg/dL. Calcium in the diet is often sufficient for meeting the calcium needs of the animal. Supplementing the diet with calcium-rich foods (e.g., dairy products) helps ensure an adequate source of dietary calcium. Once the animal's serum calcium concentration is stable and maintenance therapy has become established, reevaluation of the serum calcium concentration every 3 to 4 months is advisable.

Prognosis

The prognosis depends on the dedication of the client. The prognosis is excellent if proper therapy is instituted and timely reevaluations are performed. Proper management requires close monitoring of the serum calcium concentration. The more frequent the rechecks, the better the chance of preventing extremes in the concentration, and the better the chance of a normal life expectancy.

Suggested Readings

Feldman EC, et al. *Canine and feline endocrinology*. ed 4. St. Louis: Elsevier; 2015.

Johnston SA, Tobias KM. *Veterinary surgery: small animal*. St Louis: Elsevier Saunders; 2018.

Primary Hyperparathyroidism

Arbaugh M, et al. Evaluation of preoperative concentrations of ionized calcium and parathyroid hormone as predictors of hypocalcemia following parathyroidectomy in dogs with primary hyperparathyroidism: 17 cases (2001-2009). *J Am Vet Med Assoc*. 2012;241.

Dear JD, et al. Association of hypercalcemia before treatment with hypocalcemia after treatment in dogs with primary hyperparathyroidism. *J Vet Intern Med*. 2017;31:349.

Feldman EC, et al. Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004). *J Am Vet Med Assoc*. 2005;227:756.

Finch NC, et al. Parathyroid hormone concentration in geriatric cats with various degrees of renal function. *J Am Vet Med Assoc*. 2012;241:1326.

Goldstein RE, et al. Inheritance, mode of inheritance, and candidate genes for primary hyperparathyroidism in Keeshonden. *J Vet Intern Med*. 2007;21:199.

Graham KJ, et al. Intraoperative parathyroid hormone concentration to confirm removal of hypersecretory parathyroid tissue and time to postoperative normocalcaemia in nine dogs with primary hyperparathyroidism. *Aust Vet J*. 2012;90:203.

Guttin T, et al. Outcomes for dogs with primary hyperparathyroidism following treatment with percutaneous ultrasound-guided ethanol ablation of presumed functional parathyroid nodules: 27 cases (2008-2011). *J Am Vet Med Assoc*. 2015;247.

Ham K, et al. Validation of a rapid parathyroid hormone assay and measurement of parathyroid hormone in dogs with naturally occurring primary hyperparathyroidism. *Vet Surg*. 2009;38:122.

Milian M, Schiemdt CW. Preoperative factors associated with postoperative hypocalcemia in dogs with primary hyperparathyroidism that underwent parathyroidectomy: 62 cases (2004-2009). *J Am Vet Med Assoc*. 2013;242.

Rasor L, et al. Retrospective evaluation of three treatment methods for primary hyperparathyroidism in dogs. *J Am Anim Hosp Assoc*. 2007;43:70.

Sawyer ES, et al. Outcome of 19 dogs with parathyroid carcinoma after surgical excision. *Vet Comp Oncol*. 2011;10:57.

Primary Hypoparathyroidism

Russell NJ, et al. Primary hypoparathyroidism in dogs: a retrospective study of 17 cases. *Aust Vet J*. 2006;84:206.

Warland J, et al. Apparent resolution of canine primary hypoparathyroidism with immunosuppressive treatment. *J Vet Intern Med*. 2015;29:400.

CHAPTER 48

Disorders of the Thyroid Gland



HYPOTHYROIDISM IN DOGS

Etiology

Structural or functional abnormalities of the thyroid gland can lead to deficient production of thyroid hormones. A convenient classification scheme for hypothyroidism has been devised based on the location of the problem within the hypothalamic-pituitary-thyroid gland complex (Fig. 48.1). Primary hypothyroidism is the most common form of this disorder in dogs; it results from problems within the thyroid gland, usually destruction of the thyroid gland (Box 48.1). The two most common histologic findings in this disorder are lymphocytic thyroiditis and idiopathic atrophy of the thyroid gland (Fig. 48.2). Lymphocytic thyroiditis is an immune-mediated disorder characterized by a diffuse infiltration of lymphocytes, plasma cells, and macrophages into the thyroid gland. The factors that trigger the development of lymphocytic thyroiditis are poorly understood. Genetics undoubtedly plays a major role, especially given the increased incidence of this disorder in certain breeds and in certain lines within a breed (Table 48.1). Environmental risk factors have not been well defined in the dog. A link between infection-induced damage to the thyroid gland and development of lymphocytic thyroiditis has been the subject of speculation but has not been proven. Vaccine administration has been hypothesized to be a contributing factor to the development of lymphocytic thyroiditis, but this also has not been proven.

Destruction of the thyroid gland is progressive, and clinical signs may not become evident until more than 80% of the gland is destroyed. Development of decreased serum thyroid hormone concentrations and clinical signs is usually a gradual process, often requiring 1 to 3 years, which suggests that the destructive process is slow.

Idiopathic atrophy of the thyroid gland is characterized by loss of the thyroid parenchyma. There is no inflammatory infiltrate, even in areas where small follicles or follicular remnants are present in the thyroid gland. Tests for lymphocytic thyroiditis are negative. The cause of idiopathic thyroid atrophy is not known. It may be a primary degenerative disorder or may represent an end stage of autoimmune lymphocytic thyroiditis. There are no blood tests that establish the diagnosis of idiopathic atrophy; it is a diagnosis by exclusion.

Secondary hypothyroidism results from failure of pituitary thyrotrophs to develop (pituitary hypoplasia causing pituitary dwarfism; see Chapter 46) or from dysfunction within the pituitary thyrotropic cells, causing impaired secretion of thyroid-stimulating hormone (TSH) and a "secondary" deficiency in thyroid hormone synthesis and secretion. Follicular atrophy in the thyroid gland gradually develops as the result of lack of TSH. Secondary hypothyroidism could also result from destruction of pituitary thyrotrops (e.g., pituitary neoplasia [rare]) or from suppression of thyrotroph function by hormones or drugs (e.g., glucocorticoids [common]; see Box 48.1).

Tertiary hypothyroidism is a deficiency in the secretion of thyrotropin-releasing hormone (TRH) by peptidergic neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Neoplastic infiltration of the hypothalamus is the only recognized cause in dogs, to date. Lack of TRH secretion results in deficient TSH secretion and secondary follicular atrophy in the thyroid gland.

Congenital primary hypothyroidism is uncommon in dogs and has been caused by deficient dietary iodine intake, dyshormonogenesis (i.e., usually an iodine organification defect), and thyroid hypoplasia, aplasia, and dysgenesis. Secondary hypothyroidism resulting from an apparent deficiency of TSH has also been reported in a family of Giant Schnauzers and in a Boxer. Pedigree analysis showed that it may be inherited in an autosomal recessive fashion in the family of Giant Schnauzers (Voorbijj et al., 2016). Secondary hypothyroidism may be genetic in Miniature Schnauzers (Voorbijj et al., 2016). Development of an enlarged thyroid gland (i.e., goiter) depends on the etiology. If the hypothalamic-pituitary-thyroid gland axis is intact, TSH receptors are functional, and signal transduction is appropriate (e.g., as occurs with an iodine organification defect), goiter will develop as a result of increased serum TSH concentrations. Goiter does not develop if there are problems

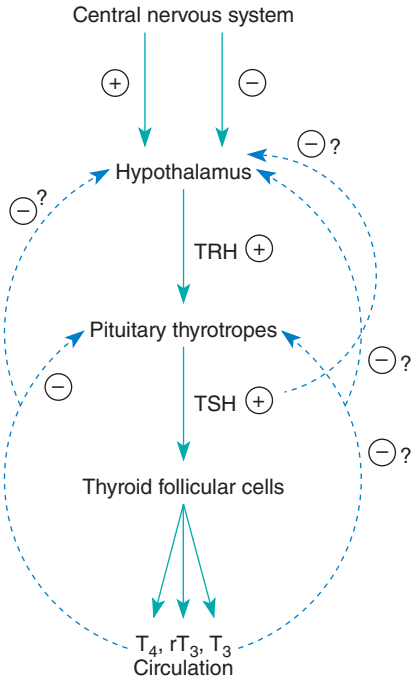


FIG 48.1
The hypothalamic-pituitary-thyroid gland axis. *TRH,* Thyrotropin-releasing hormone; *TSH,* thyrotropin; T_4, thyroxine; T_3, 3,5,3′-triiodothyronine; rT_3, 3,3′,5′-triiodothyronine; +, stimulation; –, inhibition.

with the hypothalamic-pituitary-thyroid gland axis, TSH receptors, or signal transduction (e.g., as occurs with pituitary TSH deficiency).

Clinical Features

Clinical signs of the more common forms of primary hypothyroidism usually develop during middle age (i.e., 2-6 years). Clinical signs tend to develop at an earlier age in breeds at increased risk than in other breeds (see Table 48.1). No sex-related predilection is apparent.

Clinical signs are variable and depend in part on the age of the dog at the time a deficiency in thyroid hormone develops (Box 48.2). Clinical signs may differ between breeds. For example, truncal alopecia may dominate in some breeds, whereas thinning of the haircoat may dominate in other breeds. In adult dogs the most consistent clinical signs of hypothyroidism result from decreased cellular metabolism and its effects on the dog's mental status and activity. Most dogs with hypothyroidism show some mental dullness, lethargy, exercise intolerance or unwillingness to exercise, and a propensity to gain weight without a corresponding increase in appetite or food intake. These signs are often gradual in onset, subtle, and not recognized by the client until after thyroid hormone supplementation has been initiated. Additional clinical signs of hypothyroidism typically involve the skin and, less commonly, the neuromuscular system.

BOX 48.1

Potential Causes of Hypothyroidism in Dogs

Primary Hypothyroidism

Lymphocytic thyroiditis
Idiopathic atrophy
Neoplastic destruction
Iodine deficiency
Iatrogenic causes
- Surgical removal
- Antithyroid medications
- Radioactive iodine treatment
- Drugs (e.g., sulfamethoxazole)

Secondary Hypothyroidism

Pituitary malformation
- Pituitary cyst
- Pituitary hypoplasia

Pituitary destruction
- Neoplasia

Pituitary thyrotropic cell suppression
- Naturally acquired hyperadrenocorticism
- Nonthyroidal illness syndrome (Euthyroid sick syndrome)

Iatrogenic causes
- Drug therapy, most notably glucocorticoids
- Radiation therapy
- Hypophysectomy

Tertiary Hypothyroidism

Congenital hypothalamic malformation (?)
Acquired destruction of hypothalamus (?)

Congenital Hypothyroidism

Thyroid gland dysgenesis (aplasia, hypoplasia, ectasia)
Dyshormonogenesis: iodine organification defect
Deficient dietary iodine intake

DERMATOLOGIC SIGNS

Alterations in the skin and haircoat are the most common observable abnormalities in dogs with hypothyroidism. Classic cutaneous signs include bilaterally symmetric, nonpruritic truncal alopecia that tends to spare the head and the extremities (Fig. 48.3). Alopecia may be local or generalized and symmetric or asymmetric, it may involve only the tail (i.e., "rat tail"), and it often starts over sites of wear and friction. Although nonpruritic endocrine alopecia is not pathognomonic for hypothyroidism (see Chapter 46), hypothyroidism is certainly the most likely diagnosis in an affected dog with lethargy, weight gain, and no polyuria-polydipsia.

Seborrhea and pyoderma are common signs of hypothyroidism. Depletion of thyroid hormone suppresses humoral immune reactions, impairs T-cell function, and reduces the number of circulating lymphocytes—defects that can be reversed by exogenous thyroid hormone therapy. All forms of seborrhea (i.e., sicca, oleosa, dermatitis) are possible.

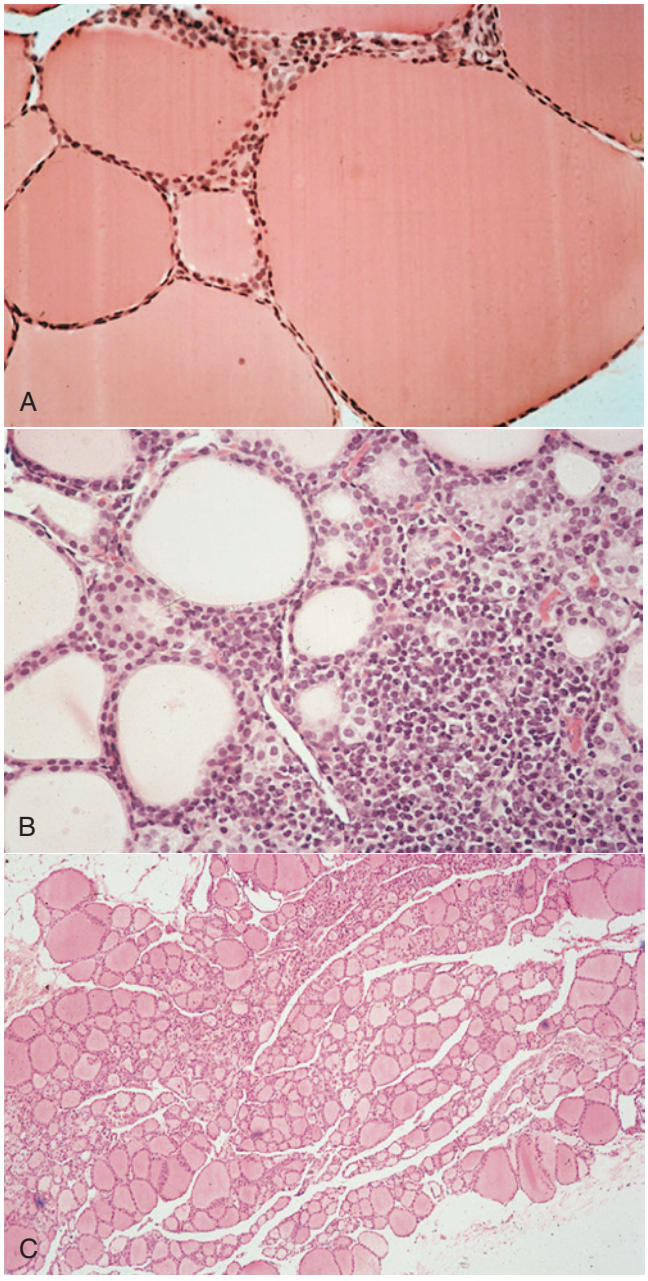


FIG 48.2
Histologic section of a thyroid gland from a healthy dog **(A),** from a dog with lymphocytic thyroiditis and hypothyroidism **(B),** and from a dog with idiopathic atrophy of the thyroid gland and hypothyroidism **(C).** Note the mononuclear cell infiltration, disruption of the normal architecture, and loss of colloid-containing follicles in **(B)** and the small size of the gland, decrease in follicular size and colloid content, and lack of cellular infiltration in **(C),** compared with **(A).** (**A** and **B,** Hematoxylin and eosin stain; ×250; **C,** Hematoxylin and eosin stain; ×40.) (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, WB Saunders.)

TABLE 48.1

Dog Breeds Reported to Have an Increased Prevalence of Thyroid Hormone Autoantibodies

BREED	ODDS RATIO*
Pointer	3.61
English Setter	3.44
English Pointer	3.31
Skye Terrier	3.04
German Wirehaired Pointer	2.72
Old English Sheepdog	2.65
Boxer	2.37
Maltese	2.25
Kuvasz	2.18
Petit Basset Griffon Vendéen	2.16
American Staffordshire Terrier	1.84
Beagle	1.79
American Pit Bull Terrier	1.78
Dalmatian	1.74
Giant Schnauzer	1.72
Rhodesian Ridgeback	1.72
Golden Retriever	1.70
Shetland Sheepdog	1.69
Chesapeake Bay Retriever	1.56
Siberian Husky	1.45
Brittany Spaniel	1.42
Borzoi	1.39
Australian Shepherd	1.28
Doberman Pinscher	1.24
Malamute	1.22
Cocker Spaniel	1.17
Mixed	1.05

*Odds of serum thyroid hormone autoantibodies (THAA) among breeds with an increased risk of having THAA, compared with dogs of all other breeds.
From Nachreiner RF et al: Prevalence of serum thyroid hormone autoantibodies in dogs with clinical signs of hypothyroidism, *J Am Vet Med Assoc* 220:466, 2002.

Seborrhea and pyoderma may be focal, multifocal, or generalized. Because both frequently result in pruritus, hypothyroid dogs with secondary pyoderma or seborrhea initially may be brought to the veterinarian because of a pruritic skin disorder.

The haircoat in dogs with hypothyroidism is often dull, dry, and easily epilated. Hair regrowth is slow. Hyperkeratosis leads to the development of scales and dandruff. Variable degrees of hyperpigmentation may be noted. Chronic otitis externa has been noted in some dogs with hypothyroidism. In severe cases of hypothyroidism, acidic and neutral

BOX 48.2

Clinical Manifestations of Hypothyroidism in the Adult Dog

Metabolic

Lethargy*
Mental dullness*
Inactivity*
Weight gain*
Cold intolerance

Dermatologic

Endocrine alopecia*
  Symmetric or asymmetric
  "Rat tail"
Dry, brittle haircoat
Hyperpigmentation
Seborrhea sicca or oleosa or dermatitis*
Pyoderma*
Otitis externa
Myxedema

Reproductive

Persistent anestrus
Weak or silent estrus
Prolonged estrual bleeding
Inappropriate galactorrhea or gynecomastia
Prolonged parturition
Stillbirth
Periparturient puppy mortality
Testicular atrophy (?)
Loss of libido (?)

Neuromuscular

Polyneuropathy
Polymyopathy
Weakness*
Exercise intolerance
Skeletal muscle wasting
Knuckling
Ataxia
Circling
Disorientation
Vestibular signs (head tilt, nystagmus)
Facial nerve paralysis
Trigeminal nerve paralysis
Laryngeal paralysis (?)
Seizures
Myxedema coma

Ocular

Corneal lipid deposits
Corneal ulceration
Uveitis

Cardiovascular

Decreased contractility
Bradycardia
Cardiac arrhythmias

Gastrointestinal

Esophageal hypomotility (?)
Diarrhea
Constipation

Hematologic

Anemia*
Hyperlipidemia*
Coagulopathy

Behavior Abnormalities (?)

*Common.

mucopolysaccharides may accumulate in the dermis and bind water, causing the skin to thicken. Referred to as *myxedema,* this condition causes the skin to thicken predominantly in the forehead and face of dogs, resulting in rounding of the temporal region of the forehead, puffiness and thickening of the facial skin folds, and drooping of the upper eyelids. Myxedema contributes to the classic "tragic facial expression" sometimes observed in dogs with hypothyroidism.

NEUROMUSCULAR SIGNS

Neuromuscular signs may be the predominant problem in some dogs with hypothyroidism (see Box 48.2). Clinical signs may be multifocal, acute or chronic, and static or progressive. Other findings consistent with hypothyroidism may be absent. Hypothyroidism-induced segmental demyelination and axonopathy may cause signs referable to the central or peripheral nervous system. Clinical signs referable to the central nervous system (CNS) may also appear after mucopolysaccharide accumulates in the perineurium and endoneurium, or after cerebral atherosclerosis, transient ischemia or brain infarction, or the development of severe hyperlipidemia; they include seizures, ataxia, circling, weakness, and proprioceptive and postural reaction deficits. These signs are often seen in conjunction with vestibular signs (e.g., head tilt, nystagmus) or facial nerve paralysis. Peripheral neuropathies identified in hypothyroid dogs include facial nerve paralysis, generalized weakness associated with diffuse lower motor neuron tetraparesis, and knuckling or dragging of the feet, with excessive wear of the dorsal part of the toenail. Hypothyroid myopathy is characterized by type II myofiber atrophy, myofiber degeneration, and depletion in skeletal muscle carnitine, and may result in skeletal muscle wasting, weakness, exercise intolerance, and increased serum of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase activities. Thyroxine-responsive unilateral forelimb lameness has also been observed in dogs. The relationship between hypothyroidism and laryngeal paralysis or esophageal hypomotility remains controversial, in part



FIG 48.3
(A) A 6-year-old female spayed Samoyed with hypothyroidism; a dry, lusterless haircoat; hyperpigmentation; and endocrine alopecia. **(B)** and **(C)** A 2-year-old female spayed Golden Retriever with hypothyroidism, diffuse thinning of the haircoat, and development of a "rat tail." In both dogs note the truncal distribution of the dermatologic problem with sparing of the head and distal extremities. **(D)** An 8-year-old male castrated Beagle with hypothyroidism, obesity, and myxedema of the face. Note the "tragic facial expression" and "mental dullness" evident from the dog's facial expression. **(E)** A 7-month-old female Malamute with congenital hypothyroidism. Note the retention of the puppy haircoat and the small stature of the dog.

because it is difficult to prove a cause-and-effect relationship between these disorders, and because treatment of hypothyroidism often does not improve the clinical signs caused by laryngeal paralysis or esophageal hypomotility.

REPRODUCTIVE SIGNS

Historically, hypothyroidism was believed to cause lack of libido, testicular atrophy, and oligospermia to azoospermia in male dogs. However, work by Johnson et al. (1999) in Beagles failed to document any deleterious effect of experimentally induced hypothyroidism on any aspect of male reproductive function. Although other classic clinical signs and clinicopathologic abnormalities of hypothyroidism developed in the dogs studied, libido, testicular size, and total sperm count per ejaculate remained normal. These findings indicate that hypothyroidism may, at best, be an uncommon cause of reproductive dysfunction in male dogs, assuming that the Beagle is representative of other dog breeds.

Clinical experience has shown that hypothyroidism can cause prolonged interestrus intervals and failure to cycle in the bitch. Additional reproductive abnormalities include

weak or silent estrous cycles, prolonged estrual bleeding (which may be caused by acquired problems in the coagulation system), and inappropriate galactorrhea and gynecomastia. An association between hypothyroidism and fetal resorption, abortion, stillbirth, and the birth of weak puppies that die shortly after birth has been suggested in the bitch. Work undertaken by Panciera et al. (2007) to examine the effects of short-term (19 weeks) experimentally induced hypothyroidism on reproduction in the bitch revealed no difference in interestrus interval, conception, litter size, or gestation length between hypothyroid and control bitches. However, parturition was prolonged, uterine contractions were weaker, stillbirths were more prevalent, puppies were smaller and more distressed at birth, and periparturient mortality was significantly higher in hypothyroid bitches than in control bitches.

MISCELLANEOUS CLINICAL SIGNS

Ocular, cardiovascular, gastrointestinal, and clotting abnormalities are uncommon clinical manifestations of hypothyroidism (see Box 48.2). More commonly, biochemical or functional abnormalities of these organ systems are identified in dogs exhibiting the more common clinical signs of hypothyroidism. Echocardiography may identify a decrease in cardiac contractility that is usually mild and asymptomatic but that may become relevant during a surgical procedure requiring prolonged anesthesia and aggressive fluid therapy. Hypothyroidism does not play a role in the etiology or progression of dilated cardiomyopathy in Doberman Pinschers (Beieret et al., 2015).

A reduction in the activity of factor VIII–related antigen (von Willebrand factor) activity has been inconsistently documented in dogs with hypothyroidism, and the development of clinical signs of a bleeding disorder in hypothyroid dogs is uncommon. An evaluation of the coagulation cascade or of von Willebrand factor activity is not indicated in dogs with untreated hypothyroidism unless concurrent bleeding problems are reported. Thyroid hormone supplementation has a variable and sometimes deleterious effect on the blood concentration of von Willebrand factor in euthyroid dogs with von Willebrand disease.

A cause-and-effect relationship between hypothyroidism and behavioral problems (e.g., aggression) has not been well established in dogs. Proposed mechanisms for hypothyroid associated aggression have focused on possible disturbances in serotonergic or adrenergic pathways in the CNS. To date, most reports have been anecdotal and based on improvement in behavior following initiation of thyroid hormone treatment. A study by Radosta et al. (2012) found no difference in thyroid function test results between aggressive and nonaggressive dogs. The benefits, if any, of using thyroid hormone to treat behavioral disorders such as aggression in dogs remain to be clarified.

Hypothyroidism may decrease glomerular filtration rate (GFR) in dogs and could worsen azotemia in dogs with concurrent kidney disease. It is interesting to note that in one study involving experimentally induced hypothyroidism, plasma creatinine concentrations did not increase despite a reduction in GFR, presumably because of decreased production of creatinine (Panciera and Lefebvre, 2009). Treatment with sodium levothyroxine improves GFR in hypothyroid dogs.

MYXEDEMA COMA

Myxedema coma is an uncommon syndrome of severe hypothyroidism characterized by profound weakness, hypothermia, bradycardia, and a diminished level of consciousness that can rapidly progress to stupor and then coma. Physical findings include profound weakness; hypothermia; nonpitting edema of the skin, face, and jowls (i.e., myxedema); bradycardia; hypotension; and hypoventilation. Laboratory findings may include hypoxemia, hypercarbia, hyponatremia, and hypoglycemia in addition to the typical findings of hyperlipidemia, hypercholesterolemia, and nonregenerative anemia. Serum thyroid hormone concentrations are usually extremely low or undetectable; serum TSH concentration is variable but typically increased. Treatment consists of intravenous levothyroxine (5 µg/kg q12h) because of concerns of sluggish absorption from the gut and subcutaneous tissues and supportive care aimed at correcting hypothermia, hypovolemia, electrolyte disturbances, and hypoventilation. Early recognition and aggressive treatment is critical to survival. The diagnosis should be made based on clinical findings and treatment initiated without waiting for thyroid hormone test results. Once the dog has stabilized, oral levothyroxine can be started. Unfortunately, mortality is high because of late recognition and concurrent illness.

CRETINISM

Hypothyroidism in puppies is termed *cretinism.* Retarded growth and impaired mental development are the hallmarks of cretinism (Box 48.3). Clinical signs are not usually present



BOX 48.3

Clinical Signs of Cretinism

Disproportionate dwarfism
Short, broad skull
Shortened mandible
Enlarged cranium
Shortened limbs
Kyphosis
Mental dullness
Constipation
Inappetence
Gait abnormalities
Delayed dental eruption
Alopecia
"Puppy haircoat"
Dry hair
Thick skin
Lethargy
Dyspnea
Goiter

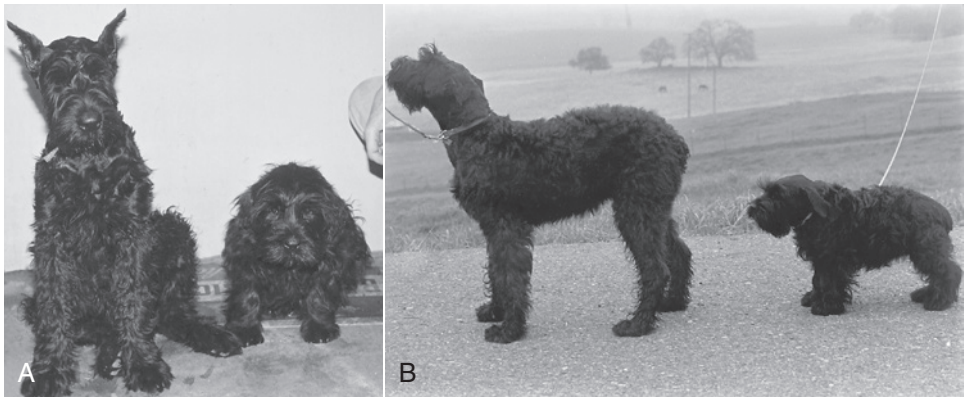


FIG 48.4
(A) and **(B)** Eight-month-old female Giant Schnauzer litter mates. The dog on the left is normal, whereas the smaller dog on the right has congenital hypothyroidism (cretinism). Note the small stature; disproportionate body size; large, broad head; wide, square trunk; and short limbs in the cretin. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, WB Saunders.)

at birth but become apparent between 1 and 3 months of age. Dogs with cretinism have a disproportionate body size, with a large, broad head; a thick, protruding tongue; a wide, square trunk; and short limbs (Fig. 48.4). This contrasts with the proportionate dwarfism caused by growth hormone deficiency. Cretins are mentally dull and lethargic, and do not show the typical playfulness seen in normal puppies. Persistence of the puppy haircoat, alopecia, inappetence, delayed dental eruption, and goiter are additional signs. Differential diagnoses for failure to grow include endocrine (e.g., dwarfism) and nonendocrine causes (see Box 46.5 and Fig. 46.9). The presence of goiter is variable and dependent on the underlying cause.

AUTOIMMUNE POLYENDOCRINE SYNDROMES

Because autoimmune mechanisms play an important role in the pathogenesis of lymphocytic thyroiditis, it is not surprising that lymphocytic thyroiditis may occur in conjunction with other immune-mediated endocrinopathies. Presumably, the immune-mediated attack is directed against antigens shared by the endocrine system. In human beings autoimmune polyglandular syndrome type II (Schmidt's syndrome) is the most common of the immunoendocrinopathy syndromes, and it usually consists of primary adrenal insufficiency, autoimmune thyroid disease, and type 1 diabetes mellitus. Autoimmune polyendocrine syndromes are uncommon in dogs and should be suspected in a dog found to have multiple endocrine gland failure. Hypothyroidism, hypoadrenocorticism, and, to a lesser extent, diabetes mellitus, hypoparathyroidism, and lymphocytic orchitis are recognized combined syndromes. In most affected dogs each endocrinopathy is manifested separately, with additional disorders ensuing one by one after variable periods (months to years). Diagnostic tests and treatment are directed at each disorder as it is recognized, because it is not possible to reliably predict or prevent any of these problems. Immunosuppressive drug therapy is not indicated for dogs with these syndromes because the adverse effects of immunosuppressive therapy and the difficulty posed by suppression of the immune destruction of affected endocrine glands outweigh the potential benefits of such therapy.

Clinical Pathology

The most consistent clinicopathologic findings in dogs with hypothyroidism are hypercholesterolemia and hypertriglyceridemia; the latter is identified as lipemia. Hypercholesterolemia is identified in approximately 75% of hypothyroid dogs, and the cholesterol concentration can exceed 1000 mg/dL. Although fasting hypercholesterolemia and hypertriglyceridemia can be associated with several other disorders (see Chapter 52), their presence in a dog with appropriate clinical signs is strong evidence for hypothyroidism.

A mild normocytic, normochromic, nonregenerative anemia (packed cell volume [PCV] of 28%-35%) is a less consistent finding, identified in approximately 30% of dogs. Evaluation of red blood cell morphology may reveal an increase in the numbers of leptocytes (target cells), which develop as a result of increased erythrocyte membrane cholesterol loading. The white blood cell count is typically normal, and platelet counts are normal to increased.

A mild to moderate increase in lactate dehydrogenase, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and, rarely, creatine kinase activities may be identified but is an extremely inconsistent finding and may not be directly related to the hypothyroid state. Mild hypercalcemia may be noted in some dogs with congenital hypothyroidism. Results of urinalysis are usually normal. Polyuria, hyposthenuria, and urinary tract infection are not typical of hypothyroidism.

DERMATOHISTOPATHOLOGIC FINDINGS

Skin biopsies are often performed in dogs with suspected endocrine alopecia, especially if screening diagnostic tests

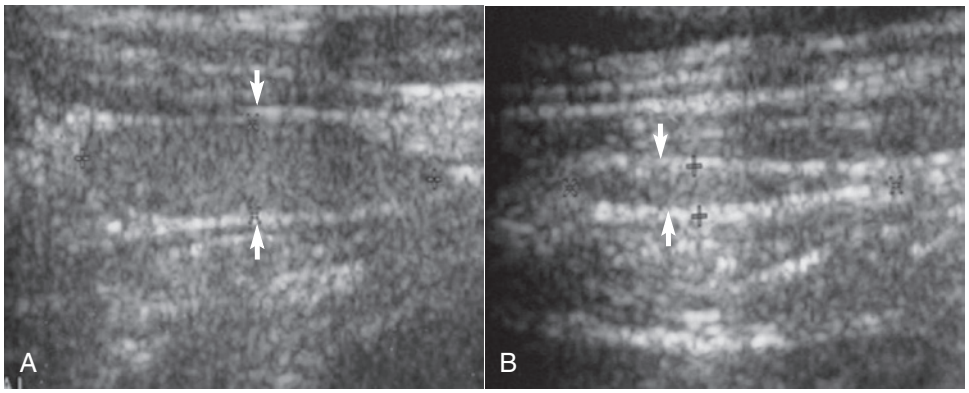


FIG 48.5
(A) Ultrasound image of the normal-appearing left thyroid lobe *(arrows)* of a healthy adult Golden Retriever. **(B)** Ultrasound image of the left thyroid lobe *(arrows)* of an adult Golden Retriever dog with primary hypothyroidism. Note the significant reduction in the size of the thyroid lobe in the dog with hypothyroidism, compared with the thyroid lobe image from the healthy dog.

(including tests to assess thyroid gland function) have failed to identify the cause. Nonspecific histologic changes are associated with various endocrinopathies, including hypothyroidism (see Table 46.5); histologic alterations that are claimed to be specific to hypothyroidism may also be seen, including vacuolated and/or hypertrophied arrector pili muscles, increased dermal mucin content, and thickened dermis. A variable inflammatory cell infiltrate may be present if a secondary pyoderma has developed.

ULTRASONOGRAPHIC FINDINGS

Ultrasound evaluation of the thyroid lobe may be helpful in differentiating dogs with hypothyroidism from euthyroid dogs with nonthyroidal illness causing low thyroid hormone test results. In early hypothyroidism the thyroid lobes may appear relatively normal. Lymphocytic thyroiditis and idiopathic atrophy eventually cause a decrease in size and alterations in echogenicity of the thyroid lobe. The thyroid lobe in euthyroid dogs is usually fusiform and triangular to oval in shape on longitudinal and transverse views, respectively; has a homogeneous echogenic pattern; is hyperechoic to isoechoic, compared with the echogenicity of the surrounding musculature; and has a hyperechoic capsule (Fig. 48.5). Although thyroid lobe shape is often similar between euthyroid and hypothyroid dogs, a significant reduction in size and volume of the thyroid lobe is often seen in hypothyroid versus euthyroid dogs. In addition, the echogenicity of the thyroid lobe in hypothyroid dogs tends to be isoechoic to hypoechoic with hyperechoic foci, and the echogenic pattern often differs between thyroid lobes in the same dog. A direct correlation between size of the dog and size and volume of the normal thyroid gland may exist; the smaller the dog, the smaller the size and volume of the thyroid lobe (Fig. 48.6). This must be considered when thyroid lobe size is evaluated in a dog with suspected hypothyroidism.

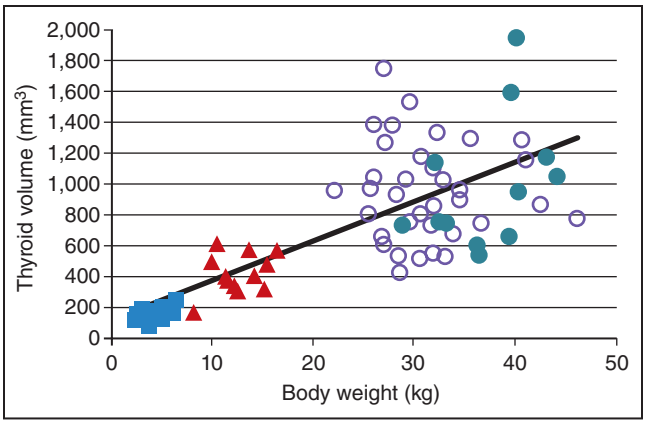


FIG 48.6
The relationship between total thyroid gland volume as determined by ultrasound and body weight in 12 healthy Akitas *(closed circles)*, 36 Golden Retrievers *(open circles)*, 12 Beagles *(triangles)*, and 12 Miniature and Toy Poodles *(squares)*. Note the positive correlation between body weight and size of the thyroid gland. (From Brömel C et al: Comparison of ultrasonographic characteristics of the thyroid gland in healthy small-, medium-, and large-breed dogs, *Am J Vet Res* 67:70, 2006.)

TESTS OF THYROID GLAND FUNCTION

Overview

Function of the thyroid gland is typically assessed by measuring baseline serum thyroid hormone concentrations. Most of the thyroid hormone secreted by the thyroid gland consists of 3,5,3′5′-tetraiodothyronine (thyroxine [T_4]), and only small quantities of 3,5,3′-triiodothyronine (T_3) and minor amounts of 3,3′,5′-triiodothyronine (reverse T_3 [rT_3]) are released. Once secreted into the circulation, more than 99% of T_4 is bound to plasma proteins; this serves as a reservoir and a buffer to maintain a steady concentration of free T_4 (fT_4) in the plasma. Unbound, or free, T_4 is biologically

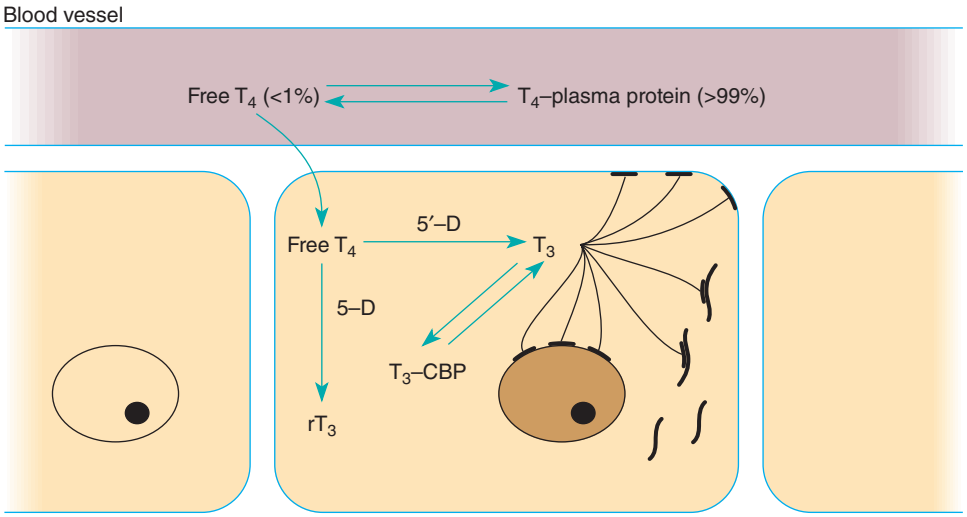


FIG 48.7
Intracellular metabolism of free T_4 to either T_3 or reverse T_3 by 5′- or 5-monodeiodinase, respectively. Intracellular T_3 formed from monodeiodination of free T_4 can interact with T_3 receptors on the cell membrane, mitochondria, or nucleus of the cell and stimulate the physiologic actions of thyroid hormone or bind to cytoplasmic binding proteins *(CBP)*. The latter form an intracellular storage pool for T_3. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

active, exerts negative feedback inhibition on pituitary TSH secretion (see Fig. 48.1), and is capable of entering cells throughout the body (Fig. 48.7). Within the cell, fT_4 is deiodinated to form either T_3 or rT_3, depending on the metabolic demands of the tissues at that particular time. T_3 is preferentially produced during normal metabolic states; rT_3 is biologically inactive and produced during periods of illness or excessive endogenous catabolism. T_3 is believed to be the primary hormone that induces physiologic effects.

All serum T_4, both protein bound and free, comes from the thyroid gland. Therefore tests that measure serum total and fT_4 concentrations, in conjunction with the serum TSH concentration, are currently recommended for assessment of thyroid gland function in dogs suspected of having hypothyroidism. Serum T_3 concentration is a poor gauge of thyroid gland function because of its predominant location within cells and the minimal amount secreted by the thyroid gland in comparison with the amount of T_4 secreted (Fig. 48.8). Thus measurement of serum T_3, free T_3, and rT_3 concentration is not recommended for assessment of thyroid gland function in dogs.

Baseline Serum T_4 Concentration

The baseline serum T_4 concentration is the sum of protein-bound and free levels circulating in the blood. Measurement of serum T_4 concentration can serve as the initial screening test for hypothyroidism or can be part of a thyroid panel containing T_4, fT_4, TSH, an antibody test for lymphocytic thyroiditis, or some combination of these tests (Box 48.4).

Most reference laboratories use radioimmunoassay (RIA) or, more commonly, chemiluminescent immunoassays for measuring serum T_4 in dogs and cats. Point-of-care enzyme-linked immunosorbent assays (ELISAs) for measuring serum T_4 are also available; are economical, quick, and easy to perform; and allow the clinician to make recommendations the same day the dog (or cat) is evaluated. Studies evaluating one point-of-care ELISA (Snap T_4 test kit and VetTest Snap Reader, IDDEX laboratories) have been conflicting. In one study, discrepancies, both overestimation and underestimation of the T_4 concentration, between the in house ELISA and RIA results were detected (Lurye et al., 2002). In contrast, serum T_4 concentrations determined in dogs and cats by RIA, chemiluminescent enzyme immunoassay, and a point-of-care ELISA provided similar and consistent results (Kemppainen and Birchfield, 2006).

For most laboratories, the lower limit of the reference range for serum T_4 in dogs is approximately 0.8 to 1.0 µg/dL (10-13 nmol/L), although in some breeds the normal range may extend to as low as 0.5 µg/dL (6 nmol/L) (see the discussion of breed variations, p. 781).

Theoretically, interpretation of baseline serum T_4 concentration should be straightforward in that dogs with hypothyroidism should have values below the reference range. Unfortunately, the serum T_4 concentration range in healthy dogs overlaps with that in hypothyroid dogs, and the serum T_4 concentration can be suppressed below the reference range in euthyroid dogs by a variety of factors, most notably nonthyroidal illness and medications (Table 48.2). Clinicians often find it difficult to judge the effects that extraneous factors, especially concurrent illness, have on serum T_4 concentration. Because these variables can suppress a baseline serum T_4 concentration to less than 0.5 µg/dL in a euthyroid dog, and because hypothyroid dogs in early stages of the disease may have a serum T_4 concentration near the lower end of the reference range, the serum T_4 concentration should be used to confirm normal thyroid gland function, not hypothyroidism per se. A serum T_4 concentration in the reference range, especially a value in the upper half of the reference range, establishes normal thyroid gland function. The exception is seen in a very small number (<2%) of hypothyroid dogs with lymphocytic thyroiditis that have serum T_4 autoantibodies that may interfere with the assay used to measure T_4. A serum T_4 concentration below the lower limit of the reference range is consistent with hypothyroidism, especially if the T_4 concentration is less than 0.5 µg/dL and all other findings are consistent with the diagnosis.

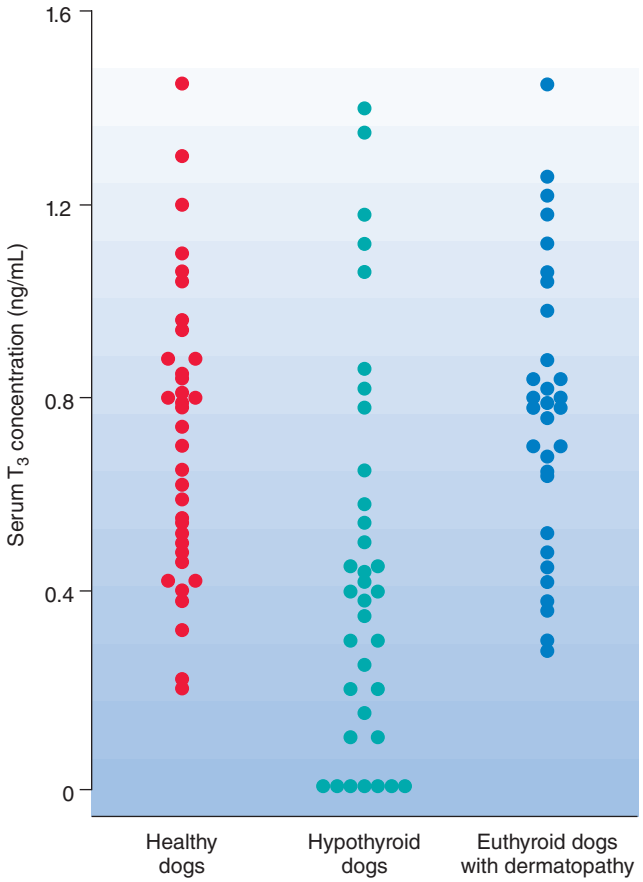


FIG 48.8
Baseline serum T_3 concentrations in 35 healthy dogs, 35 dogs with hypothyroidism, and 30 euthyroid dogs with concurrent dermatopathy. Note the overlap in serum T_3 concentrations among the three groups of dogs.

Additional diagnostic tests are indicated if the serum T_4 concentration is below the reference range, but other factors (e.g., concurrent illness, questionable clinical signs, lack of hyperlipidemia) raise doubt about hypothyroidism (see Diagnosis, p. 782).

Baseline Serum fT_4 Concentration

Free T_4, the non–protein-bound fraction of T_4 circulating in blood, accounts for less than 1% of circulating T_4. Currently, measurement of fT_4 is done by one of three methods: modified equilibrium dialysis, analog RIA, and analog chemiluminescent assay. Studies evaluating these assays for assessment of thyroid gland function in dogs and cats found comparable sensitivity, specificity, and accuracy, suggesting that any one of these three assays is acceptable for measuring fT_4 concentrations in dogs and cats. It is important that the assay used by the reference laboratory has been validated for use in dogs and reference ranges established in dogs. In general, serum fT_4 concentrations greater than 1.5 ng/dL (20 pmol/L) are consistent with euthyroidism, and values less than 0.8 ng/dL (10 pmol/L) especially less than 0.5 ng/dL (6 pmol/L) are supportive of hypothyroidism, assuming the history and

BOX 48.4

Diagnostic Tests for Evaluating Thyroid Gland Function in the Dog

The decision to assess thyroid gland function should be based on results of the history, physical examination, and routine blood work (complete blood count, serum biochemistry panel, urinalysis).

Serum Thyroxine (T_4)

This is the most commonly used initial screening test for hypothyroidism.
Normal serum T_4 rules out hypothyroidism.
Exception: T_4 autoantibodies that interfere with T_4 assay and cause spuriously high results (uncommon).
Low serum T_4 does not, by itself, confirm hypothyroidism.
Serum T_4 is commonly suppressed below the reference range by nonthyroidal illness, drugs, and other factors in dogs with normal thyroid gland function.

Serum Free Thyroxine (fT_4)

This is usually measured in dogs with nondiagnostic serum T_4 test results, severe nonthyroidal illness, or both, and is a common component of canine thyroid panels.
Normal serum fT_4 rules out hypothyroidism.
Low serum fT_4 does not, by itself, confirm hypothyroidism; severe nonthyroidal illness and drugs can suppress serum fT_4 to below the reference range.

Serum Thyrotropin (TSH)

Should be measured in conjunction of serum T_4 during initial evaluation of thyroid function but is usually measured in dogs with nondiagnostic serum T_4 test results, severe nonthyroidal illness, or both, and is a common component of canine thyroid panels.
TSH provides additional evidence for or against the diagnosis of hypothyroidism.
False-positive and false-negative serum TSH test results are common.
Serum TSH should not be used, by itself, to diagnose hypothyroidism.

Serum 3,5,3′-Triiodothyronine (T_3)

This may be a component of canine thyroid panels.
This is not the primary hormone secreted by the thyroid gland; T_3 is primarily produced from deiodination of fT_4 within cells of the body.
T_3 is a poor gauge of thyroid gland function and should not be used, by itself, to diagnose hypothyroidism.

Serum Thyroglobulin (Tg) and Thyroid Hormone (T_3 and T_4) Autoantibody Tests

This is a common component of canine thyroid panels.
These are tests of thyroid gland pathology—not of thyroid gland function.
These tests are used to identify lymphocytic thyroiditis and to explain unusual serum T_4 and T_3 test results.
They should never be used to diagnose hypothyroidism.

TABLE 48.2

Variables That May Affect Baseline Serum Thyroid Hormone Function Test Results in the Dog

FACTOR	EFFECT
Age	T_4 and free T_4 negatively correlated with age TSH positively correlated with age
Body size	T_4 and free T_4 negatively correlated with body weight TSH positively correlated with body weight
Breed Sighthounds (e.g., Greyhounds) Nordic breeds (e.g., Huskies) English Setters, Whippet, Saluki, Sloughi, Basenji, Irish Wolfhound, Conditioned Alaskan Sled Dogs, Other breeds?	T_4 and free T_4 lower than normal range established for dogs; TSH may be increased in Whippet and Sloughi; no difference for TSH in other breeds
Gender	No effect
Time of day	No effect
Weight gain/obesity	Increased T_4 and T_3
Weight loss/fasting	Decreased T_4, no effect on free T_4
Acute exercise	Decreased T_4, no effect on free T_4
Prolonged strenuous exercise	Decreased T_4 and free T_4
Estrus (estrogen)	No effect on T_4
Pregnancy (progesterone)	Increased T_4
Surgery/anesthesia	Decreased T_4
Concurrent illness*	Decreased T_4 and free T_4; depending on illness, TSH may increase, decrease, or not change
Moderate/severe osteoarthritis	No effect on T_4, free T_4, or TSH
Drugs	See Table 48.3
Dietary iodine intake	If excessive, decreased T_4 and free T_4; increased TSH
Thyroid hormone autoantibodies	Increased or decreased T_4; no effect on free T_4 results measured by equilibrium dialysis but results may be increased with chemiluminescent immunoassyays; No effect on TSH

TSH, Thyroid-stimulating hormone.
*A direct correlation has been noted between the severity and the systemic nature of the illness and suppression of serum T_4 and free T_4 concentrations.

findings on physical examination and routine bloodwork are supportive of hypothyroidism.

Measurement of serum fT_4 is usually reserved for dogs with suspected hypothyroidism and nondiagnostic serum T_4 and TSH test results, severe concurrent illness, or both. Serum fT_4 is more resistant to the suppressive effects of nonthyroidal illness and medications than is serum T_4, although severe illness can cause serum fT_4 concentrations to decrease to below 0.5 ng/dL (6 pmol/L). Serum T_4 autoantibodies do not affect serum fT_4 results determined with the use of equilibrium dialysis but can increase serum fT_4 results determined by the analog veterinary fT_4 chemiluminescent immunoassay. Serum thyroglobulin autoantibodies may also interfere with fT_4 test results measured by chemiluminescent immunoassay, resulting in an increased fT_4 test result that does not support a diagnosis of hypothyroidism (Randolph et al., 2015). Interpretation of serum fT_4 test results is similar to interpretation of serum T_4 test results. Serum fT_4 values in the reference range are consistent with normal thyroid gland function, and values below the lower limit of the reference range are consistent with hypothyroidism, given that other findings are consistent with the diagnosis. In general, serum fT_4 concentrations less than 0.8 ng/dL (10 pmol/L), especially less than 0.5 ng/dL (6 pmol/L), are supportive of hypothyroidism, assuming the history and findings on physical examination and routine bloodwork are supportive of hypothyroidism.

Baseline Serum TSH Concentration

Measurement of serum TSH provides information on the interaction between the pituitary and the thyroid gland. In theory, serum TSH concentration should be increased in dogs with hypothyroidism. The assay most commonly utilized to measure TSH in dogs is the chemiluminescent TSH

assay (Imulite Canine TSH), which has been shown to have the highest precision compared with immunoradiometric and enzyme immunometric assays (Marca et al., 2001). Unfortunately, all TSH assays have poor sensitivity for the diagnosis of hypothyroidism. In dogs with hypothyroidism, 20% to 40% have serum TSH concentrations in the reference range. However, studies have shown that a high serum TSH concentration has high specificity (>90%) for diagnosis of hypothyroidism when serum T_4 and/or fT_4 is low in the same serum sample. Proposed reasons for the poor sensitivity include loss of TSH response by pituitary thyrotophs to low serum T_4 concentrations over time, pulsatile TSH secretion resulting in fluctuations in serum TSH concentration, suppression of the TSH response by concurrent illness or drugs, and secondary hypothyroidism.

Most clinical laboratories use a serum TSH concentration of 0.6 ng/mL as the upper limit of the reference range. The lower limit of the reference range is currently below the sensitivity of these assays; differentiation between low and normal serum TSH concentrations is not possible.

Measurement of serum TSH concentration should be part of the routine evaluation of thyroid gland function or may be reserved for dogs with suspected hypothyroidism and nondiagnostic serum T_4 test results. A serum TSH concentration greater than 0.6 ng/mL in conjunction with a low serum T_4 or fT_4 is consistent with hypothyroidism. Unfortunately, serum TSH concentrations can be normal in dogs with histologically confirmed hypothyroidism and increased in euthyroid dogs with concurrent nonthyroidal illness or dogs receiving drugs such as phenobarbital (Fig. 48.9). Serum TSH test results should always be interpreted in conjunction with results of serum T_4, fT_4, or both and should not be used alone in the diagnosis of hypothyroidism. Serum TSH test results increase the likelihood of euthyroidism or hypothyroidism when results are consistent with results of serum T_4 and fT_4 tests. Normal serum T_4 and fT4 concentrations and increased serum TSH concentrations occur in the early stages of primary hypothyroidism in humans. Although similar thyroid hormone and TSH test results have been identified in dogs, it is not known what percentage of these dogs progress to clinical hypothyroidism. Clinical signs of hypothyroidism usually are not evident in these dogs, presumably because serum T_4 and fT_4 concentrations are in the reference range. Treatment with sodium levothyroxine is not indicated. Rather, assessment of thyroid gland function should be repeated in 3 to 6 months, especially if antibody tests for lymphocytic thyroiditis are positive. If progressive destruction of the thyroid gland is occurring, serum T_4 and fT_4 concentrations will gradually decrease and clinical signs will eventually develop.

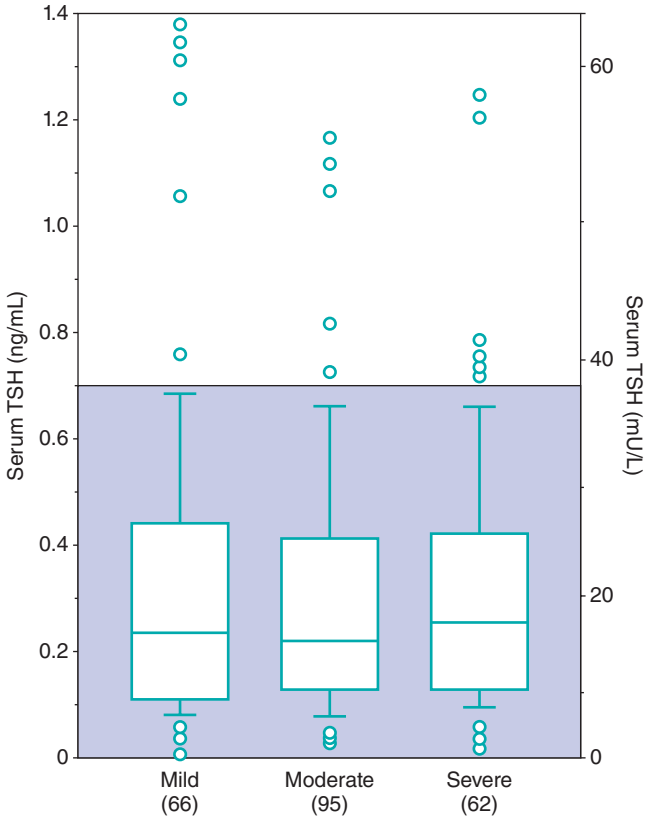


FIG 48.9
Box plots of serum concentrations of thyrotropin *(TSH)* in 223 dogs with nonthyroidal disease stratified according to severity of disease. For each box plot T-bars represent the main body of data, which in most instances is equal to the range. Each box represents an interquartile range (25th to 75th percentile). The horizontal bar in each box is the median. Open circles represent outlying data points. Numbers in parentheses indicate the numbers of dogs in each group. Shaded area is the normal range. (From Kantrowitz LB et al: Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease, *J Am Vet Med Assoc* 219:765, 2001.)

TSH and TRH Stimulation Tests

TSH and TRH stimulation tests evaluate the responsiveness of the thyroid gland to exogenous TSH and TRH administration, respectively. The primary advantage of these tests is that they help differentiate between hypothyroidism and nonthyroidal illness in dogs with low serum T_4 and fT_4 concentrations. Unfortunately, TRH for injection is currently not available. Recombinant human TSH (rhTSH) for injection is effective in stimulating thyroid hormone secretion in dogs but is not available at a reasonable cost. The current TSH stimulation protocol for dogs is 75 µg of rhTSH per dog administered intravenously, and blood for serum T_4 concentration is obtained before and 6 hours after rhTSH administration. Administration of a higher TSH dose (150 µg IV) results in significantly higher post-TSH T_4 concentrations in healthy dogs and better differentiation between euthyroid and hypothyroid dogs, suggesting that the higher dose should be used in dogs that have concurrent disease or are receiving medications (Boretti et al., 2009). In a euthyroid dog serum, T_4 concentration should be ≥ 2.5 µg/dL (30 nmol/L) 6 hours after rhTSH administration, and the 6-hour post-rhTSH serum T_4 concentration should be ≥ 1.5

times the baseline serum T_4 concentration. Reconstituted rhTSH can be stored at 4° C for 4 weeks and at −20° C for 8 weeks without loss of biological activity (De Roover et al., 2006).

Antibody Tests for Lymphocytic Thyroiditis

Circulating thyroglobulin (Tg) and thyroid hormone (T_3 and T_4) autoantibodies correlate with the presence of lymphocytic thyroiditis in dogs. Tests for the presence of Tg, T_3, and T_4 autoantibodies in the serum of dogs can be used to identify lymphocytic thyroiditis, to explain unusual serum T_4 test results, and possibly to serve as a genetic screening test for hypothyroidism caused by lymphocytic thyroiditis. Autoantibodies predominantly develop against Tg. T_3 and T_4 are haptens and are not antigenic by themselves. Tg is the protein that provides the antigenic stimulus. Because T_3 and T_4 are attached to the Tg molecule, autoantibodies develop against them as well. Dogs with T_3 and T_4 autoantibodies typically have autoantibodies against Tg, but the converse is not true. As such, the better screening test for lymphocytic thyroiditis is the Tg autoantibody test. ELISAs for detection of Tg autoantibodies are sensitive and specific for identification of Tg autoantibodies in dogs and are commercially available. Results are reported as negative, positive, and inconclusive.

A positive Tg autoantibody test suggests the possibility of lymphocytic thyroiditis but does not provide information on the severity or progressive nature of the inflammatory process. Positive Tg autoantibody test results may remain positive or may revert to negative on subsequent testing. Tg autoantibody is not a thyroid function test. Positive results increase the suspicion for hypothyroidism if serum T_4 and fT_4 concentrations are low but have no bearing on generation of clinical signs if serum T_4 and fT_4 concentrations are normal. Tg autoantibodies should not be used alone in the diagnosis of hypothyroidism. Dogs with confirmed hypothyroidism can be negative, and euthyroid dogs can be positive for Tg autoantibodies. Identification of Tg autoantibodies would support hypothyroidism caused by lymphocytic thyroiditis if the dog has clinical signs, physical findings, and thyroid hormone test results consistent with the disorder. Positive serum T_4 and T_3 autoantibody test results are interpreted in a similar manner.

The value of serum Tg autoantibodies as a marker for eventual development of hypothyroidism remains to be clarified. A 1-year prospective unpublished study performed by Graham et al at Michigan State University found that approximately 20% of 171 dogs with positive Tg autoantibody and normal fT_4 and TSH test results developed changes in fT_4, TSH, or both test results consistent with hypothyroidism; 15% reverted to a negative Tg autoantibody test with no change in fT_4 and TSH test results; and 65% remained Tg autoantibody positive or had an inconclusive result with no change in fT_4 and TSH test results 1 year later. Currently, a positive Tg autoantibody test is considered suggestive of lymphocytic thyroiditis and supports retesting of thyroid gland function in 3 to 6 months.

Testing for serum T_4 or Tg autoantibodies is indicated in dogs with unusual serum T_4 values. T_4 autoantibodies may interfere with RIAs used to measure serum T_4 concentrations and yield spurious and possibly unreliable values. Similar interference does not occur with chemiluminescence immunoassay (Piechotta et al., 2010). The type of interference depends on the separation system used in the RIA. Most T_4 RIAs use a single-step separation system with antibody-coated tubes, which results in falsely increased T_4 values. Fortunately, spurious T_4 values resulting from clinically relevant concentrations of thyroid hormone antibody account for less than 1% of such results from commercial endocrine laboratories. The effect of T_4 autoantibodies on serum fT_4 results is dependent on the fT_4 assay used (see Baseline Serum fT_4 Concentration, p. 776).

FACTORS AFFECTING THYROID GLAND FUNCTION TESTS

Many factors affect baseline thyroid hormone and endogenous TSH concentrations (see Table 48.2). Unfortunately, most of these factors decrease baseline thyroid hormone concentrations and may increase endogenous TSH in euthyroid dogs, potentially causing misdiagnosis of hypothyroidism if the clinician accepts the results out of context. The factors that most commonly result in lower baseline thyroid hormone concentrations in euthyroid dogs are nonthyroidal illness (i.e., euthyroid sick syndrome), drugs (especially glucocorticoids, phenobarbital, and sulfonamide antibiotics; see Table 48.2), and variation in the reference range between breeds (most notably sighthounds and Nordic breeds).

Nonthyroidal Illness Syndrome (Euthyroid Sick Syndrome)

Nonthyroidal Illness Syndrome (NTIS), historically referred to as euthyroid sick syndrome, refers to suppression of serum thyroid hormone concentrations in euthyroid dogs in response to concurrent illness. A decrease in serum thyroid hormone concentrations may result from a decrease in TSH secretion secondary to suppression of the hypothalamus or pituitary gland, from decreased synthesis of T_4, from decreased concentration or binding affinity of circulating binding proteins (e.g., thyroid binding globulin), from the presence of serum protein binding inhibitors, from inhibition of the deiodination of T_4 to T_3, from increased hepatic metabolism and excretion of T_4, or from any combination of these factors. The subsequent decrease in serum total T_4 and, in many cases, fT_4 concentrations is believed to represent a physiologic adaptation by the body, with the purpose being to decrease cellular metabolism during periods of illness. It is not indicative of hypothyroidism, per se. Generally, the type and magnitude of most alterations in serum thyroid hormone concentrations are not unique to a specific disorder but reflect the severity of the illness or the catabolic state and appear to represent a continuum of changes. Systemic illness has more of an effect in lowering serum thyroid hormone concentrations than do, for example, dermatologic disorders.

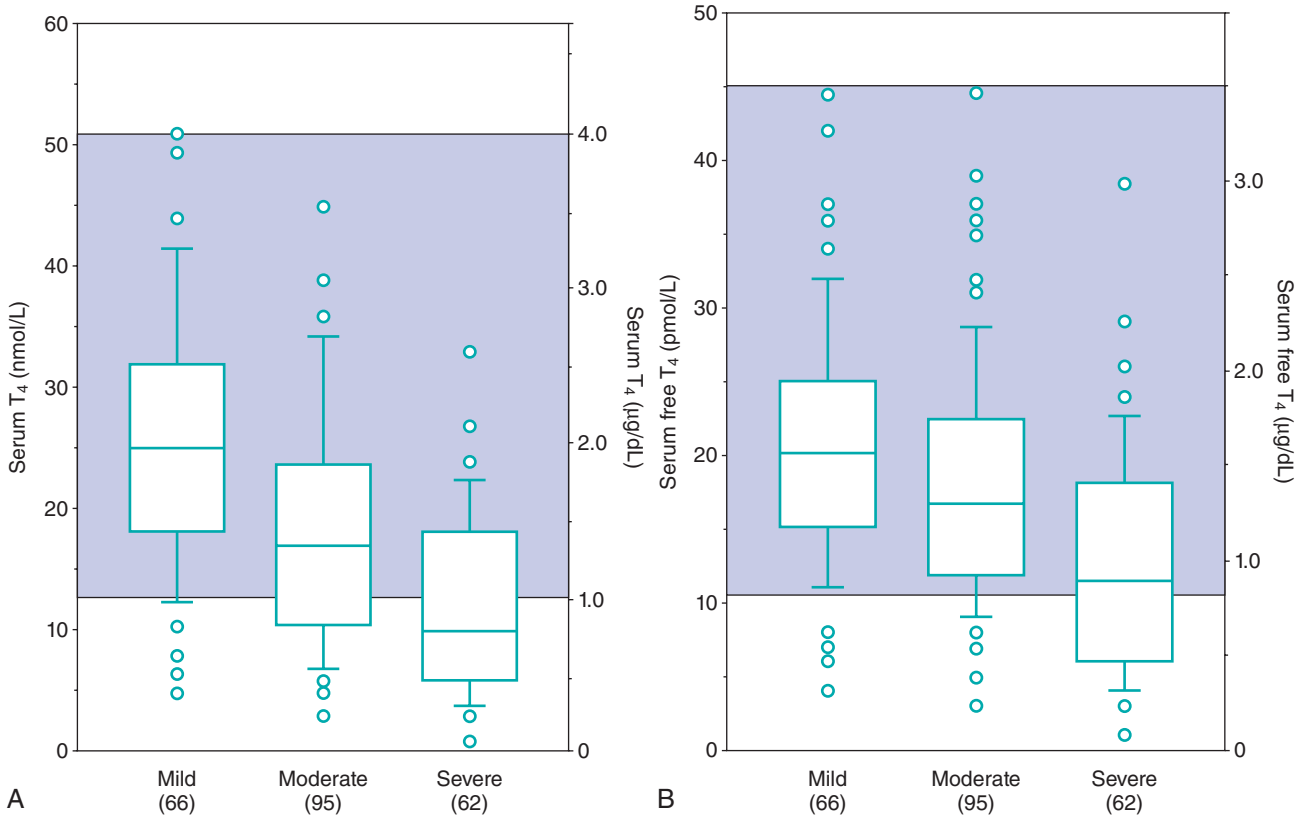


FIG 48.10
Box plots of serum total T_4 **(A)** and free T_4 **(B)** concentrations in 223 dogs with nonthyroidal disease stratified according to severity of disease. See Fig. 48.9 for an explanation. (From Kantrowitz LB et al: Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease, *J Am Vet Med Assoc* 219:765, 2001.)

In addition, the more severe the systemic illness, the more suppressive the effect on the serum thyroid hormone concentration (Fig. 48.10).

Unfortunately, euthyroid dogs with concurrent illness can have serum T_4 concentrations that often fall between 0.5 and 1.0 µg/dL (6 and 13 nmol/L), and with severe illness (e.g., cardiomyopathy, severe anemia), these concentrations can be less than 0.5 µg/dL. Alterations in serum concentrations of fT_4 and TSH are more variable and probably depend in part on the pathophysiologic mechanisms involved in the illness. In general, serum fT_4 concentrations tend to be decreased in dogs with concurrent illness but to a lesser extent than total T_4 concentrations. However, fT_4 concentrations can be less than 0.5 ng/dL if severe illness is present. TSH concentrations may be normal or increased depending, in part, on the effect of the concurrent illness on fT_4 concentrations and on pituitary function. If pituitary function is suppressed, TSH concentrations will be in the reference range or undetectable. If pituitary response to changes in fT4 concentration is not affected by the concurrent illness, TSH concentrations will increase in response to a decrease in fT_4. Serum TSH concentrations can easily exceed 1.0 ng/mL in dogs with NTIS.

It can be difficult to establish a diagnosis of hypothyroidism in a dog with NTIS, especially when relying on a single test of thyroid function, specifically serum T_4 concentration. Normal test results are indicative of euthyroidism, but abnormal test results do not confirm hypothyroidism. If possible, evaluation of thyroid function should wait until the nonthyroidal illness has resolved. If necessary, evaluation of thyroid gland function should include careful review of the history, findings on physical examination, and results of bloodwork and serum T_4, FT_4 and TSH concentrations. The simultaneous finding of low serum T_4 and f T_4 and increased serum TSH concentration is uncommon with NTIS and would suggest the presence of hypothyroidism.

Treatment of NTIS should be aimed at the concurrent illness. Serum thyroid hormone concentrations return to normal once the concurrent illness is eliminated. Treatment of NTIS with sodium levothyroxine is not recommended.

Drugs

Clinical knowledge of the effect, if any, of various drugs and hormones on serum thyroid hormone and TSH concentrations in dogs is expanding as investigators continue to examine the interplay between medications and thyroid

TABLE 48.3

Drugs That May Affect Baseline Serum Thyroid Hormone Function Test Results in the Dog

DRUG	POSSIBLE IMPACT ON TEST RESULTS
Amiodarone	Increased T_4; no effect on fT_4
Aspirin	Decreased T_4, free T_4; no effect on TSH
Cephalexin	No effect on T_4, free T_4, or TSH
Clomipramine	Decreased T_4, free T_4; no effect on TSH
Carprofen	Decreased T_4, free T_4, and TSH
Deracoxib	No effect on T_4, free T_4, or TSH
Etodolac	No effect on T_4, free T_4, or TSH
Glucocorticoids	Decreased T_4 and free T_4; decreased or no effect on TSH
Furosemide	Decreased T_4
Ipodate	Increased T_4; decreased T_3
Ketoprofen	No effect on T_4, free T_4, or TSH
Meloxicam	No effect on T_4, free T_4, or TSH
Methimazole	Decreased T_4 and free T_4; increased TSH
Phenobarbital	Decreased T_4 and free T_4; delayed increase in TSH
Phenylbutazone	Decreased T_4
Potassium bromide	No effect on T_4, free T_4, or TSH
Progestagens	Decreased T_4
Propranolol	No effect on T_4, free T_4, or TSH
Propylthiouracil	Decreased T_4 and free T_4; increased TSH
Sulfonamides	Decreased T_4 and free T_4; increased TSH

TSH, Thyroid-stimulating hormone.

hormone test results (Table 48.3). As a general rule, any drug should be suspected of affecting thyroid hormone test results, especially if the history, clinical signs, and clinicopathologic abnormalities do not support a diagnosis of hypothyroidism. Glucocorticoids, phenobarbital, and sulfonamides are the most commonly used drugs known to significantly affect serum thyroid hormone test results.

Glucocorticoids

Glucocorticoids cause a decrease in serum T_4 and fT_4 concentrations into the range consistent with a diagnosis of hypothyroidism—a decrease that can occur within days of initiation of glucocorticoid treatment. A similar effect occurs with naturally acquired hyperadrenocorticism. Serum TSH concentration is variable but usually within the reference range. The magnitude and duration of suppression of serum thyroid hormone concentrations depend on the type of glucocorticoid, dosage, route of administration, and duration of glucocorticoid administration. The higher the dosage, the longer the administration, and the more potent the glucocorticoid administered, the more severe the suppression of serum thyroid hormone concentrations. Topical glucocorticoids can have a similar effect as parenterally administered glucocorticoids, especially in small dogs. If glucocorticoids have been administered in the recent past, assay of serum thyroid hormone concentrations should be delayed or must be interpreted carefully. Ideally, glucocorticoids should be discontinued and serum thyroid hormone and TSH concentrations assessed 4 to 8 weeks later.

Typically, administration of exogenous glucocorticoids does not result in clinical signs of hypothyroidism. The exception is seen in dogs receiving daily glucocorticoids for prolonged periods (months to years) to treat chronic steroid-responsive disorders (e.g., immune-mediated disease). In these dogs the prolonged glucocorticoid-induced decrease in serum T_4 and fT_4 concentrations can result in lethargy, weight gain, and dermatologic signs that resolve after sodium levothyroxine treatment is initiated. Treatment for drug-induced hypothyroidism is indicated if the glucocorticoids cannot be discontinued.

Phenobarbital

In dogs long-term phenobarbital treatment at therapeutic dosages may decrease serum T_4 and fT_4 concentrations into the range consistent with hypothyroidism. A delayed increase in the serum TSH concentration may occur secondary to loss of negative feedback as serum T_4 and fT_4 concentrations decline. Increased serum TSH concentrations quickly return to the reference range after discontinuation of phenobarbital treatment, whereas serum T_4 and fT_4 concentrations may take up to 4 weeks to return to pretreatment values. Potassium bromide treatment does not appear to have a significant effect on serum T_4, fT_4, and TSH concentrations in dogs, and may be indicated if clinical signs of hypothyroidism develop in a dog being treated with phenobarbital.

Sulfonamide antibiotics

A decrease in serum T_4 and fT_4 and an increase in TSH concentrations have been documented in dogs treated with sulfonamides (e.g., sulfamethoxazole, sulfadiazine). Serum T_4 concentrations can decrease into the hypothyroid range within 1 to 2 weeks, and serum TSH concentrations can increase above the reference range within 2 to 3 weeks after sulfonamide therapy is initiated. Clinical signs of hypothyroidism can develop with long-term sulfonamide administration. The increase in the serum TSH concentration can lead to thyroid hyperplasia and goiter. Alterations in results of thyroid gland function tests may resolve within 1 to 2 weeks or last as long as 8 to 12 weeks after cessation of the antibiotic.

Breed Variations

Current reference ranges were established in large populations of dogs without regard for breed. It is now recognized that the reference range for serum T_4 and fT_4 concentrations

but not TSH concentration is lower in sighthounds, most notably Greyhounds, and in Nordic breeds such as the Siberian Husky, and may be lower in other breeds as well (see Table 48.2). The lower end of the reference range for serum T_4 and fT_4 in these breeds may be as low as 0.4 µg/dL (5 nmol/L) and 0.4 ng/dL (5 pmol/L), respectively. Serum T_4 and fT_4 concentrations consistent with hypothyroidism according to standard reference ranges may actually be normal in these breeds. Establishing the diagnosis of hypothyroidism in these breeds must rely on the strength of clinical signs, physical examination findings, and results of routine blood work, as well as on documentation of extremely low T_4 and fT_4 concentrations and ideally an increased serum TSH concentration.

Diagnosis

The diagnosis of hypothyroidism is based on a combination of clinical signs; findings on physical examination; and results of complete blood count (CBC), serum biochemistry panel, and tests of thyroid gland function. The presence of appropriate clinical signs is imperative, especially when one is relying on baseline thyroid hormone concentrations for a diagnosis. In the adult dog the most consistent clinical signs include lethargy, weight gain, and abnormalities affecting the skin (e.g., alopecia, seborrhea, pyoderma) and neuromuscular system (e.g., weakness). Other organ systems may be affected by thyroid hormone deficiency, but clinical signs related to these other systems are not usually the primary reason for presentation of the dog to the veterinarian. Identification of a mild nonregenerative anemia on the CBC, and especially lipemia (hypertriglyceridemia) in the blood sample and an increased serum cholesterol concentration on a serum biochemistry panel, adds further evidence for hypothyroidism.

Baseline serum T_4 concentration is often used as the initial screening test for thyroid gland function because it is widely available at low cost and can be measured in-house. It is important to remember that serum T_4 concentrations can be suppressed by a variety of factors, most notably nonthyroidal illness and medications such as prednisone and phenobarbital. As such, measurement of the serum T_4 concentration should be used to confirm normal thyroid gland function, not hypothyroidism per se. A normal serum T_4 concentration establishes normal thyroid gland function unless serum T_4 autoantibodies are present and are interfering with the assay. A low serum T_4 concentration (ideally <0.5 µg/dL [6 nmol/L]) in conjunction with hypercholesterolemia and clinical signs strongly suggestive of the disease supports the diagnosis of hypothyroidism, especially if systemic illness is not present. The definitive diagnosis must then rely on response to trial therapy with synthetic levothyroxine. Additional tests of thyroid gland function (i.e., TSH and fT_4) are warranted if the serum T_4 concentration is equivocal.

Evaluation of a thyroid panel that includes serum T_4, fT_4, TSH, and Tg autoantibody provides a more informative analysis of the pituitary-thyroid axis and thyroid gland function, can be used as the initial screening test for hypothyroidism, and should be used when serum T_4 concentration alone fails to establish the diagnosis. Low serum T_4 and fT_4 and increased serum TSH concentrations in a dog with appropriate clinical signs and clinicopathologic abnormalities strongly support the diagnosis of hypothyroidism. Concurrent presence of Tg autoantibodies suggests lymphocytic thyroiditis as the underlying cause.

Unfortunately, discordant thyroid hormone test results are common. When this occurs, the appropriateness of clinical signs, clinicopathologic abnormalities, and clinician index of suspicion become the most important parameters in determining whether to treat the dog with levothyroxine or repeat testing in 3 to 6 months.

Normal serum T_4 or fT_4 and high TSH may suggest early compensated hypothyroidism, but one has to wonder why clinical signs would develop when the serum T_4 and fT_4 concentration are normal. Positive Tg autoantibody findings merely suggest the possibility of lymphocytic thyroiditis; Tg autoantibody determination is not a thyroid function test. Positive results increase the suspicion for hypothyroidism if serum T_4 and fT_4 concentrations are low but have no bearing on the generation of clinical signs if serum T_4 and fT_4 concentrations are normal.

Interpretation of serum T_4, fT_4, and TSH concentrations is not always simple. Because of the expense and frustration of working with tests that are not always reliable, many veterinarians and some clients prefer trial therapy as a diagnostic test. Trial therapy should be done only when thyroid hormone supplementation does not pose a risk to the patient. Response to trial therapy with sodium levothyroxine is nonspecific. A dog that has a positive response to therapy has either hypothyroidism or "thyroid hormone–responsive disease." Because of its anabolic nature, thyroid hormone supplementation can create an effect in a dog without thyroid dysfunction, especially regarding quality of the haircoat. Therefore if a positive response to trial therapy is observed, thyroid supplementation should be gradually discontinued once clinical signs have resolved. If clinical signs recur, hypothyroidism is likely and the supplement should be reinitiated. If clinical signs do not recur, a thyroid hormone–responsive disorder or a beneficial response to concurrent therapy (e.g., antibiotics, flea control) should be suspected.

DIAGNOSIS IN A PREVIOUSLY TREATED DOG

Occasionally, a clinician wishes to determine whether a dog receiving thyroid hormone supplementation is in fact hypothyroid. Exogenous administration of thyroid hormone, either T_4 or T_3, will suppress pituitary TSH secretion and cause pituitary thyrotroph atrophy and subsequent thyroid gland atrophy in a healthy euthyroid dog. Serum T_4, fT_4, and TSH concentrations are decreased or undetectable; the severity of the decrease is dependent on the severity of thyroid gland atrophy induced by the thyroid supplement. Serum T_4 and fT_4 results are often suggestive

of hypothyroidism, even in a previously euthyroid dog, if testing is performed within a month of treatment discontinuation. Thyroid hormone supplementation must be discontinued, either by stopping all at once or by gradual reduction over 2 to 3 weeks, and the pituitary-thyroid axis allowed to regain function before meaningful baseline serum thyroid hormone concentrations can be obtained. The time between discontinuation of thyroid hormone supplementation and acquisition of meaningful test results depends on the duration of treatment, the dose and frequency of administration of the thyroid hormone supplement, and individual variability. As a general rule, thyroid hormone supplements should be discontinued for a minimum of 4 weeks, preferably 6 to 8 weeks, before thyroid gland function is critically assessed.

DIAGNOSIS IN PUPPIES

An approach similar to that discussed for the adult dog is used to diagnose congenital hypothyroidism. However, serum TSH concentrations are dependent on the cause of the disorder. TSH concentrations will be increased in dogs with primary dysfunction of the thyroid gland (e.g., iodine organification defect) and an intact hypothalamic-pituitary-thyroid gland axis. TSH concentrations will be within the reference range or undetectable in dogs with pituitary or hypothalamic dysfunction as the cause of the hypothyroidism. Identification of an enlarged thyroid gland (i.e., goiter) implies an intact hypothalamic-pituitary-thyroid gland axis, functional TSH receptors, and appropriate signal transduction following binding of TSH to receptors and suggests a post-TSH receptor problem in the follicular cells, such as an iodine organification defect as the cause of the hypothyroidism.

Treatment

THERAPY WITH SODIUM LEVOTHYROXINE (SYNTHETIC T_4)

Initial treatment and monitoring recommendations are summarized in Box 48.5. Synthetic levothyroxine is the treatment of choice for hypothyroidism. Its oral administration should result in normal serum concentrations of T_4, T_3, and TSH, which attests to the fact that these products can be converted to the more metabolically active T_3 by peripheral tissues. A sodium levothyroxine product approved for use in dogs is recommended. Liquid and tablet formulations are effective. The initial dosage is 0.01 to 0.02 mg/kg body weight. The plasma half-life of sodium levothyroxine ranges from 9 to 14 hours and depends, in part, on the dosage and frequency of administration. Twice-daily administration is recommended initially unless the levothyroxine product has been specifically formulated for once-daily administration (Le Traon et al., 2009). Because of the variability in levothyroxine absorption and metabolism, the dose and frequency may have to be adjusted before a satisfactory clinical response is observed; this variability is one reason for monitoring therapy in dogs.

BOX 48.5

Recommendations for Initial Treatment and Monitoring of Hypothyroidism in Dogs

Initial Treatment

- Use a synthetic levothyroxine product approved for use in dogs.
- Tablet and liquid formulations of levothyroxine are effective.
- The initial dosage per administration should be 0.01 to 0.02 mg/kg of body weight./
- The initial frequency of administration is every 12 hours unless the levothyroxine product has been specifically formulated for once-daily administration.

Initial Monitoring

- Response to treatment should be critically evaluated 4 to 8 weeks after treatment initiation.
- Serum T_4 and TSH concentrations should be measured 4 to 6 hours after administration of levothyroxine.
- Serum T_4 should be in the reference range or mildly increased.
- Serum TSH concentration should be in the reference range.
- Measuring serum T_4 concentration immediately before levothyroxine administration (i.e., trough level) is optional but is recommended if levothyroxine is being given once a day.
- The trough concentration of serum T_4 should be in the reference range.

TSH, Thyroid-stimulating hormone.

Response to Sodium Levothyroxine Therapy

Thyroid hormone supplementation should be continued for a minimum of 4 weeks before the effectiveness of treatment is critically evaluated. With appropriate therapy, all clinical signs and clinicopathologic abnormalities associated with hypothyroidism are reversible. Improvement in mental alertness and activity usually occurs within the first week of treatment; this is an important early indicator that the diagnosis of hypothyroidism was correct. Although some hair regrowth usually occurs within the first month in dogs with endocrine alopecia, it may take several months for complete regrowth and a marked reduction in hyperpigmentation of the skin to occur. Initially, the haircoat may worsen as large amounts of hair in the telogen stage of the hair cycle are shed. Improvement in neurologic manifestations is usually evident within days of treatment initiation; complete resolution of neurologic signs is unpredictable and may require treatment for 4 to 8 weeks or longer before it occurs.

Failure to Respond to Sodium Levothyroxine Therapy

Problems with levothyroxine therapy should be suspected if clinical improvement is not seen by 8 weeks after therapy is

initiated. An inappropriate diagnosis of hypothyroidism is the most obvious. Hyperadrenocorticism can be mistaken for hypothyroidism if other clinical signs (e.g., polyuria, polydipsia) commonly associated with hyperadrenocorticism are not present because of the suppressive effects of cortisol on serum thyroid hormone concentrations (see p. 781). Failure to recognize the impact of concurrent illness on thyroid hormone test results is another common reason for misdiagnosing hypothyroidism. Concurrent disease (e.g., allergic skin disease, flea hypersensitivity) is common in dogs with hypothyroidism and may affect the clinical impression of response to levothyroxine therapy if the disease is not recognized. Other possible reasons for a poor response to therapy are listed in Box 48.6. Whenever a dog shows a poor response to levothyroxine therapy, the history, physical examination findings, and diagnostic test results that prompted the initiation of levothyroxine therapy should be critically reevaluated and serum thyroid hormone concentrations measured.

THERAPEUTIC MONITORING

Therapeutic monitoring includes evaluation of the clinical response to levothyroxine treatment, measurement of serum T_4 concentration before or after levothyroxine administration, or both, and measurement of serum TSH concentration. These concentrations should be measured 4 weeks after therapy is initiated, whenever signs of thyrotoxicosis develop, or in the event that minimal or no response to therapy has occurred. Concentrations should also be measured 2 to 4 weeks after an adjustment in levothyroxine therapy in dogs showing a poor response to treatment.

Serum T_4 and TSH concentrations are typically evaluated 4 to 6 hours after administration of levothyroxine in dogs. Measuring serum T_4 concentration immediately before levothyroxine administration (i.e., trough level) is optional but is recommended if levothyroxine is being given once a day. Measurement of serum fT_4 can be done in lieu of measurement of T_4 but is more expensive and usually does not offer additional information, except in dogs with T_4 autoantibodies. The presence of thyroid hormone autoantibodies does not interfere with the physiologic actions of levothyroxine.

Ideally, the serum T_4 concentration should be in the upper half of the reference range, typically between 2.0 and 5.0 µg/dL (26 and 65 nmol/L) when measured 4 to 6 hours after thyroid hormone administration, and the TSH concentration should be in the reference range (i.e., <0.6 ng/mL). Postdosing serum T_4 concentrations measured at times other than 4 to 6 hours after sodium levothyroxine administration should be interpreted with the realization that serum T_4 concentrations may not be at peak concentrations. The postpill serum T_4 concentration may also be affected by diet (i.e., decreased absorption). Consistency between the timing of levothyroxine administration and feeding should be maintained when monitoring therapy.

Postdosing serum T_4 concentrations are frequently above the reference range. The finding of an increased postdosing serum T_4 concentration is not an absolute indication to reduce the dose of levothyroxine, especially if no clinical signs of thyrotoxicosis are noted. However, a reduction in the dose is recommended whenever serum T_4 concentrations exceed 6.0 µg/dL (75 nmol/L). Postdosing serum T_4 concentrations may also be less than 2 µg/dL. In this situation, an increase in the dose or frequency of administration of levothyroxine is indicated if clinical manifestations of hypothyroidism persist, the serum TSH concentration remains increased, or both but is not necessarily indicated if the clinical response to treatment is good and the serum TSH concentration is in the reference range. Resolution of clinical signs and a satisfied owner are the most important parameters when one is considering adjusting the levothyroxine dose simply because the postpill serum T_4 concentration is near the lower end of the reference interval. Postdosing serum T_4 and TSH concentrations and recommendations for changes in therapy are given in Fig. 48.11.

BOX 48.6

Potential Reasons for Poor Clinical Response to Treatment With Sodium Levothyroxine (Synthetic T_4)

- Client compliance problems
- Use of inactivated or outdated product
- Inappropriate levothyroxine dose
- Inappropriate frequency of administration
- Low tablet strength*
- Poor bioavailability (e.g., poor gastrointestinal tract absorption)
- Inadequate time for clinical response to occur
- Concurrent illness causing similar clinical signs (e.g., flea hypersensitivity)
- Incorrect diagnosis of hypothyroidism

**Tablet strength* refers to the actual amount of active drug in a tablet, as opposed to the stated amount.

THYROTOXICOSIS

Thyrotoxicosis may develop in dogs receiving excessive amounts of levothyroxine; in dogs in which the plasma half-life for levothyroxine is inherently prolonged, especially in those receiving levothyroxine twice daily; in dogs with impaired metabolism of levothyroxine (e.g., concurrent renal or hepatic insufficiency); and in dogs consuming all-meat commercial dog food. Rarely, thyrotoxicosis develops in a dog given minute amounts of levothyroxine. The reason for this marked sensitivity to the hormone is not known. Diagnosis of thyrotoxicosis is based primarily on the presence of clinical signs, which include nervousness, panting, tachypnea, tachycardia, aggressive behavior, polyuria, polydipsia, polyphagia, and weight loss. Documenting increased serum T_4 and fT_4 and undetectable serum TSH concentrations supports the diagnosis. However, serum T_4 and fT_4 concentrations can occasionally be within the reference range in a dog with signs of thyrotoxicosis and are

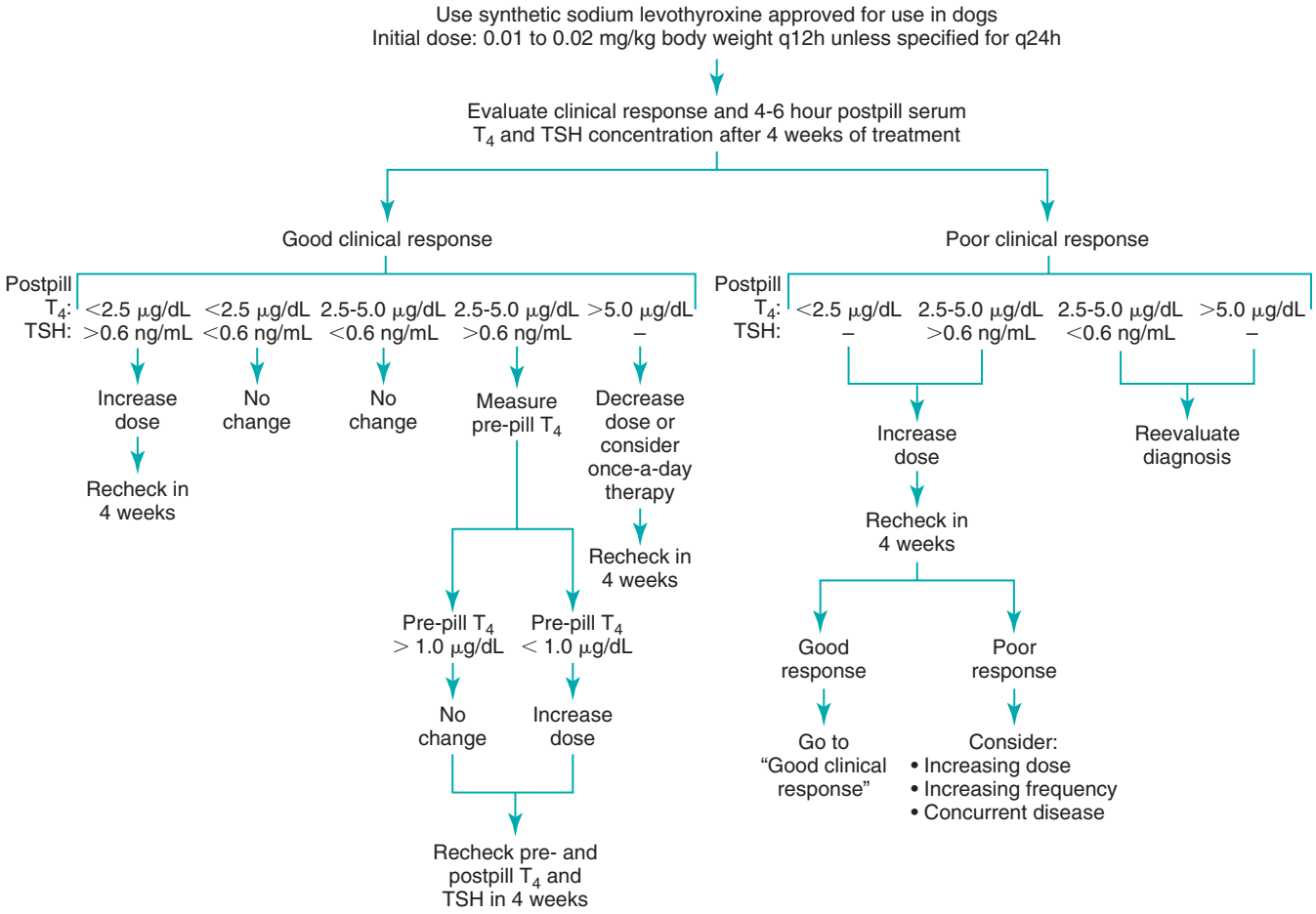


FIG 48.11
Initial therapeutic approach and monitoring recommendations for dogs with hypothyroidism.

commonly increased in dogs with no signs of thyrotoxicosis. Adjustments in the dose or frequency of administration of levothyroxine, or in both measures, are indicated if clinical signs of thyrotoxicosis develop in a dog receiving thyroid hormone supplements. Supplementation should be discontinued for a few days if clinical signs are severe. Signs of thyrotoxicosis should resolve within 1 to 3 days if they are due to the thyroid medication and the adjustment in treatment has been appropriate.

Prognosis

The prognosis for adult dogs with primary hypothyroidism receiving appropriate therapy is excellent. The prognosis for puppies with hypothyroidism (i.e., cretinism) is guarded and depends on the severity of skeletal and joint abnormalities at the time treatment is initiated. Although many of the clinical signs resolve with therapy, musculoskeletal problems, especially degenerative osteoarthritis, may develop as the result of abnormal bone and joint development. The prognosis for dogs with secondary hypothyroidism caused by congenital malformation of the pituitary gland (i.e., pituitary dwarfism) is guarded and dependent on the extent of pituitary hormone deficiencies (see Chapter 46). The prognosis for dogs with acquired secondary hypothyroidism caused by suppression of pituitary function by medications (e.g., glucocorticoids) is excellent, although treatment with levothyroxine may be necessary if the medication cannot be discontinued. The prognosis for dogs with acquired secondary hypothyroidism caused by destruction of the pituitary region by a space-occupying mass is grave.

HYPOTHYROIDISM IN CATS

Etiology

Iatrogenic hypothyroidism is the most common cause of hypothyroidism in cats and can result from bilateral thyroidectomy, radioactive iodine treatment, or an overdose of antithyroid drugs. Naturally acquired adult-onset primary hypothyroidism is rare. Low serum T_4 concentrations are commonly identified in blood samples submitted for a feline geriatric panel that includes serum T_4 measurement, but the low serum T_4 result is almost always a result of the suppressive effects of nonthyroid illness. Congenital primary

hypothyroidism causing disproportionate dwarfism is recognized more frequently in cats than adult-onset hypothyroidism. Reported causes of congenital hypothyroidism include a defect in thyroid hormone biosynthesis, most notably an iodine organification defect, and thyroid dysgenesis. Goiter is common in cats with defects in thyroid hormone biosynthesis because the hypothalamic-pituitary-thyroid gland axis and post-TSH receptor signal transduction remain intact. A suspected autosomal recessive inherited defect in iodine organification was documented in a family of Abyssinian cats with congenital hypothyroidism. Although rare, iodine deficiency may cause hypothyroidism in kittens fed a strict all-meat diet.

Clinical Signs

Clinical signs of feline hypothyroidism are listed in Box 48.7. The most common are lethargy, inappetence, obesity, and seborrhea sicca. Lethargy and inappetence may become severe. Additional dermatologic signs may include a dry, lusterless, unkempt haircoat; easily epilated hair; poor regrowth of hair; and alopecia. Bradycardia and mild hypothermia may be additional findings on physical examination.

The clinical signs of congenital hypothyroidism are similar to those in dogs. Affected kittens typically appear normal at birth, but delayed growth usually becomes evident by 8 weeks of age. Disproportionate dwarfism develops over ensuing months, with a large head, a short broad neck, and short limbs developing in affected kittens (Fig. 48.12). Additional findings include lethargy, mental dullness, constipation, hypothermia, bradycardia, and prolonged retention of deciduous teeth. The haircoat may consist mainly of an undercoat with primary guard hairs scattered thinly throughout.

BOX 48.7

Clinical Manifestations of Feline Hypothyroidism

Adult-Onset Hypothyroidism

- Lethargy
- Inappetence
- Obesity
- Dermatologic events
  - Seborrhea sicca
  - Dry, lusterless haircoat
  - Easily epilated hair
  - Poor regrowth of hair
  - Endocrine alopecia
  - Alopecia of pinnae
  - Thickened skin
  - Myxedema of the face
- Reproduction
  - Failure to cycle
  - Dystocia
- Bradycardia
- Mild hypothermia

Congenital Hypothyroidism

- Disproportionate dwarfism
- Failure to grow
- Large head
- Short, broad neck
- Short limbs
- Lethargy
- Mental dullness
- Constipation
- Hypothermia
- Bradycardia
- Retention of kitten haircoat
- Retention of deciduous teeth

Diagnosis

Establishing a diagnosis of hypothyroidism in the cat should be based on a combination of history, clinical signs, physical examination findings, results of routine blood and urine tests, and baseline serum T_4, fT_4, and TSH concentrations. Abnormalities identified on routine blood and urine tests include hypercholesterolemia and a mild nonregenerative anemia. Serum T_4 concentration is often used as the initial screening test of thyroid gland function. A normal serum T_4 concentration indicates that the cat is euthyroid. A low serum T_4 concentration in a cat that has undergone thyroidectomy or radioactive iodine treatment or in a kitten with disproportionate dwarfism supports the diagnosis of hypothyroidism. The effect of age should be considered when serum T_4 concentrations in kittens are interpreted (see Table 48.2). Because naturally acquired primary hypothyroidism is



FIG 48.12
A 1-year-old domestic long-haired cat with pituitary dwarfism. A comparably aged cat is also present to illustrate the small size of the pituitary dwarf. Note the square, chunky contour of the head and the dull facial expression of the cat—findings that are suggestive of cretinism (see Fig. 49.8, for comparison). The cat had concurrent growth hormone and thyroid hormone deficiency. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

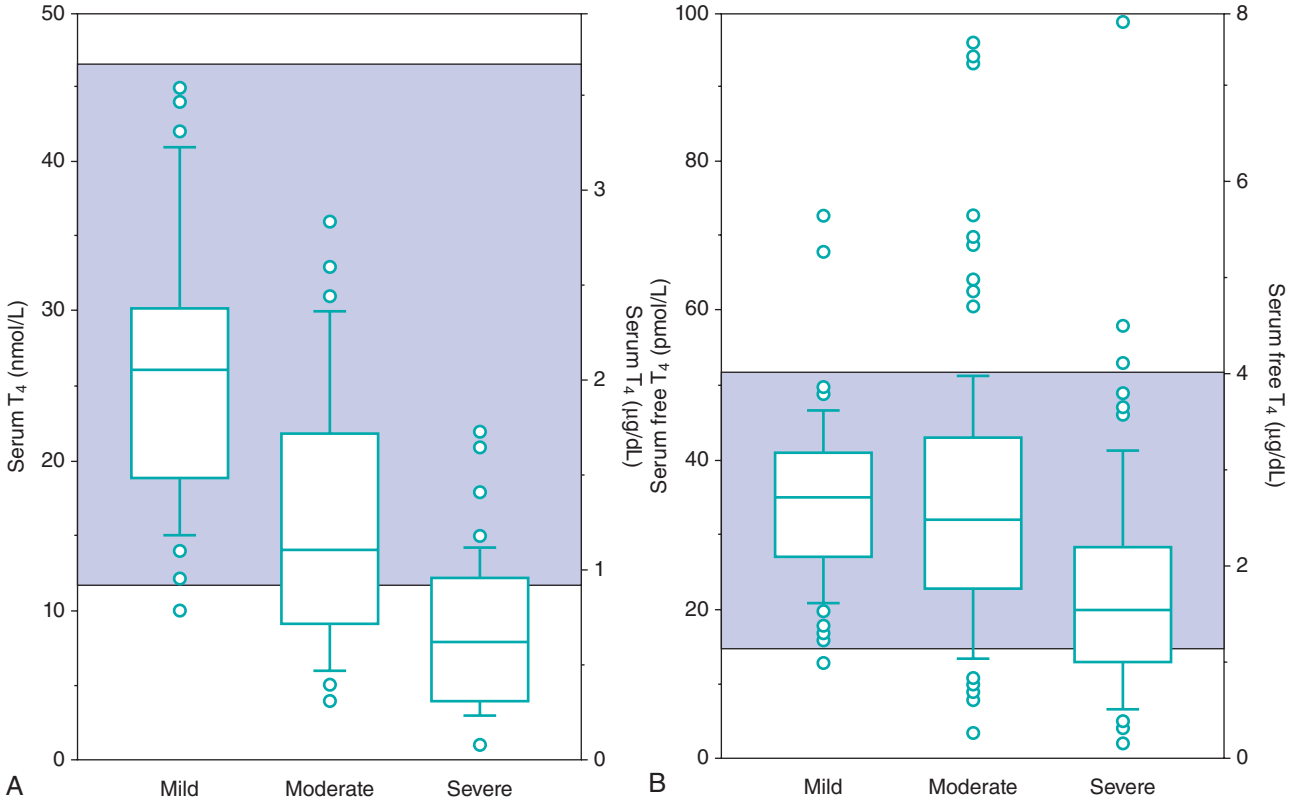


FIG 48.13
Box plots of serum total T_4 **(A)** and free T_4 **(B)** concentrations in 221 cats with nonthyroidal disease, grouped according to severity of illness. Of 221 cats with nonthyroidal illness, 65 had mild disease, 83 had moderate disease, and 73 had severe disease. See Fig. 48.9 for explanation. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218:529, 2001.)

rare and low serum T_4 concentrations in adult cats are almost always caused by nonthyroidal illness (Fig. 48.13) or some other nonthyroidal factor, the diagnosis of hypothyroidism should not be made solely on the basis of the serum T_4 concentration in an adult cat that has not been previously treated for hyperthyroidism. Documenting a low serum fT_4 and a high serum TSH concentration adds further evidence for the diagnosis of hypothyroidism. The definitive diagnosis relies on the cat's response to trial therapy with levothyroxine.

Treatment

Treatment of hypothyroidism in cats is similar to that in dogs, which is described in detail on page 783. Treatment with levothyroxine is indicated for cats with congenital and naturally acquired adult-onset hypothyroidism and for cats with iatrogenic hypothyroidism that are symptomatic for the disease following treatment for hyperthyroidism. Asymptomatic cats with a low serum T_4 concentration after receiving treatment for hyperthyroidism should not be treated until clinical signs become evident, in the hope that additional time will allow atrophied or ectopic thyroid tissue to become functional. Kidney function should be monitored because hypothyroidism may decrease GFR and unmask or exacerbate azotemia in cats (see page 790) versus bilateral thyroid lobe involvement. Synthetic levothyroxine is recommended at an initial dosage of 0.05 or 0.1 mg once daily initially. A minimum of 4 weeks should elapse before the cat's clinical response to treatment is critically assessed. Subsequent evaluations should include a history, physical examination, and measurement of serum T_4 and TSH concentrations (see the discussion of therapeutic monitoring, p. 784). The goal of therapy is to eliminate the clinical signs of hypothyroidism and prevent signs of hyperthyroidism. This can usually be accomplished by maintaining the serum T_4 concentration at between 1.0 and 3.0 µg/dL (13 and 40 nmol/L). Normalization of the serum TSH concentration supports an effective levothyroxine treatment regimen. The dose and frequency of levothyroxine administration should be adjusted accordingly to attain these goals. If the serum T_4 concentration is within the reference range after 4 to 8 weeks of treatment but there is minimal or no clinical response, the clinician should reassess the diagnosis.

Prognosis

The prognosis for adult cats with hypothyroidism receiving appropriate therapy is excellent. The prognosis for kittens with congenital hypothyroidism is guarded and depends on the severity of skeletal changes at the time treatment is initiated. Many of the clinical signs resolve and body size may increase if hypothyroidism is identified early, before abnormal bone and joint development occurs.

HYPERTHYROIDISM IN CATS

Etiology

Hyperthyroidism is a multisystemic disorder resulting from excessive production and secretion of T_4 and T_3 by the thyroid gland and is almost always a result of chronic intrinsic disease in one or both thyroid lobes. One or more usually small, discrete thyroid masses are palpable in the ventral region of the neck in most cats with hyperthyroidism. Follicular cell adenoma and multinodular adenomatous hyperplasia are the most common histologic findings. Both are benign and both may occur together within the same thyroid lobe. Less common are thyroid adenomas that cause the lobes to become markedly enlarged and distorted; thyroid carcinoma accounts for less than 5% of clinical cases.

One or both thyroid lobes can be affected in thyrotoxic cats. Approximately 30% of hyperthyroid cats have involvement of a single thyroid lobe (Fig. 48.14). The contralateral unaffected thyroid lobe is nonfunctioning and atrophied because of the suppressive effects of the hyperactive thyroid tissue on TSH secretion. Approximately 65% of hyperthyroid cats have involvement of both thyroid lobes (Fig. 48.15). Among these cats the thyroid lobes are symmetrically enlarged in 10% to 15% and asymmetrically enlarged in the remainder. Approximately 10% of enlarged thyroid lobes descend to the thoracic inlet and can be difficult to palpate. Less than 5% of thyrotoxic cats have hyperactive thyroid tissue in an ectopic location, most commonly the anterior mediastinum, with or without a palpable mass in the neck (Fig. 48.16). Functional thyroid carcinoma is the most likely diagnosis if more than two thyroid masses are present (see Fig. 48.16), although adenomatous hyperplasia of ectopic sites in addition to the thyroid lobes is possible. Some cats with thyroid carcinoma initially have only one or two thyroid masses, emphasizing the importance of histologic evaluation of surgically removed tissue.

The pathogenesis of adenomatous hyperplastic changes in the thyroid gland remains unclear. It has been postulated that immunologic, infectious, nutritional, environmental, or genetic factors may interact to cause pathologic changes. Nondietary risk factors identified by case-controlled studies include increasing age; indoor housing; use of fertilizers, herbicides, flea powders, and sprays; and use of cat litter. Epidemiologic studies have identified consumption of commercial canned cat foods as a risk factor for development of hyperthyroidism, suggesting that a goitrogenic compound may

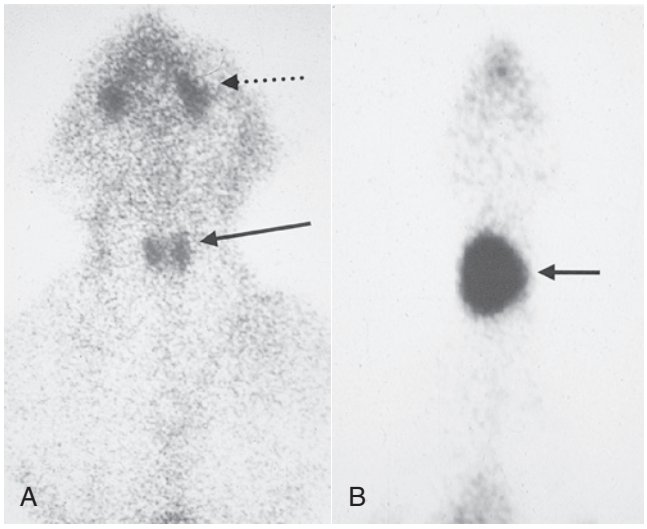


FIG 48.14
(A) Sodium pertechnetate scan of the head, neck, and proximal thorax of a healthy cat. Note that the uptake of pertechnetate (i.e., darkness) is comparable between the two thyroid lobes *(solid arrow)* and the salivary glands *(broken arrow)*. **(B)** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by unilateral disease affecting the right thyroid lobe *(arrow)*. Note the difference in uptake of pertechnetate between the hyperfunctioning thyroid lobe and the salivary glands.

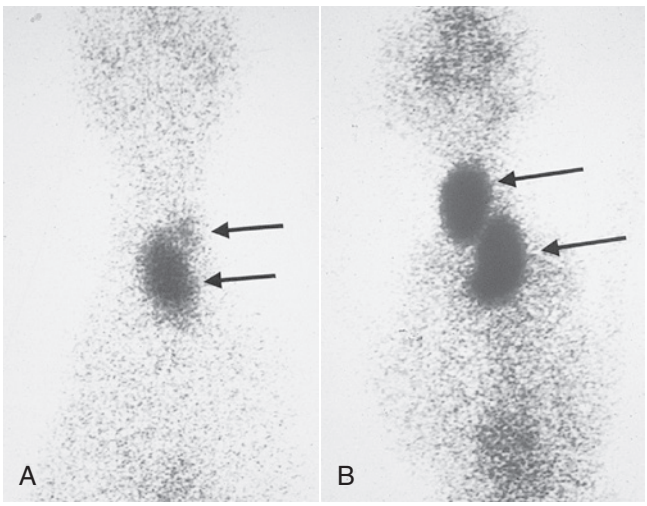


FIG 48.15
(A) Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by bilateral, asymmetric disease affecting both thyroid lobes *(arrows)*, with the right lobe more severely involved. This is the most common form of the disease. **(B)** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by bilateral, symmetric disease affecting both thyroid lobes *(arrows)*. Hypocalcemia after bilateral thyroidectomy is a major concern.

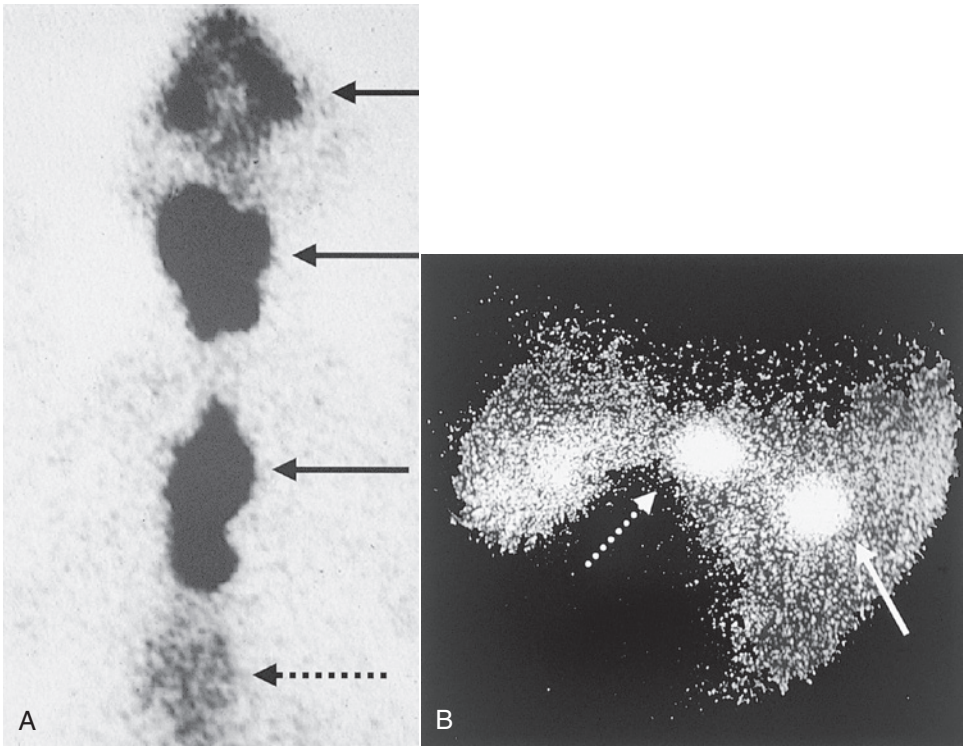


FIG 48.16
(A) Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by metastatic thyroid adenocarcinoma with multiple masses present in the head, neck, and anterior mediastinum *(solid arrows)*. Heart *(broken arrow)*. **(B)** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by two hyperfunctioning masses: one located in the neck *(broken arrow)* and one in the anterior mediastinum (i.e., ectopic site) *(solid arrow)*. ^{131}I therapy is the treatment of choice for both forms of hyperthyroidism illustrated in this figure.

be present in the diet. Excessive or deficient iodine content, isoflavones from soybeans, chemicals lining pop-top canned foods (specifically bisphenol A) that have migrated into the food during storage, and exposure to endocrine disruptors such as polybrominated diphenyl ethers (PBDEs) identified in cat food and house dust have been proposed as possible etiologic factors. Studies have identified overexpression of the *c-ras* oncogene in areas of nodular follicular hyperplasia in feline thyroid glands (Merryman et al., 1999) and altered expression of G proteins involved in TSH receptor signal transduction in hyperthyroid cats (Ward et al., 2010). The significance, if any, of these findings in the development of hyperthyroidism and the pathogenesis of adenomatous hyperplastic changes in the thyroid gland is not known.

Clinical Features

SIGNALMENT

Hyperthyroidism is the most common endocrine disease affecting cats older than 8 years. The average age at the time of initial presentation to the veterinarian is 13 years, with a range of 4 to 20 years. Less than 5% of cats with this disorder are younger than 8 years. No sex-related predisposition has been noted; domestic short-haired and long-haired cats are the most frequently affected breeds. Siamese and Himalayans are at decreased risk for development of hyperthyroidism.

CLINICAL SIGNS

Clinical signs are a result of excessive secretion of thyroid hormone by the thyroid mass. Rarely, a client will seek veterinary care because of an observed mass in the ventrocervical region of the neck. The classic clinical signs of hyperthyroidism are weight loss and muscle wasting (which may progress to cachexia), polyphagia, and restlessness or hyperactivity. Additional clinical signs include haircoat changes (patchy alopecia, matted hair, minimal or excessive grooming behavior), polyuria, polydipsia, vomiting, and diarrhea (Table 48.4). Some cats develop aggressive behavior that resolves in response to successful treatment of the hyperthyroid state. In some cats lethargy, weakness, and anorexia are the dominant clinical features, in addition to weight loss. Because of the multisystemic effects of hyperthyroidism, the variable clinical signs, and its resemblance to many other diseases of the cat, hyperthyroidism should be suspected in any aged cat with medical problems.

PHYSICAL EXAMINATION

Physical examination findings are listed in Table 48.4. A discrete thyroid mass is palpable in approximately 90% of cats with hyperthyroidism (Video 48.1). However, palpation of a cervical mass is not pathognomonic for hyperthyroidism. Some cats with palpable thyroid lobes are clinically normal, and some palpable cervical masses are not thyroid in origin. It is frequently difficult to accurately assess unilateral on the basis of palpation. Two distinct masses cannot always be appreciated on palpation, even if both lobes are large. Large thyroid masses may gravitate to the region of the thoracic inlet, and this can interfere with their palpation. The thyroid mass may even descend into the anterior mediastinum. This should be suspected when a thyroid mass is not palpable in a hyperthyroid cat, although a small, nonpalpable mass is also possible.

TABLE 48.4

Clinical Signs and Physical Examination Findings in Cats With Hyperthyroidism

CLINICAL SIGNS	PHYSICAL EXAMINATION FINDINGS
Weight loss*	Palpable thyroid*
Polyphagia*	Thin cat*
Unkempt haircoat, patchy alopecia*	Hyperactive cat, difficult to examine*
Polyuria-polydipsia*	Tachycardia*
Vomiting*	Hair loss, unkempt haircoat*
Nervous, restless, hyperactive*	Small kidneys
Diarrhea, bulky stools	Heart murmur
Decreased appetite	Easily stressed cat
Tremor	Cachectic appearance, muscle wasting
Weakness	Premature beats
Dyspnea, panting	Gallop rhythm
Decreased activity, lethargy	Aggressive cat
Anorexia	Lethargic, weak cat Ventral flexion of the neck

*Common.

Clinical Pathology

Results of a CBC are usually normal. The most common abnormalities are a mild increase in PCV and mean corpuscular volume. Neutrophilia, lymphopenia, eosinopenia, or monocytopenia is identified in less than 20% of hyperthyroid cats. Common serum biochemical abnormalities include an increase in serum activities of alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase; this increase is typically in the mild to moderate range (i.e., 100-400 IU/L). One or more of these liver enzymes are increased in approximately 90% of hyperthyroid cats. Additional evaluation of the liver should be considered if liver enzyme activities are greater than 500 IU/L. Hyperthyroid-induced increases in liver enzymes resolve following treatment of hyperthyroidism. Increased serum urea nitrogen and creatinine concentrations are identified in approximately 25%, and hyperphosphatemia in 20%, of hyperthyroid cats at our clinic—findings that have important implications regarding treatment (see the discussion on chronic kidney disease [CKD], p. 790). Urine specific gravity ranges from 1.008 to greater than 1.050. Most hyperthyroid cats have urine specific gravities greater than 1.035. Mild proteinuria is also common and is a risk factor for the development and progression of CKD. The severity of proteinuria, as determined by UPC, tends to decrease once a euthyroid state is attained. The remainder of the urinalysis is usually unremarkable unless concurrent diabetes mellitus or urinary tract infection exists.

COMMON CONCURRENT PROBLEMS

Thyrotoxic Cardiomyopathy

Hypertrophic and, less commonly, dilative thyrotoxic cardiomyopathy may develop in cats with hyperthyroidism. Cardiovascular abnormalities detectable during physical examination include tachycardia; a pounding heartbeat noted on palpation of the ventral thorax; and, less frequently, pulse deficits, gallop rhythms, cardiac murmur, and muffled heart sounds resulting from a pleural effusion. Electrocardiographic abnormalities include tachycardia; increased R-wave amplitude in lead II; and, less commonly, a right bundle branch block, a left anterior fascicular block, widened QRS complexes, and atrial and ventricular arrhythmias. Thoracic radiographs may reveal cardiomegaly, pulmonary edema, or a pleural effusion. Echocardiographic abnormalities identified in cats with hypertrophic thyrotoxic cardiomyopathy include left ventricular hypertrophy, thickening of the interventricular septum, left atrial and ventricular dilation, and myocardial hypercontractility. Those seen in cats with dilative thyrotoxic cardiomyopathy include subnormal myocardial contractility and marked ventricular dilation. Either form of cardiomyopathy may result in the development of congestive heart failure. Hypertrophic thyrotoxic cardiomyopathy is usually reversible once the hyperthyroid state is corrected, whereas dilative thyrotoxic cardiomyopathy is not.

Chronic Kidney Disease and Iatrogenic Hpothyroidism

Hyperthyroidism and CKD are common in older cats and often occur concurrently. Identification of small kidneys on physical examination, increased serum urea nitrogen and creatinine concentrations, and urine specific gravity between 1.008 and 1.020 should raise suspicion for concurrent CKD in a cat with hyperthyroidism. Unfortunately, hyperthyroidism increases GFR, renal blood flow, and renal tubular resorptive and secretory capabilities in normal and compromised kidneys. Renal perfusion and GFR may acutely decrease, and azotemia or clinical signs of CKD become apparent or significantly worsen after treatment of the hyperthyroid state. It is not easy to determine what impact the hyperthyroid state is having on kidney function in cats. The clinical and biochemical manifestations of CKD may be masked in cats with both thyroid and kidney disease in which renal perfusion is enhanced by the circulatory dynamics produced by hyperthyroidism. Biochemical parameters, blood pressure, urine specific gravity, and proteinuria are poor predictors of the onset of azotemia following treatment of hyperthyroidism. For these reasons cats with hyperthyroidism should initially be given reversible therapy (i.e., oral antithyroid drugs or limited iodine diet) until the impact of establishing euthyroidism on kidney function can be determined. Maximum reduction in GFR is usually attained

within 1 month of establishing euthyroidism. Fortunately, most hyperthyroid cats will stay within or increase only one IRIS (International Renal Interest Society) stage in the classification of CKD.

It is important to maintain serum T_4 concentration in the lower half of the reference range when assessing kidney status during methimazole treatment. Iatrogenic hypothyroidism is associated with an increased incidence of azotemia in hyperthyroid cats as a result of hypothyroid–induced decrease in GFR. Restoration of serum T_4 concentration into the reference range may improve GFR, decrease serum creatinine concentration, and provide a more accurate assessment of kidney function.

Urinary Tract Infection

Urinary tract infection is relatively common in untreated hyperthyroid cats, with a reported prevalence of 12% to 22%. The most common bacterial isolate is *Escherichia coli*. Urine culture is indicated in hyperthyroid cats with lower urinary tract signs or the presence of bacteriuria, pyuria, or both on urinalysis. Unfortunately, most hyperthyroid cats are asymptomatic for urinary tract infection, suggesting that urine culture should be a routine part of the complete diagnostic evaluation of cats with newly diagnosed hyperthyroidism.

Systemic Hypertension

Systemic hypertension is common in cats with hyperthyroidism and results from the effects of increased β-adrenergic activity on heart rate, myocardial contractility, systemic vasodilation, and activation of the renin-angiotensin-aldosterone system. Hypertension caused by hyperthyroidism is usually clinically silent. Retinal hemorrhage and retinal detachment are the most common clinical complications of systemic hypertension in hyperthyroid cats, but in general, ocular lesions are not commonly identified. Resolution of systemic hypertension following treatment of the hyperthyroid state is unpredictable and dependent, in part, on the underlying cause of the hypertension. Hyperthyroid-induced hypertension will resolve in most cats following treatment. As a general rule, we initiate amlodipine treatment if the systolic blood pressure is consistently greater than 180 mm Hg or if ocular lesions are identified. Otherwise we prefer to reevaluate blood pressure once the hyperthyroidism is treated and initiate amlodipine if hypertension persists despite correction of the hyperthyroid state (see Chapter 11).

Gastrointestinal Tract Disorders

Gastrointestinal tract signs are common in cats with hyperthyroidism and include polyphagia, weight loss, anorexia, vomiting, diarrhea, increased frequency of defecation, and increased volume of feces. Intestinal hypermotility and malassimilation have been documented in some cats with hyperthyroidism and are responsible for producing some of the gastrointestinal tract signs. Inflammatory bowel disease is a common concurrent gastrointestinal tract disorder that should be considered in any hyperthyroid cat that shows persistence of gastrointestinal signs after correction of the hyperthyroid state (see Chapter 31). Intestinal neoplasia, most notably lymphoma, is perhaps the most important differential diagnosis in cats seen because of polyphagia and weight loss. The abdomen should be carefully palpated in a search for thickening of the intestinal tract and mesenteric lymphadenopathy—findings that may be the only clues for intestinal lymphoma. Abdominal ultrasonography may also provide clues to the possibility of lymphoma.

Diagnosis

The diagnosis of hyperthyroidism is based on identification of appropriate clinical signs, palpation of a thyroid mass, and documentation of an increased serum T_4 concentration.

Baseline Serum T_4 Concentration

Measurement of random baseline serum T_4 concentrations has been extremely reliable in differentiating hyperthyroid cats from those without thyroid disease (Fig. 48.17). The typical reference range for serum T_4 is approximately 1.0 to 4.0 µg/dL (50-65 mmol/L), although reference ranges for individual laboratories vary. A serum T_4 concentration above the reference range strongly supports the diagnosis of hyperthyroidism, especially if appropriate clinical signs are present, and a low serum T_4 concentration rules out hyperthyroidism (Table 48.5). Serum T_4 concentrations that fall within the upper half of the reference range create a diagnostic dilemma, especially if clinical signs are suggestive of hyperthyroidism and a mass is palpable in the ventral region of the neck. This combination of findings is referred to as *occult hyperthyroidism* and is most commonly identified in cats in the early stages of hyperthyroidism. Serum T_4 concentrations are more likely to be influenced by nonthyroidal factors such as concurrent illness and are more likely to randomly fluctuate into the reference range in cats with mild hyperthyroidism, compared with cats with more advanced disease (Fig. 48.18; see also Fig. 48.13). The diagnosis of hyperthyroidism should not be excluded on the basis of one "normal" serum T_4 test result, especially in a cat with appropriate, albeit often mild, clinical signs and a palpable mass in the neck. Additional diagnostic tests for consideration

TABLE 48.5

Interpretation of Baseline Serum Thyroxine (T_4) Concentration in Cats With Suspected Hyperthyroidism

SERUM T_4 CONCENTRATION[+]	PROBABILITY OF HYPERTHYROIDISM
>4.0 µg/dL	Likely
3.0-4.0 µg/dL	Possible
2.0-3.0 µg/dL	Unlikely*
<2.0 µg/dL	Very unlikely*

[+]Reference range: 1.0-4.0 µg/dL
*If a severe systemic illness is not present.

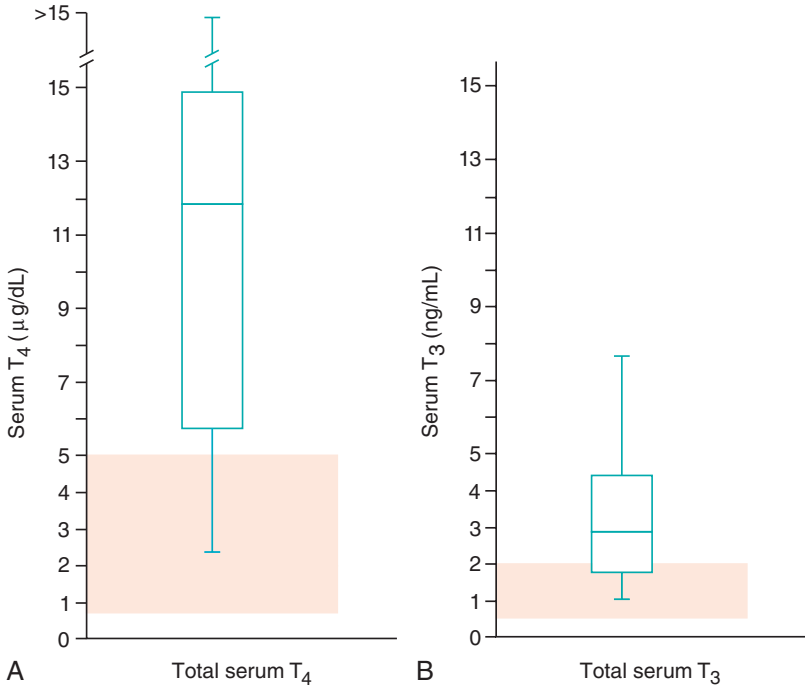


FIG 48.17
Mean and range of random total serum T_4 **(A)** and total serum T_3 **(B)** concentrations in hyperthyroid cats. Seventy-five percent of hyperthyroid cats have values within the box, and the balance is within the limitation bars above and below the box. Note that virtually all hyperthyroid cats have abnormal or borderline serum T_4 concentrations, whereas serum T_3 concentrations are less sensitive. The pink region represents the normal reference range.

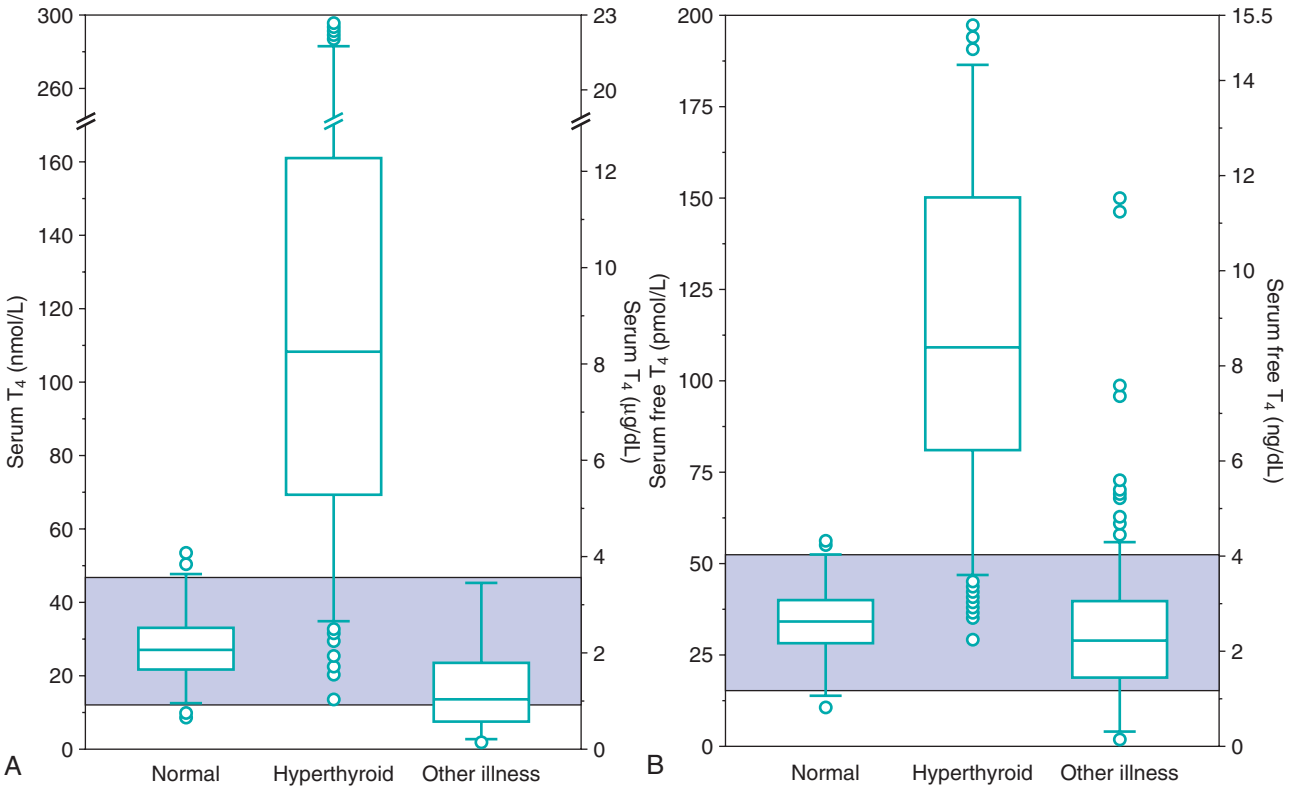


FIG 48.18
Box plots of serum total T_4 **(A)** and free T_4 **(B)** concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. See Fig. 48.9 for explanation. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218:529, 2001.)

in a cat with a nondiagnostic serum T_4 test result include measurement of serum free T_4 (fT_4) and TSH concentrations, the T_3 suppression test, sodium pertechnetate thyroid scan, or repetition of the serum T_4 test 4 to 8 weeks later. It is important to remember that the thyroid mass may be nonfunctional, and the clinical signs may be the result of another disease.

Serum Free T_4 Concentration

Measurement of serum fT_4 using one of the methods discussed under Canine Hypothyroidism (see p. 776) is the current recommendation of choice to try to confirm hyperthyroidism in a cat with nondiagnostic serum T_4 test results. Measurement of serum fT_4 is considered a more reliable means of assessing thyroid gland function than measurement of serum T_4 concentration, in part because nonthyroidal illness has less of a suppressive effect on serum fT_4 than on T_4 (see Fig. 48.13), and serum fT_4 is increased in many cats with occult hyperthyroidism and "normal" T_4 test results. Because of cost, measurement of serum fT_4 is often reserved for cats with suspected hyperthyroidism in which T_4 values are nondiagnostic. Concurrent illness may increase the serum fT_4 concentration in cats—an increase that can exceed the reference range (see Fig. 48.18). For this reason, serum fT_4 concentration should always be interpreted in conjunction with a T_4 concentration measured from the same blood sample. An increased serum fT_4 concentration in conjunction with a serum T_4 concentration in the upper half of the reference range or higher is supportive of hyperthyroidism if the clinical presentation is consistent with the disease. An increased serum fT_4 concentration in conjunction with a serum T_4 concentration in the lower half of the reference range or lower is suggestive of nonthyroidal illness in a euthyroid cat rather than hyperthyroidism.

Serum TSH Concentration

Although a commercial feline-specific TSH assay is not currently available, a canine TSH assay (Immulite Canine TSH, DPC) has been validated for use in cats (Wakeling et al., 2008). Although sensitivity of the assay is suboptimal, in my experience measurement of baseline serum TSH concentration has provided additional information when thyroid gland function is assessed in cats with suspected early-onset or occult hyperthyroidism. The reference interval in senior cats (>8 years) is < 0.03 to 0.15 ng/mL (Wakeling et al., 2007). Reference ranges will vary depending on the laboratory and the assay used to measure TSH. Serum TSH should not be detectable (i.e., <0.03 ng/mL) in cats with hyperthyroidism. In theory, the finding of a measurable serum TSH concentration is inconsistent with hyperthyroidism and would be a negative indicator for occult hyperthyroidism. In a recent study, serum TSH concentrations were suppressed (i.e., nondetectable) in 98% of 917 hyperthyroid cats, but concentrations were measurable in a few cats with mild to moderate hyperthyroidism (Peterson et al., 2015). In comparison, 70% of 163 euthyroid cats had detectable TSH concentrations. Measurement of serum TSH concentration cannot, by itself, be used to diagnose hyperthyroidism because the reference range extends to nondetectable; a nondetectable TSH result occurs in hyperthyroid and euthyroid cats. Serum TSH concentrations should always be measured in combination with serum T_4 or fT_4.

T_3 Suppression Test

The T_3 suppression test is used to distinguish euthyroid from mildly hyperthyroid cats in cases in which T_4 and fT_4 test results are nebulous and serum TSH is not detectable. The T_3 suppression test is based on the theory that oral administration of liothyronine (T_3) will suppress pituitary TSH secretion in euthyroid cats, resulting in a decrease in circulating T_4 (Fig. 48.19). In contrast, pituitary TSH secretion is already suppressed in cats with hyperthyroidism, oral administration of T_3 will not cause further suppression, and serum T_4 will not decrease following T_3 administration. In this test, 25 µg of T_3 (e.g., Cytomel, King Pharmaceuticals) is administered orally three times per day for seven treatments, and serum T_4 and T_3 concentrations are determined before the first T_3 and 8 hours after the last T_3 administration. Normal cats consistently have postdosing serum T_4 concentrations less than 1.5 µg/dL (20 nmol/L), whereas hyperthyroid cats have postdosing T_4 concentrations greater than 2.0 µg/dL (26 nmol/L). Values of 1.5 to 2.0 µg/dL are nondiagnostic. The percentage decrease in serum T_4 concentration is not as reliable a gauge as the absolute value,

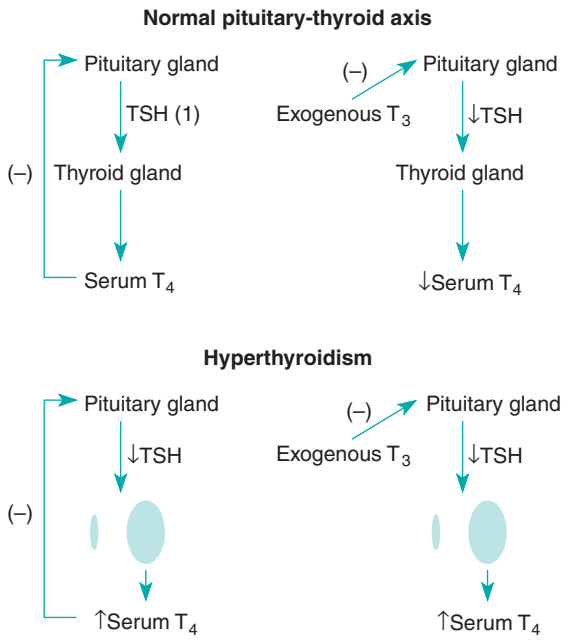


FIG 48.19
Effect of T_3 supplementation on the pituitary-thyroid axis in healthy cats and cats with hyperthyroidism. Suppression of pituitary TSH secretion by the T_3 supplement decreases serum T_4 concentration in healthy cats. In hyperthyroid cats the serum TSH concentration is already suppressed; the T_3 supplementation has no effect. The serum T_4 concentration remains increased.

although suppression of more than 50% below the baseline value occurs in normal but not hyperthyroid cats. Serum T_3 concentrations are used to determine whether the client has successfully administered the thyroid medication to the cat. Serum T_3 concentration measured in the postpill blood sample should be increased compared with results obtained before the test is initiated in all cats properly tested, regardless of the status of thyroid gland function.

Thyroid Scintigraphy

Thyroid scintigraphy identifies functional thyroid tissue and is used as a diagnostic test in cats with suspected occult hyperthyroidism; to identify ectopic thyroid tissue in cats with appropriate signs of hyperthyroidism and increased serum T_4 concentrations but no palpable thyroid nodule in the neck; to identify sites of metastasis in cats with thyroid carcinoma; and to provide guidance for developing the best treatment plan, especially if thyroidectomy is being considered. Radioactive technetium-99m (pertechnetate) is used for routine imaging of the thyroid gland in cats. It has a short physical half-life (6 hours), is concentrated within functioning thyroid follicular cells, and reflects the trapping mechanism of the gland. Because antithyroid drugs do not affect the trapping mechanism of the thyroid pump, thyroid scintigraphy can be done in cats being treated with antithyroid drugs. Salivary glands and the gastric mucosa also concentrate pertechnetate; it is excreted by the kidneys.

Scanning of the thyroid provides a picture of all functioning thyroid tissue and permits the delineation and localization of functioning as opposed to nonfunctioning areas of the thyroid but does not differentiate between adenomatous hyperplasia, adenoma, and carcinoma. Fig. 48.14 shows the similarity between the size and shape of the thyroid lobes and the similarity of radionuclide uptake by the thyroid and salivary glands in a normal cat. This 1:1 ratio of salivary gland to thyroid lobe uptake is the standard by which the status of the thyroid should be judged. Findings in most hyperthyroid cats are markedly abnormal and usually easy to interpret (see Figs. 48.14 to 48.16).

Cervical Ultrasound

Ultrasonographic evaluation of the thyroid gland can be used to confirm the origin of the palpable cervical mass, differentiate unilateral versus bilateral thyroid lobe involvement, assess the size of the thyroid mass(es), and provide guidance for developing the best treatment plan (Fig. 48.20). Ultrasound does not provide information on the functional status of the thyroid mass and should not be used in establishing the diagnosis of hyperthyroidism. Rather, cervical ultrasound should be used as an adjunctive tool for locating cervical thyroid tissue.

Treatment

Hyperthyroidism in cats can be managed by oral antithyroid medications, thyroidectomy, radioactive iodine, or an iodine-restricted diet (Table 48.6). All four modes of therapy are effective. Surgery and radioactive iodine treatments are used in the hope of providing a permanent cure for the disease; oral antithyroid drugs and an iodine-restricted diet only control the hyperthyroidism and must be given daily to achieve and maintain their effects.

Initial Treatment Recommendation

Hyperthyroid cats should be treated initially with an oral antithyroid drug (i.e., methimazole, carbimazole) to reverse hyperthyroid-induced metabolic and cardiac derangements, decrease the anesthetic risk associated with thyroidectomy, and assess the impact of treatment on kidney function. Feeding an iodine-restricted diet (Prescription Diet y/d, Hill's Pet Products) should be considered in situations where owners are unable to administer methimazole to their cat. Hyperthyroidism may mask CKD in some cats (see p. 790); azotemia may develop or worsen and clinical signs of CKD may develop after treatment of the hyperthyroid state. Because it is not easy to determine what impact the hyperthyroid state is having on kidney function, it is preferable to treat cats with reversible therapy (i.e., methimazole) until the impact of hyperthyroidism on kidney function can be determined. If the serum creatinine concentration remains static or improves after resolution of hyperthyroidism with methimazole, a more permanent treatment can be recommended. Idiopathic hypothyroidism can decrease GFR or increase serum creatinine concentration, and must be avoided during methimazole treatment. If the serum creatinine concentration increases significantly (i.e., to IRIS stage 3 or higher) during methimazole therapy, the treatment protocol for methimazole should be modified to attain the best possible control of both disorders, and treatment for CKD should be instituted.

Oral Antithyroid Drugs

Oral antithyroid drugs include methimazole, propylthiouracil, and carbimazole. Oral antithyroid drugs are inexpensive, readily available, relatively safe, and effective in the treatment of hyperthyroidism in cats. They inhibit the synthesis of thyroid hormone by blocking the incorporation of iodine into the tyrosyl groups in thyroglobulin and by preventing the coupling of these iodotyrosyl groups to form T_3 and T_4. Antithyroid drugs do not block the release of stored thyroid hormone into the circulation and do not have antitumor actions. In our experience, oral antithyroid drugs do not interfere with results of pertechnetate scans or radioactive iodine therapy; however, many treatment centers request that methimazole be withdrawn 1 to 2 weeks before pertechnetate scan or radioactive iodine treatment. Indications for oral antithyroid drugs include (1) test treatment to normalize serum T_4 concentrations and assess the effect of resolving hyperthyroidism on kidney function; (2) initial treatment to alleviate or eliminate any medical problems associated with the syndrome before thyroidectomy is performed or before the hospitalization required for radioactive iodine treatment; and (3) long-term treatment of hyperthyroidism.

Methimazole (Felimazole, Dechra Veterinary Products) is currently the antithyroid drug of choice because the

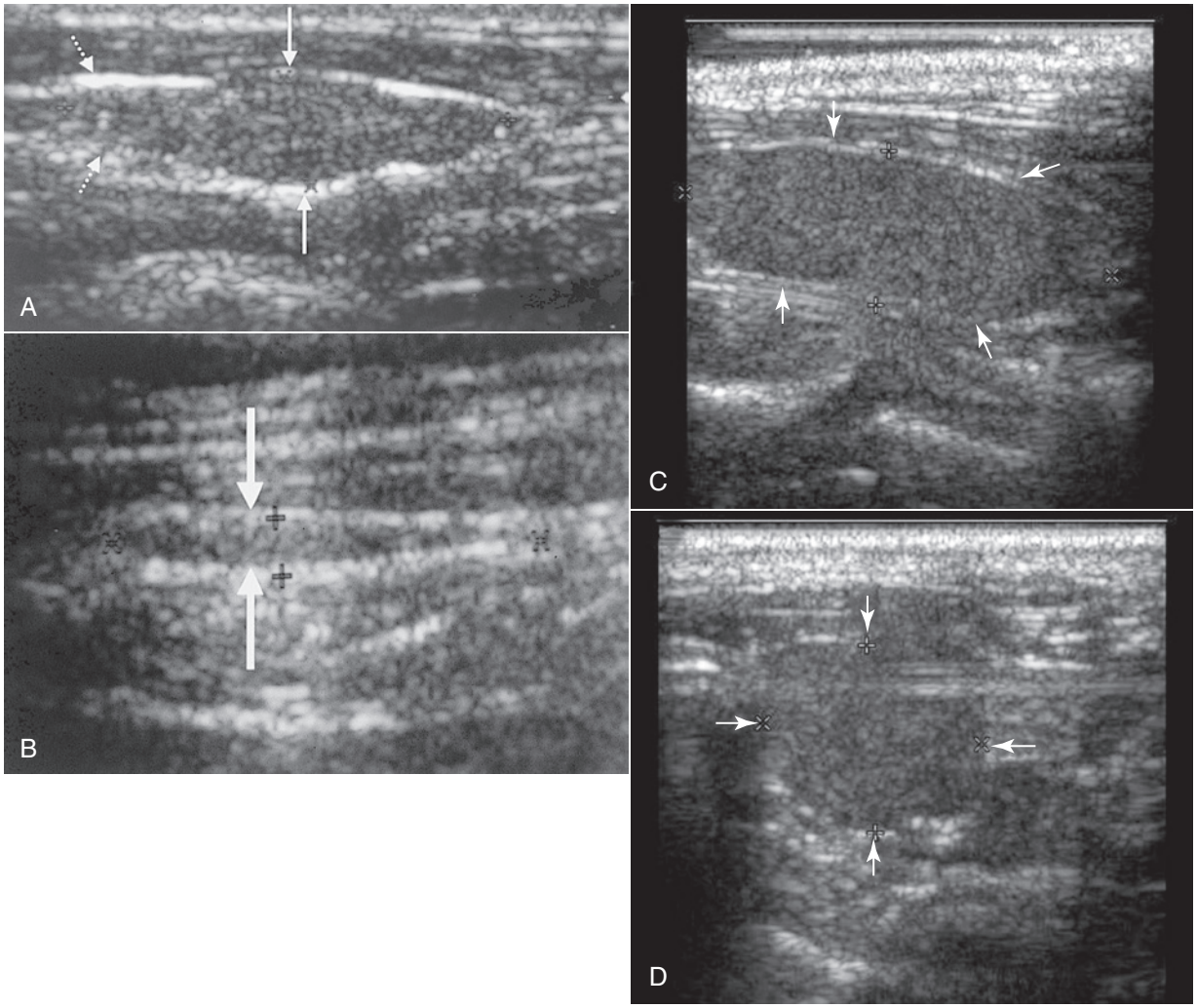


FIG 48.20
(A) Ultrasound image of the right thyroid lobe of a 13-year-old domestic short-haired cat with hyperthyroidism. A mass is seen in the midregion of the thyroid lobe *(solid arrows)*. Normal-appearing portion of thyroid lobe *(broken arrows)*. **(B)** Ultrasound image of the small (atrophied) normal left thyroid lobe *(solid arrows)*. Left thyroid lobe *(small arrows)*. Results of the ultrasound examination supported unilateral disease affecting the right thyroid lobe, which was confirmed with a sodium pertechnetate scan. Longitudinal **(C)** and transverse **(D)** ultrasound images of a markedly enlarged left thyroid lobe (measuring approximately 1.1 × 2.2 cm) in a 14-year-old domestic short-haired cat with hyperthyroidism. The right thyroid lobe was similar in size. Results of the ultrasound examination support bilateral disease with symmetric enlargement of both thyroid lobes, which was confirmed with a sodium pertechnetate scan.

incidence of adverse reactions associated with its use is lower than that associated with the use of propylthiouracil (Table 48.7). Adverse reactions are less likely to occur when the dosage of methimazole is started low and gradually increased to effect. The recommended initial dose of methimazole is 2.5 mg administered orally twice a day for 2 weeks. If adverse reactions are not observed by the client, if the physical examination reveals no new problems, if results of a CBC and platelet count are within reference limits, if the serum creatinine concentration has not increased, and if serum T_4 concentration is in the upper half of the reference range or higher after 2 weeks of therapy, the dose is increased by 2.5 mg per day (i.e., 5 mg in the morning and 2.5 mg in the evening) twice daily, and the same parameters are evaluated 2 weeks later. The dosage should continue to be increased every 2 weeks by 2.5-mg/day increments until the serum T_4 concentration is in the lower half of the reference range without creating hypothyroidism or until adverse reactions develop. Timing of blood sampling after oral methimazole administration does not appear to be a significant factor in assessing response to methimazole treatment. Serum T_4 concentrations decline into the reference range within 2 weeks once the cat is receiving an effective dose of methimazole; clinical improvement is usually noted by clients within 2 to

TABLE 48.6

Indications, Contraindications, and Disadvantages of the Four Modes of Therapy for Hyperthyroidism in Cats

THERAPY	INDICATIONS	RELATIVE CONTRAINDICATIONS	DISADVANTAGES
Methimazole, propylthiouracil, carbimazole	Long-term therapy for all forms of hyperthyroidism; initial therapy to stabilize cat's condition and assess kidney function before thyroidectomy or radioactive iodine	None	Daily therapy required; no effect on growth of thyroid; mild adverse reactions common; severe reactions possible
Iodine-restricted diet	Therapy for all forms of hyperthyroidism; initial therapy to stabilize cat's condition and assess kidney function before thyroidectomy or radioactive iodine; reversible treatment option for cats that develop adverse reactions to methimazole or for clients unable to administer methimazole to their cat	Concurrent administration of antithyroid medications not recommended by manufacturer of the diet	Rigid requirements to ensure absolutely no access to any other source of dietary iodine; cat must be kept strictly indoors; problematic in multicat households; long term consequences of iodine restriction are unknown
Thyroidectomy	Unilateral lobe involvement; bilateral lobe involvement, asymmetric sizes	Ectopic thyroid lobe; metastatic carcinoma; bilateral, symmetric, large lobes (high risk of hypocalcemia); severe systemic signs; cardiac arrhythmias or failure; renal insufficiency	Anesthetic risks; relapse of disease; postoperative complications, especially hypocalcemia
Radioactive iodine (^{131}I)	Therapy for all forms of hyperthyroidism; treatment of choice for ectopic thyroid lobe and thyroid carcinoma	Renal insufficiency	Limited availability; hospitalization time; potential for retreatment; hazardous to humans

TABLE 48.7

Abnormalities Associated With Methimazole Therapy in 262 Cats With Hyperthyroidism

CLINICAL SIGNS AND PATHOLOGY	PERCENTAGE OF CATS	TIME TO DEVELOP (DAYS)	
		MEAN	RANGE
Clinical Signs			
Anorexia	11	24	1-78
Vomiting	11	22	7-60
Lethargy	9	24	1-60
Excoriations	2	21	6-40
Bleeding	2	31	15-50
Clinical Pathology			
Positive antinuclear antibody titer	22	91	10-870
Eosinophilia	11	57	12-490
Lymphocytosis	7	25	14-90
Leukopenia	5	23	10-41
Thrombocytopenia	3	37	14-90
Agranulocytosis	2	62	26-95
Hepatopathy	2	39	15-60

Adapted from Peterson ME, Kintzer PP, Hurvitz AI: Methimazole treatment of 262 cats with hyperthyroidism, *J Vet Intern Med* 2:150, 1988.

4 weeks once control of serum T_4 concentration is achieved. Most cats respond to 5 to 7.5 mg of methimazole per day, and the drug is most effective when given twice a day. Attempts at decreasing the daily dosage, the frequency of administration, or both can take place once clinical signs have resolved and a euthyroid state is attained, especially for cats receiving long-term methimazole treatment.

Rarely, cats are encountered that seem particularly resistant to methimazole, requiring as much as 20 mg/day. The most common causes for apparent resistance to methimazole are the inability of some clients to administer the drug to their cats and the presence of thyroid carcinoma as the etiology. One alternative for inability to administer methimazole is to have a compounding pharmacy incorporate methimazole into tasty kitty treats. Another alternative is the topical application of methimazole to the nonhaired pinna of the ear. Compounding veterinary pharmacies offer transdermal methimazole in a pluronic lecithin organogel (PLO) formulation. PLO is a permeation enhancer that disrupts the stratum corneum and allows absorption into the skin. There is a slightly slower onset of control of the hyperthyroidism and slightly lower efficacy, compared with oral methimazole, and some cats develop erythema and inflammation of the pinna, necessitating switching to oral methimazole. Creams can be made with methimazole at any concentration and are usually provided in tuberculin syringes that allow the client to place the appropriate dose on the fingertip and rub the cream into the pinna of the inner ear. The client must wear gloves to avoid absorption of methimazole, should alternate ears, and should wipe away any residual cream 30 to 60 minutes after each administration. The dosage and frequency of administration are the same as discussed with oral methimazole treatment. The bioavailability of transdermal methimazole is more variable, the overall effectiveness is not as good, and the prevalence of gastrointestinal adverse effects but not other adverse effects is lower, compared with oral methimazole. Higher doses may be required after prolonged treatment. One important concern in using transdermal methimazole is the lack of regulation of compounding pharmacies; consistency between products created can vary considerably.

Adverse reactions to methimazole typically occur within the first 4 to 8 weeks of therapy (see Table 48.7). The cat should be examined every 2 weeks during the initial 3 months of methimazole treatment and a CBC, platelet count, assessment of kidney function, and serum T_4 concentration evaluated at each visit. After the initial 3 months of therapy, CBC, platelet count, serum biochemistry panel, and serum T_4 concentration should be evaluated every 3 to 6 months. When the dosing protocol described previously is used, lethargy, vomiting, and anorexia occur in less than 10% of cats; these mild adverse reactions are usually transient and often resolve despite continued administration of the drug. Mild methimazole-induced hematologic changes are seen in less than 10% of cats and include eosinophilia, lymphocytosis, and transient leukopenia. More worrisome but less common (less than 5% of cats) alterations include facial excoriations, thrombocytopenia (platelet counts < 75,000/mm^3), leukopenia (total white blood cell counts < 2000/mm^3), and immune-mediated hemolytic anemia. Apparent hepatic toxicity or injury occurs in less than 2% of cats receiving methimazole and is characterized by clinical signs of liver disease (i.e., lethargy, anorexia, vomiting), icterus, and increased serum alanine transaminase and alkaline phosphatase activities. Some cats test positive for antinuclear antibodies, but the importance of this finding is not known. Development of myasthenia gravis has also been reported with methimazole treatment. If any of these serious complications are noted, methimazole treatment should be discontinued and supportive care given. Adverse reactions typically resolve within 1 week after methimazole treatment is discontinued. It is common for these potentially life-threatening adverse reactions to recur, regardless of the dose or type of antithyroid drug used; thus alternative therapy (e.g., surgery, radioactive iodine, iodine-restricted diet) is recommended.

Carbimazole (Neo-Mercazole) is an antithyroid drug that is converted to methimazole in vivo; it is an effective alternative treatment if methimazole is not available. The dosage and frequency of administration are the same as those in oral methimazole treatment. Adverse reactions are similar to those seen in cats receiving methimazole, but they occur less frequently. Cats treated with carbimazole should be monitored in the same manner suggested for cats receiving methimazole.

Long-term, twice-daily schedules for methimazole are effective in controlling hyperthyroidism. However, feline hyperthyroidism is a progressive disease which cannot be arrested with methimazole or an iodine restricted diet. Only radioactive iodine or thyroidectomy remove or destroy the hyperfunctioning tissue. In a recent study evaluating cats treated with methimazole for 1 to 6 years, the prevalence of multifocal disease (3 or more masses), large and huge masses, intrathoracic thyroid tissue, and suspected thyroid carcinoma increased with increasing disease duration (Peterson et al., 2016). Median thyroid mass volume and serum T_4 concentrations also increased with increasing disease duration; a finding which supports periodic evaluation of serum T_4 concentrations in cats on long-term methimazole treatment.

Iodine-Restricted Diet

A commercially available iodine restricted diet (Prescription Diet, y/d, Hill's Pet Products) provides another option for the treatment of hyperthyroidism in cats. Feeding an iodine-restricted diet limits production of thyroid hormone by the thyroid gland, thereby decreasing serum T_4 concentrations. Clinical trials have documented a reduction in serum T_4 concentrations when hyperthyroid cats are fed only Prescription Diet y/d and do not have access to any other source of dietary iodine. Serum T_4 concentrations returned to the reference range within 4 to 8 to weeks of initiation of the diet and remained there for longer than a year of feeding the diet. It is critical that the hyperthyroid cat does not have access to any other source of iodine. Iodine is present in a wide array

of foods, supplements, and even some water sources. Examples include all other pet foods, dairy products, egg yolks, seafood, dried fruit, canned vegetables, cured meats, fresh chicken or turkey, soy products, seaweed products, flavored or artificially colored medications or supplements, and liquids used by some compounding pharmacies. Cats must be kept strictly indoors. Healthy cats in the household can be fed Prescription Diet y/d but must have an additional source of food as an iodine supplement. Concurrent administration of antithyroid medications is not recommended, and these medications should be tapered and stopped over a 1- to 2-week period before the iodine-restricted diet is initiated. Initial recheck of serum T_4 concentration is recommended 4 and 8 weeks after Prescription Diet y/d is initiated. Serum T_4 concentration should be within the reference range by 8 weeks. The most common reason for failure of the diet to control hyperthyroidism is access of the cat to iodine-containing food, water, treats, or medications. The long-term consequences of dietary iodine restriction are unknown. For now, long-term monitoring should include a complete physical examination and evaluation of CBC, serum biochemistry panel, urinalysis, and serum T_4 concentration every 4 to 6 months once the serum T_4 concentration is in the reference range.

Surgery

Thyroidectomy is an effective treatment but should always be considered an elective procedure. Surgery is not indicated if the risk of anesthesia in the cat is unacceptable, its kidney function is questionable, the likelihood of postoperative hypocalcemia is great, ectopic thyroid tissue is present in the thorax, or thyroid carcinoma with metastasis is suspected. Treatment with methimazole for 1 to 2 months before thyroidectomy is recommended for reasons previously discussed. If possible, an ultrasound examination of the ventral neck or thyroid scintigraphy should be performed before surgery to identify the location of the abnormal thyroid tissue, differentiate unilateral from bilateral lobe involvement, and gain some insight into the probability of hypocalcemia developing postoperatively (see Fig. 48.15). Similar information can be gained by direct visualization at the time of surgery although ectopic tissue and early stages of the disease with minimal gross changes of the thyroid lobe may be missed.

Postoperative complications are listed in Box 48.8. The most worrisome is hypocalcemia. A direct correlation has been noted between the size of the thyroid lobes, the inability to visualize the external parathyroid glands, and the risk of hypocalcemia. Care must be taken to preserve at least one (preferably two) parathyroid glands. If all four parathyroid glands are inadvertently removed, the two external parathyroid glands should be removed from their respective thyroid lobes, minced, and placed within the muscle belly of one of the sternohyoideus muscles by blunt dissection parallel to the muscle fibers. Hypoparathyroidism usually resolves within a month of surgery if revascularization of the parathyroid autotransplant occurs.

BOX 48.8

Complications of Thyroidectomy in Cats With Hyperthyroidism

- Transient or permanent hypoparathyroidism causing hypocalcemia:
  - Restlessness
  - Irritability
  - Abnormal behavior
  - Muscle cramping, pain
  - Muscle tremors, especially of ears and face
  - Tetany
  - Convulsions
- Laryngeal paralysis
- Horner syndrome
- Hypothyroidism
- Exacerbation of concurrent renal insufficiency
- No amelioration of hyperthyroidism

Serum calcium concentration should be assessed at least once daily for 5 to 7 days if a bilateral thyroidectomy has been performed. Clinical signs of hypocalcemia typically develop within 72 hours of surgery, although signs may not develop for 7 to 10 days. These signs include lethargy, anorexia, reluctance to move, facial twitching (especially the ears), muscle tremors and cramping, tetany, and convulsions. If all four parathyroid glands are removed at surgery, appropriate calcium and vitamin D supplementation should be initiated once the cat has recovered from anesthesia (see Chapter 47). If at least one parathyroid gland has been spared, transient hypocalcemia may still develop and last for several days to weeks, probably as a result of disruption of blood flow to the parathyroid gland after surgical manipulation. In these cats oral vitamin D and calcium therapy should be initiated only if clinical signs develop or if hypocalcemia becomes severe (i.e., serum total or ionized calcium concentration < 8 mg/dL or < 0.8 mmol/L, respectively). A decline in the blood calcium concentration is not an absolute indication to begin therapy because the remaining parathyroid glands may respond before clinical signs or severe hypocalcemia develop.

The persistence of hypoparathyroidism is unpredictable. Parathyroid function may recover after days, weeks, or months of vitamin D and calcium supplementation. Whenever resolution of hypoparathyroidism is observed, it is assumed that reversible parathyroid damage occurred, accessory parathyroid tissue may be starting to compensate for glands damaged or removed at surgery, or the parathyroid autotransplant (if performed at surgery) has revascularized and become functional. It is also possible that calcium-regulating mechanisms are functioning in the absence of parathyroid hormone. Because it is difficult to predict the long-term requirement for vitamin D therapy in any cat, an attempt should be made to gradually wean all treated cats off medication while the serum calcium concentration is monitored. The tapering process should extend over a period of 3

to 4 months. The goal is to maintain the serum calcium concentration between 8 and 10 mg/dL. If hypocalcemia recurs, therapy with vitamin D and calcium should be reinstituted.

Hypothyroidism may develop in some cats after bilateral thyroidectomy. The clinical signs, diagnosis, and treatment are discussed on page 790. The decision to initiate levothyroxine treatment should be based on the presence or absence of clinical signs and changes in the serum creatinine concentration—not on the serum T_4 concentration, per se. Serum T_4 concentrations commonly decrease after surgery, often to less than 0.5 µg/dL (6 nmol/L), but thyroid function returns in most cats before clinical signs become apparent. Thyroid hormone supplementation should be initiated in cats that develop clinical signs in conjunction with a low serum T_4 concentration and in cats that develop azotemia as a result of decreased GFR induced by the low serum T_4 concentration. Because thyroid hormone replacement therapy may not be needed long term in some of these cats, it should be tapered slowly and then discontinued after 2 to 3 months while monitoring serum T_4 and creatinine concentrations so the continued need for treatment can be determined.

If clinical signs of hyperthyroidism persist despite thyroidectomy, the serum T_4 concentration should be measured. If the serum T_4 concentration is in the lower half of the reference range or lower, another disorder should be suspected. If the serum T_4 concentration is in the upper half of the reference range or higher, ectopic abnormal thyroid tissue, metastatic thyroid carcinoma, or, if unilateral thyroidectomy was performed, abnormal tissue in the remaining thyroid lobe should be suspected. Ectopic thyroid tissue would most likely be found in the mediastinum, cranial to the heart (see Fig. 48.16). Thyroid scintigraphy is recommended to identify ectopic or metastatic thyroid tissue. Alternatively, oral methimazole, radioactive iodine treatment, or an iodine-restricted diet can be considered. Clinical signs of hyperthyroidism may recur months to years after thyroidectomy. The serum T_4 concentration should be monitored two or three times a year in all cats successfully treated with surgery.

Radioactive Iodine

If available, radioactive iodine (^{131}I) is the treatment of choice for hyperthyroidism because of the very low morbidity and mortality and the very high success rate associated with treatment (Fig. 48.21). Hypoparathyroidism is not a concern with radioactive iodine treatment. Radioactive iodine treatment is effective in cats with hyperfunctioning ectopic thyroid tissue and is the only option offering the potential for cure in cats with metastatic or nonresectable thyroid carcinoma. Treatment with methimazole for 1 to 2 months before radioactive iodine treatment is provided is recommended for reasons previously discussed. Prior or current treatment with methimazole does not alter the efficacy of radioactive iodine treatment; however, most treatment centers recommend methimazole treatment be stopped 1 to 2 weeks before treatment with radioactive iodine. Iodine 131 (^{131}I) has a half-life of 8 days. ^{131}I administered intravenously

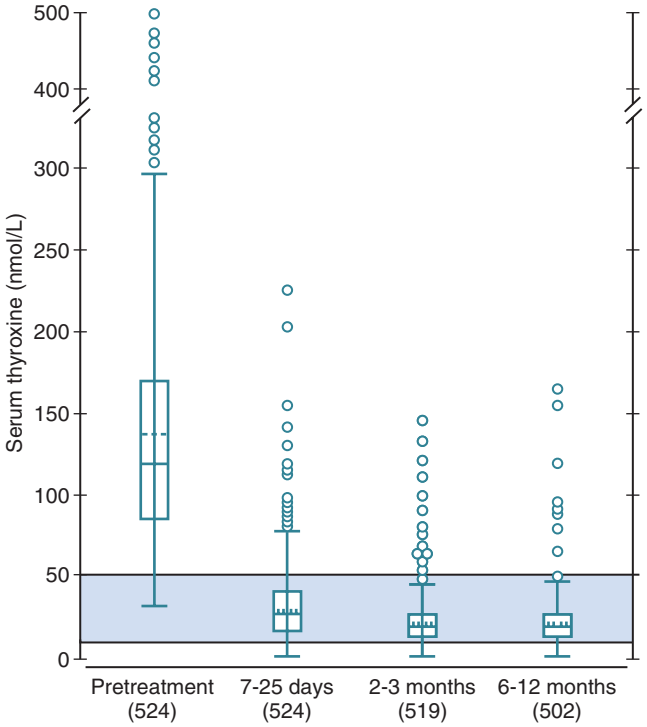


FIG 48.21
Box plots of serum thyroxine (T_4) concentrations in 524 cats before and at various times after administration of radioiodine for treatment of hyperthyroidism. The shaded area indicates the reference range for serum T_4 concentration. Please see Fig. 48.9 for the key. (From Peterson ME et al: Radioiodine treatment of 524 cats with hyperthyroidism, *J Am Vet Med Assoc* 207:1422, 1995.)

or subcutaneously is concentrated within the thyroid, and the emitted radiation destroys surrounding functioning follicular cells while causing minimal radiation damage to contiguous structures. For cats with typical hyperthyroidism (i.e., adenomatous hyperplasia, adenoma), doses of 2 to 5 mCi of ^{131}I kill only the thyroid cells that are functioning. Atrophied normal thyroid cells receive a relatively small dose of radiation and are usually able to return to function, thereby preventing permanent hypothyroidism in most cats. Depending on the dose administered, more than 80% of treated cats become euthyroid within 3 months—most within 1 week—and more than 95% of treated cats are euthyroid at 6 months. The most common complication following radioactive iodine treatment is hypothyroidism, which typically develops in cats with bilateral large, diffusely affected thyroid lobes and cats treated with high doses of radioactive iodine. Initially, serum T_4 and creatinine concentration should be monitored monthly. Thyroid hormone supplementation should be initiated if serum T_4 concentration declines below the reference range and clinical signs of hypothyroidism develop or the cat develops azotemia as a result of decreased GFR induced by the low serum T_4 concentration. If initiated, periodic slow tapering of the dose and frequency of administration should be attempted to determine the need for thyroid hormone treatment.

Approximately 5% of cats require a second ^{131}I treatment. Factors such as dose of radioactive iodine administered, extent of abnormal thyroid tissue, iodine excretion rate, and thyroid pathology may explain treatment failure. Most worrisome is the possibility of thyroid carcinoma. Cats with thyroid carcinoma require higher doses of radioactive iodine than is typically administered to attain a successful outcome. The duration of hospitalization and home care of the cat following ^{131}I administration varies depending on state regulations and the dosage of ^{131}I administered. Hyperthyroidism may recur 1 year or longer after successful treatment.

Prognosis

The prognosis is excellent for most cats with hyperthyroidism, as long as concurrent disease can be managed and thyroid carcinoma is not the cause. Surgery and ^{131}I therapy have the potential for cure, although hyperthyroidism may recur months to years (or not at all) after thyroidectomy or ^{131}I treatment. Hyperthyroid cats with adenomatous hyperplasia or adenoma can potentially be treated with methimazole for years, as long as adverse reactions related to the medication are avoided. In one retrospective study, cats with concurrent CKD had significantly shorter survival times than cats with normal kidney function, and the survival time in cats treated with methimazole alone (median, 2 years; interquartile range, 1-3.9 years) was significantly shorter than in cats treated with ^{131}I alone (4.0 years; 3.0-4.8 years) or methimazole followed by ^{131}I (5.3 years; 2.2-6.5 years; Milner et al., 2006). Age also has an impact on survival data; hyperthyroidism is a geriatric cat disease with an average age at the time of diagnosis of 13 years.

Complications and efficacy of feeding an iodine-deficient diet for a prolonged period (i.e., greater than a year) have yet to be reported.

CANINE THYROID NEOPLASIA

Etiology

Thyroid tumors are relatively common in dogs, where they represent approximately 1% to 3% of all tumors in the dog (Broome et al., 2014). Thyroid adenomas are usually small, nonfunctional masses that do not cause clinical signs and are usually found incidentally at necropsy. Exceptions are thyroid adenomas that are functional and cause hyperthyroidism or are unexpectedly identified during ultrasound examination of the ventral neck. Thyroid carcinomas are more commonly identified antemortem because of their large size, presence of clinical signs that can be recognized by clients, and ease of palpation by veterinarians. One or both thyroid lobes may be involved, and ectopic thyroid tissue located sublingual, in the mediastinum and at the base of the heart occasionally become neoplastic. Thyroid carcinomas are highly vascular, locally invasive, and frequently infiltrate surrounding structures such as the esophagus, trachea, and cervical musculature. Regional and distant metastasis to the retropharyngeal, mandibular, and superficial cervical lymph nodes and lungs are common. Metastasis to other locations such as the liver, kidney, bone, and brain is also possible. Most dogs with thyroid tumor are euthyroid or hypothyroid; less than 15% of dogs have functional thyroid tumors that secrete excess thyroid hormone, causing hyperthyroidism. Clinical signs of hyperthyroidism may predominate in these dogs. Hyperthyroidism may be caused by functional thyroid adenomas and carcinomas. Adenomatous hyperplasia is the most common cause of hyperthyroidism in cats but has not been described in dogs.

Clinical Features

Thyroid tumors occur in middle-aged to older dogs, typically 10 years of age and older. No sex-related predilection has been noted. Although any breed can be affected, Boxers, Beagles, Golden Retrievers, and Siberian Huskies may be at increased risk.

Dogs with nonfunctional thyroid tumors are usually brought to veterinarians because the owner has seen or felt a mass in the ventral cervical region of the dog's neck (Fig. 48.22). Clinical signs may develop as a result of the mass compressing on adjacent structures (e.g., dyspnea, dysphagia) or as a result of metastasis (e.g., exercise intolerance, weight loss; Box 48.9). Clinical signs of hypothyroidism may be noted with large invasive tumors that destroy

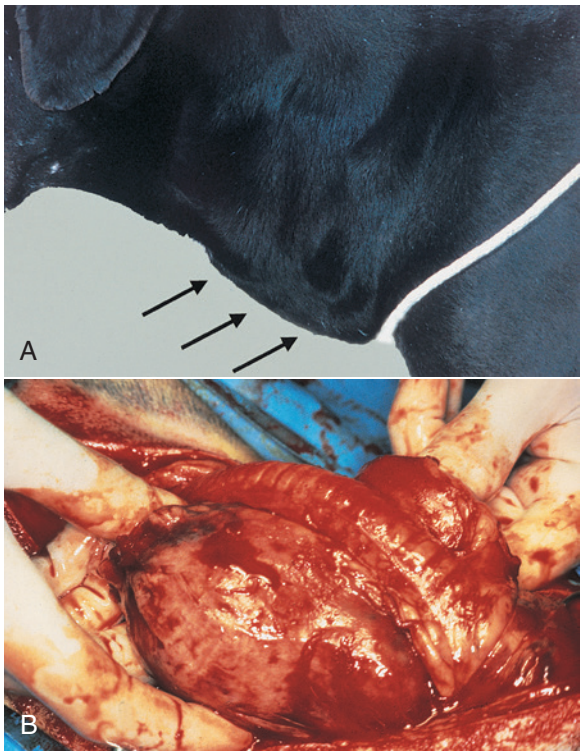


FIG 48.22
(A) A 13-year-old male Labrador Retriever was presented to the veterinarian because the client noticed a mass in the neck *(arrows)*. The mass was a thyroid adenocarcinoma. **(B)** Thyroid adenocarcinoma in an 11-year-old mixed-breed dog. Clinical signs included dysphagia, coughing, and a visible mass in the ventral region of the neck.

BOX 48.9

Clinical Signs Caused by Thyroid Neoplasia in Dogs

Nonfunctional

Swelling or mass in neck
Dyspnea
Cough
Lethargy
Dysphagia
Regurgitation
Anorexia
Weight loss
Horner syndrome
Change in bark
Facial edema

Functional (Hyperthyroid)

Swelling or mass in neck
Polyphagia and weight loss
Hyperactivity
Polyuria and polydipsia
Panting
Change in behavior
Aggression

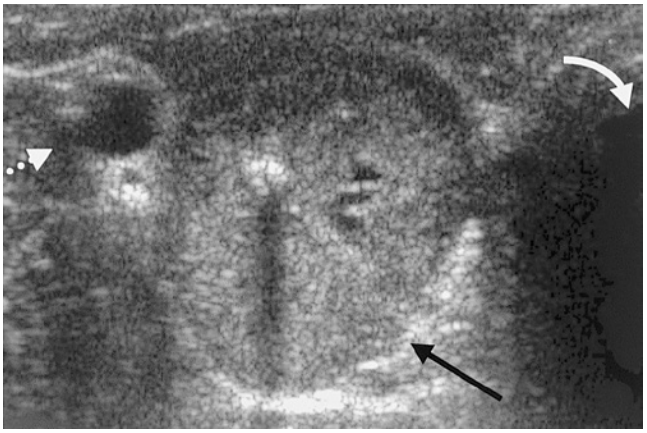


FIG 48.23
Ultrasound image of a mass in the region of the right thyroid lobe *(straight arrow)*, the carotid artery *(broken arrow)*, and the trachea *(curved arrow)* in an 11-year-old female spayed Labrador mix. A small region of mineralization causing a shadowing effect is evident within the mass. The mass was an unexpected finding during a routine physical examination. Thyroid adenocarcinoma was the histopathologic diagnosis after surgical removal of the mass.

both thyroid lobes. Clinical signs of hyperthyroidism occur in dogs with functional thyroid tumors and are similar to those seen in hyperthyroid cats. Most thyroid tumors are firm, asymmetric, lobulated, and nonpainful masses located close to the typical thyroid region in the neck, although larger tumors may extend to the thoracic inlet. The mass usually is well embedded in surrounding tissue and not freely movable; the latter finding suggestive of invasive carcinoma. In some tumors, a bruit, due to the presence of an arteriovenous fistula, can be palpated or auscultated. Additional physical examination findings may include dyspnea, stridor, cough, cachexia, lethargy, Horner syndrome, and a dry, lusterless haircoat. Mandibular or superficial cervical lymph nodes (or both) may be enlarged as a result of tumor spread or lymphatic obstruction. Dogs with functional thyroid tumors may be restless, thin, and panting, and auscultation of the heart frequently reveals tachycardia. Many dogs are found to be remarkably healthy on physical examination.

Findings of CBC, serum biochemistry panel, and urinalysis usually do not help establish the diagnosis. A mild normocytic, normochromic, nonregenerative anemia, hypercholesterolemia, and hypertriglyceridemia causing lipemia may be present in dogs with concurrent hypothyroidism. A mild increase in the blood urea nitrogen concentration and liver enzyme activities may be identified; however, the latter changes are not necessarily indicative of hepatic metastasis. Hypercalcemia has also been noted in a few dogs, and is attributed to a paraneoplastic condition. Systemic hypertension may be present in dogs with functional thyroid tumors causing hyperthyroidism.

Baseline serum T_4 and fT_4 concentrations are increased and serum TSH is undetectable in dogs with a functional thyroid tumor causing hyperthyroidism. However, most canine thyroid tumors are nonfunctional, and most of these dogs are found to be euthyroid when serum thyroid hormone concentrations are evaluated. Approximately 30% of dogs with a thyroid tumor have serum T_4 and fT_4 concentrations below the reference range and an increased serum TSH concentration, suggestive of hypothyroidism resulting from destruction of normal thyroid tissue by the tumor. However, low serum thyroid hormone concentrations must be interpreted with caution and the suppressive effects of nonthyroidal illness on thyroid function considered (see p. 779).

Cervical ultrasonography will confirm the presence of a mass, regardless of its size and location; can distinguish among cavitary, cystic, and solid tumors; can identify the presence and severity of local tumor invasion; can identify the presence and location of metastatic sites in the cervical region; and improve the likelihood that representative tissue for cytologic or histologic evaluation is obtained during fine-needle aspiration or percutaneous biopsy of the mass (Fig. 48.23). Because metastasis to the lungs and to the base of the heart is common with thyroid carcinoma, thoracic radiographs should always be included in the diagnostic evaluation of dogs with a suspected thyroid mass. Cervical radiographs may identify a small mass that was suspected but not definitively identified on physical examination, may show the severity of displacement of adjacent structures, and may identify local invasion of the mass into the larynx and trachea. Abdominal ultrasonography can be used to identify abdominal (most notably hepatic) metastatic lesions.

Computed tomographic (CT) and magnetic resonance imaging (MRI) can define the extent of tumor invasion into surrounding structures, identify distant metastasis to the lymph nodes and lung, and identify ectopic thyroid tissue in the mediastinum (Fig. 48.24)—information that is valuable if surgery or radiation therapy is being considered. Both CT and MRI are superior to ultrasound for establishing extent of invasion of thyroid tumors.

Thyroid scans using sodium pertechnetate can be used to confirm that a cervical mass is thyroid in origin; to assess the degree of regional tissue invasion; and to identify unusual areas of uptake in the head, neck, and thorax suggestive of metastatic sites. Most thyroid carcinomas demonstrate heterogeneous uptake of pertechnetate, irregular gland shape, and evidence of regional tissue invasion. Tumors with a more homogenous diffuse uptake of pertechnetate are more likely to be functional tumors that cause hyperthyroidism. If the malignancy, especially a distant site of metastasis, does not trap iodine effectively, the scintigraphic study will fail to identify the site. Failure to identify distant metastatic sites with scintigraphy does not mean that distant metastasis does not exist. The amount of radionuclide uptake by the thyroid tumor is not a reliable indicator of its functional status (i.e., euthyroid, hypothyroid, or hyperthyroid) or of the benign versus malignant nature of the tumor. Thoracic radiographs are more sensitive than a thyroid scan in identifying pulmonary metastasis.

Diagnosis

Definitive diagnosis can be obtained either by doing a fine needle aspirate for cytology or a biopsy. Unfortunately, canine thyroid tumors are highly vascular, and it is common for hemorrhage to occur after biopsy. Fine-needle aspiration using a 21- or 23-gauge needle and cytologic examination of the mass are recommended initially to confirm that the mass is of thyroid origin. Contamination of the aspirate with blood is common, and differentiation between adenoma and carcinoma is difficult. Large-bore needle biopsy, surgical exploration, or ultrasound-guided biopsy is often required to confirm the diagnosis. Ultrasonography identifies solid areas of the mass to biopsy and large blood vessels to be avoided. This procedure is preferred if the findings yielded by needle aspiration are inconclusive.

Treatment

Treatment options for thyroid tumor in dogs include surgery, chemotherapy, radiation therapy, radioactive iodine treatment, and antithyroid drugs. In many cases more than one treatment option (e.g., surgery and chemotherapy) is used either concurrently or sequentially.

The therapeutic approach is based, in part, on the size and invasiveness of the tumor and the presence of regional and distant metastasis. Approximately 30% to 40% of dogs with thyroid tumors have detectable distant metastasis at the time of diagnosis. Tumor size appears to be predictive of metastatic behavior, with thyroid tumor volume less than 21 cm^3 having a significantly lower risk of metastasis and thyroid tumor volume approaching 100 cm^3 having essentially a 100% probability of metastasis. The functional status of the thyroid tumor does not dramatically alter the treatment approach. All thyroid tumors in dogs should be considered malignant until proven otherwise, regardless of size (Fig. 48.25). Treatment is warranted even for large, locally invasive tumors. Many dogs with large invasive tumors appear more

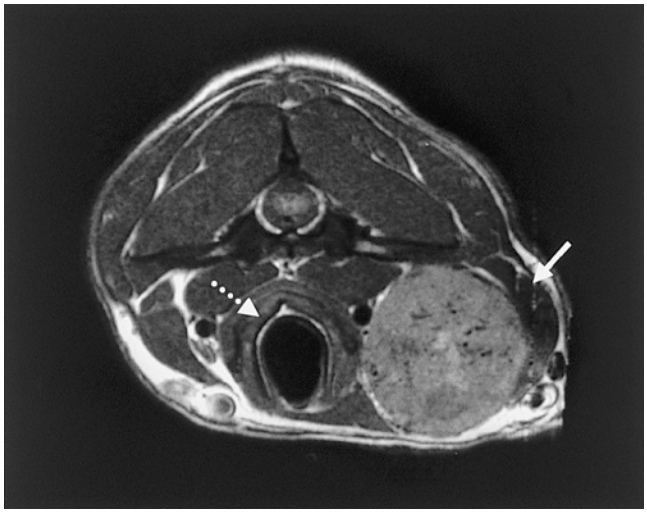


FIG 48.24
Magnetic resonance image of a right-sided thyroid mass *(solid arrow)* adjacent to the trachea *(broken arrow)* in a 10-year-old male castrated Golden Retriever that was presented for a swelling in the neck. The histopathologic diagnosis was thyroid C-cell carcinoma with vascular invasion. The affected region of the neck was treated with radiation after thyroidectomy.

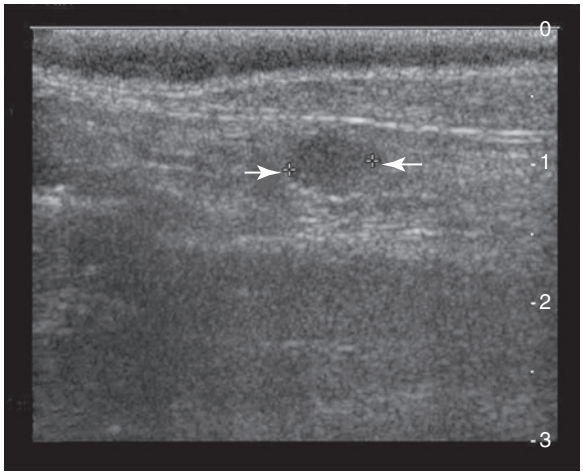


FIG 48.25
Ultrasound image of a 0.61-cm-diameter mass in the right thyroid lobe *(arrows)* in an 11-year-old male castrated Pug. The thyroid mass was an unexpected finding during cervical ultrasound to assess the parathyroid glands during a diagnostic evaluation for hypercalcemia. Thyroid carcinoma was the histopathologic diagnosis after surgical removal of the mass.

comfortable and have the potential for increased longevity after treatment. In addition, local control of the tumor may halt or reduce metastatic dissemination, and the presence of metastases may not ultimately affect outcome. Local control of the thyroid carcinoma is of primary importance in managing this disease.

SURGERY

Surgical excision of thyroid adenomas and small, well-encapsulated, freely movable thyroid carcinomas is likely to be curative. Surgical removal of a fixed, locally invasive thyroid carcinoma, regardless of size, carries a guarded to poor prognosis for complete excision of the tumor. Radiation is the treatment of choice for these tumors. Chemotherapy is indicated if distant metastases are identified, or in some cases, postoperatively in dogs with vascular or lymphatic invasion, or "aggressive" histologic appearance. Surgical debulking of fixed, locally invasive tumors may be indicated to relieve tumor-induced problems such as dysphagia or dyspnea and to allow more time for other therapies to work. Surgical cytoreduction may also be considered after radiation or chemotherapy has caused large invasive tumors to decrease in size. Aggressive attempts at surgical removal, especially of bilateral tumors, threaten the integrity of recurrent laryngeal nerves, parathyroid glands, and normal thyroid tissue. It is important to monitor serum calcium concentrations before and for 2 to 3 weeks after surgery if there is any chance that the parathyroid glands have been excised or damaged. Vitamin D and calcium therapy should be initiated if hypocalcemia develops postoperative (see Chapter 47). Serum T_4 and TSH concentrations should be assessed 4 and 8 weeks after surgery and treatment initiated if clinical signs and blood test results suggest hypothyroidism. (See Tobias and Johnston, 2018, for information on surgical techniques for the thyroparathyroid complex.)

EXTERNAL BEAM RADIATION THERAPY

Radiation therapy is the treatment of choice for locally advanced thyroid carcinoma. External beam radiation can be used alone or in conjunction with surgery or chemotherapy. A slow regression rate of thyroid carcinoma has been noted after radiation therapy in dogs. In one study involving 25 dogs with unresectable differentiated thyroid carcinoma and no evidence of metastasis, the time to attain maximum reduction in tumor size ranged from 8 to 22 months after megavoltage irradiation (Theon et al., 2000). Progression-free survival rates (defined as the time between completion of irradiation and detection of measurable local tumor recurrence or death from causes unrelated to tumor progression) were 80% at 1 year and 72% at 3 years, with a mean progression-free survival time of 55 months in the 25 dogs. Acute adverse reactions to radiation include esophageal, tracheal, or laryngeal mucositis causing dysphagia, cough, hoarseness, and transient neutropenia. These reactions tend to be mild and self-limiting. Chronic radiation reactions include skin fibrosis, permanent alopecia, chronic tracheitis causing a dry cough, and hypothyroidism.

RADIOACTIVE IODINE (^{131}I)

Studies suggest that radioactive iodine therapy will prolong survival time when used as sole therapy or in combination with surgery for the treatment of thyroid tumors in dogs. Worth et al. (2005) reported a median survival time of 30 months for dogs treated with radioiodine alone, 34 months when radioiodine was combined with surgery, and 3 months for dogs that did not receive treatment. Turrel et al. (2006) reported median survival times of 839 days for dogs with local or regional tumors (i.e., stage II and III disease) and 366 days for dogs with metastasis. Tumor site (cervical versus ectopic), age, body weight, treatment protocol (^{131}I alone or with surgery), and serum T_4 concentration were not significantly associated with survival time. Radioactive iodine therapy is useful for any thyroid tumor tissue that retains the ability to trap iodine, including metastatic sites. A technetium scan can be used to determine whether the tumor can trap iodine. Large doses of ^{131}I (i.e., 30-100 mCi or more) are typically administered intravenously to treat canine thyroid carcinoma. Advantages of radioactive iodine treatment include the low risk of adverse effects and the potential to treat both the primary tumor and metastatic lesions. One disadvantage is the need for prolonged isolation of the dog after treatment. Potential adverse reactions include esophagitis, tracheitis, and bone marrow suppression.

CHEMOTHERAPY

Chemotherapy is indicated when total surgical removal or destruction with radiation therapy is not successful, when distant metastatic lesions have been identified, and when the size of the primary tumor is such that local invasion or metastases are likely, even though it cannot be identified with diagnostic tests. A number of different chemotherapeutic drugs have been used to treat thyroid tumors in dogs, including doxorubicin, cisplatin, carboplatin, mitoxantrone, toceranib phosphate, and chlorambucil. Doxorubicin and carboplatin are the two most commonly used to treat thyroid carcinoma in dogs and may be administered on an alternating schedule at 3-week intervals for a combined total of 6 doses. The response of canine thyroid tumors to doxorubicin and carboplatin is variable and unpredictable. In most dogs doxorubicin and carboplatin prevent further growth of the tumor and may cause the tumor to shrink, but total remission is uncommon. One should always consult with an oncologist whenever chemotherapy is being considered. (See Chapters 76 and 77 for discussion of the use of these chemotherapeutic agents.)

ORAL ANTITHYROID DRUGS

Oral antithyroid drugs are used as palliative therapy to control the clinical signs of hyperthyroidism in dogs with functional thyroid tumor; they are not used as primary treatment because they are not cytotoxic. The therapeutic approach is similar to that used in hyperthyroid cats (see p. 794), beginning with 2.5 to 5 mg of methimazole administered twice a day, with subsequent increases in the dosage and frequency of administration as needed to control clinical

signs and maintain the serum T_4 concentration within the reference range.

Prognosis

The prognosis for thyroid adenoma is excellent after surgical removal. The prognosis is guarded to good for dogs that undergo surgical resection of a small, well-encapsulated carcinoma. Unfortunately, most dogs have relatively large thyroid masses, which frequently have invaded surrounding tissues or metastasized at the time of diagnosis. In these dogs aggressive therapy using multiple treatments can alleviate the clinical signs and in some cases dramatically reduce the tumor burden. The long-term prognosis, however, remains guarded to poor, with survival times typically ranging from 6 to 24 months, depending on the aggressiveness of treatment.

Suggested Readings

Feldman EC, et al. *Canine and feline endocrinology*. ed 4. St. Louis: Elsevier; 2015.

Johnston SA, Tobias KM. *Veterinary surgery: small animal*. ed 2. St Louis: Elsevier-Saunders; 2018.

Tobias KM, Johnston SA. *Veterinary surgery: small animal*. St Louis: Elsevier Saunders; 2012.

Canine and Feline Hypothyroidism

Beier P, et al. The role of hypothyroidism in the etiology and progression of dilated cardiomyopathy in Doberman Pinschers. *J Vet Intern Med*. 2015;29:141.

Boretti FS, et al. Comparison of 2 doses of recombinant human thyrotropin for thyroid function testing in healthy and suspected hypothyroid dogs. *J Vet Intern Med*. 2009;23:856.

Broome MR, et al. Exogenous thyrotoxicosis in dogs attributable to consumption of all-meat commercial dog food or treats containing excessive thyroid hormone: 14 cases (2008-2013). *J Am Med Assoc*. 2015;246:105.

De Roover K, et al. Effect of storage of reconstituted recombinant human thyroid-stimulating hormone (rhTSH) on thyroid-stimulating hormone (TSH) response testing in euthyroid dogs. *J Vet Intern Med*. 2006;20:812.

Gommeren K, et al. Effect of thyroxine supplementation on glomerular filtration rate in hypothyroid dogs. *J Vet Intern Med*. 2009;23:844.

Johnson C, et al. Effect of ^{131}I-induced hypothyroidism on indices of reproductive function in adult male dogs. *J Vet Intern Med*. 1999;13:104.

Kemppainen RJ, Birchfield JR. Measurement of total thyroxine concentration in serum from dogs and cats by use of various methods. *Am J Vet Res*. 2006;67:259.

Le Traon G, et al. Clinical evaluation of a novel liquid formulation of L-thyroxine for once daily treatment of dogs with hypothyroidism. *J Vet Intern Med*. 2009;23:43.

Lurye JC, et al. Evaluation of an in-house enzyme-linked immunosorbent assay for quantitative measurement of serum total thyroxine concentrations in dogs and cats. *J Am Vet Med Assoc*. 2002;221:243.

Marca MC, et al. Evaluation of canine serum thyrotropin (TSH) concentration: comparison of three analytical procedures. *J Vet Diagn Invest*. 2001;13:106.

Panciera DL, et al. Effect of short-term hypothyroidism on reproduction in the bitch. *Theriogenology*. 2007;68:316.

Panciera DL, Lefebvre HP. Effect of experimental hypothyroidism on glomerular filtration rate and plasma creatinine concentration in dogs. *J Vet Intern Med*. 2009;23:1045.

Piechotta M, et al. Autoantibodies against thyroid hormones and their influence on thyroxine determination with chemiluminescence immunoassay in dogs. *J Vet Sci*. 2010;11:191.

Radosta LA, et al. Comparison of thyroid analytes in dogs aggressive to familiar people and in non-aggressive dogs. *Vet J*. 2012;192:472.

Randolph JF, et al. Free thyroxine concentrations by equilibrium dialysis and chemiluminescent immunoassays in 13 hypothyroid dogs positive for thyroglobulin antibody. *J Vet Intern Med*. 2015;29:877.

Scott-Moncrieff JCR, et al. Lack of association between repeated vaccination and thyroiditis in laboratory Beagles. *J Vet Intern Med*. 2006;20:818.

Van Dijl IC, et al. Pharmacokinetics of total thyroxine after repeated oral administration of levothyroxine solution and its clinical efficacy in hypothyroid dogs. *J Vet Intern Med*. 2014;28:1229.

Voorbij A, et al. Central hypothyroidism n miniature schnauzers. *J Vet Intern Med*. 2016;30:85.

Feline Hyperthyroidism

Aldridge EN, et al. Evaluation of thyroid-stimulating hormone, total thyroxine, and free thyroxine concentrations in hyperthyroid cats receiving methimazole treatment. *J Vet Intern Med*. 2015;29:862.

Boag AK, et al. Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine. *Vet Rec*. 2007;161:711.

Borett FS, et al. Transdermal application of methimazole in hyperthyroid cats: a long-term follow-up study. *J Feline Med Surg*. 2014;16:453.

Harvey AM, et al. Scintigraphic findings in 120 hyperthyroid cats. *J Feline Med Surg*. 2009;11:96.

Hibbert A, et al. Feline thyroid carcinoma: diagnosis and response to high-dose radioactive iodine treatment. *J Feline Med Surg*. 2009;11:116.

Hui TY, et al. Effect of feeding an iodine-restricted diet in cats with spontaneous hyperthyroidism. *J Vet Intern Med*. 2015;29:1063.

Merryman JI, et al. Overexpression of c-ras in hyperplasia and adenomas of the feline thyroid gland: an immunohistochemical analysis of 34 cases. *Vet Pathol*. 1999;36:117.

Milner RJ, et al. Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996-2003). *J Am Vet Med Assoc*. 2006;228:559.

Peterson ME, et al. Evaluation of serum thyroid-stimulating hormone concentration as a diagnostic test for hyperthyroidism in cats. *J Vet Intern Med*. 2015;29:1327.

Peterson ME, et al. Prevalence and degree of thyroid pathology in hyperthyroid cats increases with disease duration: a cross-sectional analysis of 2096 cats. *J Feline Med Surg*. 2016;18:92.

Rutland BE, et al. Optimal testing for thyroid hormone concentration after treatment with methimazole in healthy and hyperthyroid cats. *J Vet Intern Med*. 2009;23:1025.

van der Kooji M, et al. Effects of an iodine-restricted food on client-owned cats with hyperthyroidism. *J Feline Med Surg*. 2014;16:491.

van Hoek I, et al. A critical review of food-associated factors proposed in the etiology of feline hyperthyroidism. *J Feline Med Surg*. 2015;17:837.

Vaske HH, et al. Effects of feline hyperthyroidism on kidney function: a review. *J Feline Med Surg*. 2016;18.

Wakeling J, et al. Subclinical hyperthyroidism in cats: a spontaneous model of subclinical toxic nodular goiter in humans? *Thyroid*. 2007;17:1201.

Wakeling J, et al. Diagnosis of hyperthyroidism in cats with mild chronic kidney disease. *J Small Anim Pract*. 2008;49:287.

Ward CR, et al. Evaluation of activation of G proteins in response to thyroid stimulating hormone in thyroid gland cells from euthyroid and hyperthyroid cats. *Am J Vet Res*. 2010;71:643.

Williams TL, et al. Survival and the development of azotemia after treatment of hyperthyroid cats. *J Vet Intern Med*. 2010;24:863.

Williams TL, et al. Effect on renal function of restoration of euthyroidism in hyperthyroid cats with iatrogenic hypothyroidism. *J Vet Intern Med*. 2014;28:1251.

Canine Thyroid Neoplasia

Broome MR, et al. Clinical features and treatment outcomes of 41 dogs with sublingual ectopic thyroid neoplasia. *J Vet Intern Med*. 2014;28:1560.

Nadeau ME, Kitchell BE. Evaluation of the use of chemotherapy and other prognostic variables for surgically excised canine thyroid carcinoma with and without metastasis. *Can Vet J*. 2011;52:994.

Theon AP, et al. Prognostic factors and patterns of treatment failure in dogs with unresectable differentiated thyroid carcinomas treated with megavoltage irradiation. *J Am Vet Med Assoc*. 2000;216:1775.

Tuohy JL, et al. Outcome following simultaneous bilateral thyroid lobectomy for treatment of thyroid gland carcinoma in dogs: 15 cases (1994-2010). *J Am Vet Med Assoc*. 2012;241:95.

Turrel JM, et al. Sodium iodide I 131 treatment of dogs with nonresectable thyroid tumors: 39 cases (1990-2003). *J Am Vet Med Assoc*. 2006;229:542.

Worth AJ, et al. Radioiodide (^{131}I) therapy for treatment of canine thyroid carcinoma. *Aust Vet J*. 2005;83:208.

Wucherer KL, Wilke V. Thyroid cancer in dogs: an update based on 638 cases (1995-2005). *J Am Anim Hosp Assoc*. 2010;46:249.

CHAPTER 49

Disorders of the Endocrine Pancreas



HYPERGLYCEMIA

Etiology

Hyperglycemia is present if the blood glucose concentration is greater than 125 mg/dL, although clinical signs of hyperglycemia do not develop until the renal tubular threshold for the resorption of glucose is exceeded. In dogs this typically occurs whenever the blood glucose concentration exceeds 180 to 220 mg/dL. The threshold for glucose resorption appears to be more variable in cats, ranging from 200 to 280 mg/dL. Glycosuria causes an osmotic diuresis, which in turn causes polyuria and polydipsia, the hallmark clinical signs of severe hyperglycemia. The most common cause of hyperglycemia and glycosuria is diabetes mellitus. Severe hyperglycemia without glycosuria also occurs commonly in cats with stress-induced hyperglycemia, presumably resulting from the secretion of catecholamines. Transient glycosuria (typically < 1% on urine glucose test strips) may occur in some cats with severe or prolonged stress-induced hyperglycemia.

Clinical Features

Hyperglycemia of between 125 and 180 mg/dL (often as high as 250 mg/dL in cats) is clinically silent and is an unsuspected finding encountered during blood testing for another reason. If a dog or cat with mild hyperglycemia (<180 mg/dL) and no glycosuria is seen because of polyuria and polydipsia, a disorder other than overt diabetes mellitus should be suspected. Mild hyperglycemia can occur in some dogs and cats up to 2 hours after consumption of diets containing increased quantities of monosaccharides and disaccharides, corn syrup, or propylene glycol; during intravenous (IV) administration of total parenteral nutrition fluids; in stressed, agitated, or excitable cats and dogs; in animals in the early stages of diabetes mellitus (i.e., subclinical diabetes); and in animals with disorders and drugs causing insulin resistance (Box 49.1). A diagnostic evaluation for disorders causing insulin resistance is indicated if mild hyperglycemia is found to persist in a fasted, unstressed dog or cat, especially if the blood glucose concentration is increasing over time (see p. 828).

HYPOGLYCEMIA

Etiology

Hypoglycemia is present if the blood glucose concentration is less than 60 mg/dL. It typically results from excessive uptake of glucose by normal cells (e.g., during periods of hyperinsulinism as with a β-cell tumor or xylitol ingestion) or neoplastic cells, impaired hepatic gluconeogenesis and glycogenolysis (e.g., portal shunt, hepatic cirrhosis), a deficiency in diabetogenic hormones (e.g., hypocortisolism), an inadequate dietary intake of glucose and other substrates required for hepatic gluconeogenesis (e.g., anorexia in the neonate or in toy breeds), or a combination of these mechanisms (e.g., sepsis; Box 49.2). Iatrogenic hypoglycemia is a common problem resulting from overzealous insulin administration in diabetic dogs and cats.

Prolonged storage of blood before separation of serum or plasma causes the glucose concentration to decrease at a rate of approximately 7 mg/dL/h. Glycolysis by red and white blood cells becomes even more apparent in dogs and cats with erythrocytosis, leukocytosis, or sepsis. Therefore whole blood obtained for the measurement of glucose concentration should be separated soon after collection (within 30 minutes), and the serum or plasma should be refrigerated or frozen until the assay is performed to minimize artifactual lowering of the blood glucose concentration. Glucose determinations from separated and refrigerated plasma or serum are reliable for as long as 48 hours after separation and refrigeration of the specimen. Alternatively, plasma can be collected in sodium fluoride tubes. Unfortunately, hemolysis is common in blood collected in sodium fluoride–treated tubes, which can result in slight decrements in glucose values related to methodologic problems in laboratory determinations. Blood glucose values as determined by many portable home blood glucose–monitoring devices designed for use by human patients with diabetes are almost

BOX 49.1

Causes of Hyperglycemia in Dogs and Cats

- Diabetes mellitus*
- Stress, aggression, excitement, nervousness, fright*
- Postprandial (within 2 hours of consuming diets containing monosaccharides, disaccharides, propylene glycol, corn syrup)
- Hyperadrenocorticism*
- Acromegaly (cat)
- Diestrus (bitch)
- Pheochromocytoma (dog)
- Pancreatitis
- Exocrine pancreatic neoplasia
- Chronic kidney disease
- Head trauma
- Drug therapy*
  - Glucocorticoids
  - Progestins
  - Megestrol acetate
- Dextrose-containing fluids*
- Parenteral nutrition solutions*

*Common cause.

BOX 49.2

Causes of Hypoglycemia in Dogs and Cats

- β-Cell tumor (insulinoma)*
- Primary and metastatic neoplasia
  - Hepatocellular carcinoma, hepatoma*
  - Leiomyosarcoma, leiomyoma*
  - Hemangiosarcoma
  - Carcinoma (mammary, salivary, pulmonary, gastric, small intestine, renal, splenic)
  - Leukemia
  - Plasmacytoma
  - Melanoma
- Hepatobiliary disease*
  - Portosystemic shunts
  - Chronic fibrosis, cirrhosis
  - Hepatic necrosis (toxins)
- Sepsis*
  - Severe canine babesiosis
  - Septic peritonitis
- Hypoadrenocorticism*
- Idiopathic hypoglycemia*
  - Neonatal hypoglycemia
  - Juvenile hypoglycemia (especially toy breeds)
  - Hunting dog hypoglycemia
- Exocrine pancreatic neoplasia
- Pancreatitis
- Chronic kidney disease
- Hypopituitarism
- Severe polycythemia
- Hepatic enzyme deficiencies
  - Von Gierke's disease (type I glycogen storage disease)
  - Cori's disease (type III glycogen storage disease)
- Severe malnutrition
- Prolonged storage of whole blood*
- Iatrogenic*
  - Insulin overdose
  - Sulfonylurea therapy
  - Ethylene glycol ingestion
  - Xylitol ingestion
  - Alpha lipoic acid
  - Dried chicken jerky treats
- Artifact*
  - Portable blood glucose–monitoring devices
  - Laboratory error

*Common cause.

always lower than actual glucose values as determined by benchtop methods, and this may result in an incorrect diagnosis of hypoglycemia. In contrast, an erroneous reading with the AlphaTRAK glucometer (Abbott Laboratories), designed for use in diabetic dogs and cats, can be high or low compared with actual glucose values. Finally, laboratory error may result in an incorrect value. It is wise to confirm hypoglycemia by determining the blood glucose concentration from a second blood sample and using benchtop methods before embarking on a search for the cause of hypoglycemia.

Clinical Features

Clinical signs of hypoglycemia usually develop when the blood glucose concentration is less than 45 mg/dL, although this can be variable. The development of clinical signs depends on the severity and duration (acute versus chronic) of hypoglycemia and the rate of decline in the blood glucose concentration. Clinical signs are a result of neuroglycopenia- and hypoglycemia-induced stimulation of the sympathoadrenal nervous system. Neuroglycopenic signs include seizures; weakness; collapse; ataxia; and, less commonly, lethargy, blindness, bizarre behavior, and coma. Signs of increased secretion of catecholamines include restlessness, nervousness, and muscle fasciculations.

Depending on the cause, the signs of hypoglycemia may be persistent or intermittent. The hallmark clinical sign of hypoglycemia (i.e., seizures) tends to be intermittent, regardless of the cause. Dogs and cats usually recover from hypoglycemic seizures within a couple of minutes as a result of activation of counterregulatory mechanisms (e.g., secretion of glucagon and catecholamines) that block the effects of insulin, stimulate hepatic glucose secretion, and promote an increase in the blood glucose concentration.

Diagnostic Approach

Hypoglycemia should always be confirmed before diagnostic studies are begun to identify the cause. Careful evaluation of the animal's history, physical examination findings, and results of routine blood and urine tests (i.e., complete blood count [CBC], serum biochemistry panel, urinalysis) usually provides clues to the underlying cause. Hypoglycemia in the

puppy or kitten is usually caused by idiopathic hypoglycemia, starvation, congenital portosystemic shunt, or sepsis. In young adult dogs or cats hypoglycemia is usually caused by hepatobiliary disease, portosystemic shunt, hypoadrenocorticism, or sepsis. In older dogs or cats, hepatobiliary disease, β-cell neoplasia, extrapancreatic neoplasia, hypoadrenocorticism, and sepsis are the most common causes.

Hypoglycemia tends to be mild (>45 mg/dL) and is often an incidental finding in dogs and cats with hypoadrenocorticism or liver insufficiency. Additional clinical pathologic alterations are usually present (e.g., hyponatremia and hyperkalemia in animals with hypoadrenocorticism or increased alanine aminotransferase [ALT] activity, hypocholesterolemia, hypoalbuminemia, low blood urea nitrogen [BUN] concentration in animals with hepatobiliary disease). A baseline serum cortisol concentration, adrenocorticotropic hormone (ACTH) stimulation test or liver function test (i.e., preprandial and postprandial bile acids) may be required to confirm the diagnosis. Severe hypoglycemia (<40 mg/dL) may develop in neonates and juvenile kittens and puppies (especially toy breeds) and in animals with sepsis, β-cell neoplasia, and extrapancreatic neoplasia, most notably hepatic adenocarcinoma and leiomyosarcoma. Sepsis is readily identified on the basis of physical examination findings and abnormal CBC findings, such as a neutrophilic leukocytosis (typically > 30,000/μL), a shift toward immaturity, and signs of toxicity. Extrapancreatic neoplasia can usually be identified on the basis of the physical examination, abdominal or thoracic radiography, and findings on abdominal ultrasonography. Dogs with β-cell neoplasia typically have normal physical examination findings with no abnormalities other than hypoglycemia identified on routine blood and urine tests. Measurement of baseline serum insulin concentration when the blood glucose is less than 60 mg/dL (preferably < 50 mg/dL) is necessary to confirm the diagnosis of a β-cell tumor.

Treatment

Whenever possible, therapy should be directed at eliminating the underlying cause of the hypoglycemia. If the disorder cannot be eliminated and the clinical signs of hypoglycemia persist, long-term symptomatic therapy designed to increase the blood glucose concentration may be necessary to minimize clinical signs (see p. 850). Such therapy is usually required for animals with metastatic β-cell or extrapancreatic neoplasia.

Symptomatic therapy for animals with severe hypoglycemia of acute onset relies on the administration of glucose (Box 49.3). If the dog or cat is having a hypoglycemic seizure at home, the client should rub a sugar solution on the pet's buccal mucosa. Most animals respond within 1 to 2 minutes. Clients should be instructed never to place fingers into, or pour the sugar solution down, the pet's mouth. Once the dog or cat is sternal and cognizant of its surroundings, it should be fed a small meal and brought to the veterinarian. Although clinical trials are needed, at-home glucagon emergency kits used to treat severe hypoglycemia in human patients with diabetes may become a viable option for treating severe hypoglycemia in diabetic dogs and cats (Zeugswetter et al., 2012). If collapse, seizures, or coma develops in the hospital, a blood sample should be obtained to measure the glucose concentration before reversing the signs with IV administration of 50% dextrose, diluted, followed by continuous IV infusion of 5% dextrose. Dextrose should be administered in small amounts slowly (1-5 mL aliquots) rather than in large boluses rapidly. This is especially important in dogs with suspected β-cell neoplasia, in which aggressive glucose administration can result in severe hypoglycemia after excessive insulin secretion by the tumor in response to glucose. Dogs and cats with hypoglycemia usually respond to glucose administration within 2 minutes. Recurrence of hypoglycemia is dependent on the ability to correct the underlying cause.

Occasionally, a dog or cat with severe central nervous system signs (e.g., blindness, coma) does not respond to initial glucose therapy. Irreversible cerebral lesions may result from prolonged severe hypoglycemia and the resultant cerebral hypoxia. The prognosis in these animals is guarded to poor. Therapy is directed at providing a continuous supply of glucose by administering a 2.5% to 5% solution intravenously or by increasing hepatic gluconeogenesis with a

BOX 49.3

Medical Therapy for Acute Hypoglycemic Seizures

Seizures at Home

Step 1. Apply sugar solution to pet's gums.
Step 2. Once pet is sternal, feed a small meal.
Step 3. Call the veterinarian.

Seizures in Hospital

Step 1. Administer 1 to 5 mL (depending on dog size) of 50% dextrose (diluted) IV *slowly* over 1 to 2 minutes followed by continuous infusion of 5% dextrose in water (i.e., D5W).
Step 2. Once animal is sternal, feed a small meal.
Step 3. Initiate long-term medical therapy if necessary (see Box 49.14).

Intractable Seizures in Hospital

Step 1. Administer 2.5% to 5% dextrose in water intravenously at 1.5 to 2 times maintenance fluid rate.
Step 2. Add 0.5 to 1 mg of dexamethasone/kg to IV fluids and administer over 6 hours; repeat every 12 to 24 hours, as necessary.
Step 3. If previous step fails, administer IV glucagon USP (Eli Lilly) by constant-rate infusion at an initial dosage of 5 to 10 ng/kg/min.
Step 4. If preceding steps fail, control seizure activity with diazepam or phenobarbital until medical treatment becomes effective in controlling hypoglycemia.

IV, Intravenous.

constant-rate infusion of glucagon (see p. 851). Seizure activity is controlled with diazepam or a stronger anticonvulsant medication. Glucocorticoids and mannitol may be necessary to combat cerebral edema.

DIABETES MELLITUS IN DOGS

Etiology and Classification

The reported prevalence of diabetes mellitus in dogs varies between countries, ranging from 1.2% in Sweden (Fall et al., 2007) to 0.32% in the United Kingdom (Davison et al., 2005). Guptill et al. (2003) reported a hospital prevalence of 0.64% in the United States. Virtually all dogs with diabetes have type 1 insulin-dependent diabetes mellitus (IDDM) at the time of diagnosis. Type 1 diabetes is characterized by permanent hypoinsulinemia, essentially no increase in the endogenous serum insulin concentration after administration of an insulin secretagogue (e.g., glucose, glucagon) at any time after diagnosis of the disease, failure to establish glycemic control in response to diet or treatment with oral hypoglycemic drugs (or both), and an absolute need for exogenous insulin to maintain glycemic control. The cause of diabetes mellitus in dogs is undoubtedly multifactorial. A genetic predisposition, infection, insulin-antagonistic diseases and drugs, obesity, immune-mediated mechanisms, and pancreatitis have been identified as inciting factors. The end result consists of loss of β cells, hypoinsulinemia, impaired transport of circulating glucose into most cells, and accelerated hepatic gluconeogenesis and glycogenolysis. The subsequent development of hyperglycemia and glycosuria causes polyuria, polydipsia, polyphagia, and weight loss. Ketoacidosis develops as the production of ketone bodies increases to compensate for the underutilization of blood glucose (see p. 840). Loss of β-cell function is irreversible in dogs with IDDM, and lifelong insulin therapy is mandatory to maintain glycemic control of the diabetic state.

Unlike cats, dogs very rarely have a transient or reversible form of diabetes mellitus. The most common scenario for diabetic remission in dogs is correction of insulin antagonism after ovariohysterectomy in a bitch in diestrus. Progesterone stimulates secretion of growth hormone in the bitch. Ovariohysterectomy removes the source of progesterone, plasma growth hormone concentration declines, and insulin antagonism resolves. If an adequate population of functional β cells is still present in the pancreas, hyperglycemia may resolve without the need for insulin treatment after ovariohysterectomy or more commonly within a month of initiation of insulin therapy after ovariohysterectomy. These dogs have a significant reduction in β-cell numbers (i.e., subclinical diabetes), compared with healthy dogs, before the development of hyperglycemia during diestrus and are prone to redevelopment of hyperglycemia and diabetes mellitus if insulin antagonism recurs for any reason after ovariohysterectomy. Although uncommon, a similar situation can occur in dogs with subclinical diabetes treated with insulin-antagonistic drugs (e.g., glucocorticoids) or in the very early stages of an insulin-antagonistic disorder (e.g., hyperadrenocorticism). Failure to quickly correct the insulin antagonism will result in IDDM and the lifelong requirement for insulin treatment to control hyperglycemia.

A honeymoon period occurs in some dogs with newly diagnosed IDDM. It is characterized by excellent glycemic control in response to small doses of insulin (<0.2 U/kg/injection), presumably because of the presence of residual β-cell function. However, glycemic control becomes more difficult and insulin doses usually increase within 3 to 6 months of the start of treatment as residual functioning β cells are destroyed and endogenous insulin secretion declines.

Type 2 non–insulin-dependent diabetes mellitus (NIDDM) is not recognized clinically in dogs. Obesity-induced insulin resistance has been documented in dogs but progression to type 2 diabetes does not occur (Verkest et al., 2012). Studies suggest that at least some of the etiopathogenic mechanisms responsible for development of obesity-associated type 2 diabetes in humans and cats do not occur in dogs.

Clinical Features

SIGNALMENT

Most dogs are 5 to 15 years old at the time diabetes mellitus is diagnosed. Juvenile-onset diabetes occurs in dogs younger than 1 year of age and is uncommon. One large epidemiologic study involving 6807 diabetic dogs and 6807 matched controls in the United States and Canada identified the following: female dogs were at increased risk for diabetes compared with male dogs, neutered male dogs were at increased risk compared with intact male dogs, and mixed-breed dogs were at increased risk compared with pure breeds (Guptill et al., 2003). A seasonal pattern in prevalence of diabetes was not identified. Breeds with a significantly increased or decreased risk for developing diabetes are listed in Table 49.1. Breed popularity and regions of the world may also impact breed predispositions. For example, breeds with the highest risk for diabetes in Italy include the Irish Setter, Poodle, Yorkshire Terrier, and English Setter (Fracassi et al., 2004). In Sweden, high risk breeds included Spitz-type breeds (Samoyed, Swedish Elkhound, and Swedish Lapphund) and Scandinavian hound dogs (Finnish Hound, Hamilton Hound, and Drever) (Fall et al., 2007).

HISTORY

The history in virtually all diabetic dogs includes polyuria, polydipsia, polyphagia, and weight loss. Polyuria and polydipsia do not develop until hyperglycemia results in glycosuria. Occasionally, a client brings in a dog because of blindness caused by cataract formation (Fig. 49.1). If clinical signs associated with uncomplicated diabetes are not observed or are considered irrelevant by the client a diabetic dog is at risk for the development of systemic signs of illness as progressive ketonemia and metabolic acidosis develop. The time sequence from the onset of initial clinical signs to

TABLE 49.1

Breeds Recognized to Have High and Low Risk for Developing Diabetes Mellitus Based on Analysis of the Veterinary Medical Database (VMDB) From 1970 to 1993*

BREEDS WITH HIGH RISK	ODDS RATIO	BREEDS WITH LOW RISK	ODDS RATIO
Australian Terrier	9.39	German Shepherd dog†	0.18
Standard Schnauzer	5.85	Collie	0.21
Miniature Schnauzer†	5.10	Shetland Sheepdog	0.21
Bichon Frise	3.03	Golden Retriever†	0.28
Spitz	2.90	Cocker Spaniel	0.35
Fox Terrier	2.68	Australian Shepherd	0.44
Miniature Poodle†	2.49	Labrador Retriever	0.45
Samoyed†	2.42	Doberman Pinscher	0.49
Cairn Terrier	2.26	Boston Terrier	0.51
Keeshond	2.23	Rottweiler	0.51
Maltese	1.79	Basset Hound	0.56
Toy Poodle†	1.76	English Setter	0.60
Lhasa Apso	1.54	Beagle	0.64
Yorkshire Terrier	1.44	Irish Setter	0.67
Pug†	—	English Springer Spaniel	0.69
		American Pit Bull Terrier†	—

Mixed-breed dogs were used as the reference group (odds ratio, 1.00) for comparison with other breeds.
*The VMDB comprises medical records of 24 veterinary schools in the United States and Canada. VMDB case records analyzed included those from first hospital visits of 6078 dogs with a diagnosis of diabetes mellitus and 5922 randomly selected dogs with first hospital visits for any diagnosis other than diabetes mellitus seen at the same veterinary schools in the same year. Only breeds with more than 25 cases of diabetes mellitus are included.
†Breeds also identified with significant high or low risk for developing diabetes in a study by Hess RS et al: Breed distribution of dogs with diabetes mellitus admitted to a tertiary care facility, *J Am Vet Med Assoc* 216:1414, 2000.
From Guptill L et al: Is canine diabetes on the increase? In *Recent advances in clinical management of diabetes mellitus,* Dayton, Ohio, 1999, Iams Company, p 24.



FIG 49.1
Bilateral cataracts causing blindness in a diabetic dog. (From Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, WB Saunders.)

the development of diabetic ketoacidosis (DKA) is unpredictable, ranging from days to weeks.

PHYSICAL EXAMINATION

Physical examination findings depend on the presence and severity of DKA, the duration of diabetes before its diagnosis, and the nature of any other concurrent disorder. The nonketotic diabetic dog has no classic physical examination findings. Many diabetic dogs are obese but are otherwise in good physical condition. Dogs with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., pancreatic exocrine insufficiency) is present. The haircoat may be sparse; the hairs may be dry, brittle, and lusterless; and scales from hyperkeratosis may be present. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Lenticular changes consistent with cataract formation are common. Anterior uveitis and keratoconjunctivitis sicca may also be present. In contrast to diabetic cats, clinical signs suggestive of diabetic neuropathy (e.g., rear limb weakness, ataxia) are uncommon in newly diagnosed diabetic dogs. Additional abnormalities may be identified if DKA is present (see p. 840).

Diagnosis

The diagnosis of diabetes mellitus is based on three findings: appropriate clinical signs, persistent fasting hyperglycemia, and glycosuria. Measurement of the blood glucose concentration using a portable blood glucose–monitoring device and testing for the presence of glycosuria using urine reagent test strips (e.g., KetoDiastix) provide rapid confirmation of diabetes mellitus. Concurrent documentation of ketonuria establishes a diagnosis of diabetic ketosis (DK), and documentation of metabolic acidosis establishes a diagnosis of DKA.

It is important to document both persistent hyperglycemia and glycosuria to establish a diagnosis of diabetes mellitus because hyperglycemia differentiates diabetes mellitus from primary renal glycosuria, and glycosuria differentiates diabetes mellitus from other causes of hyperglycemia (see Box 49.1), most notably epinephrine-induced stress hyperglycemia that may develop around the time of blood sampling. Stress-induced hyperglycemia is a common problem in cats and occasionally occurs in dogs, especially those that are very excited, hyperactive, or aggressive. The reader is referred to page 837 for more information on stress-induced hyperglycemia.

Documenting an increase in the serum fructosamine concentration supports the presence of sustained hyperglycemia; however, a serum fructosamine concentration in the upper end of the reference range can occur in symptomatic diabetic dogs if the diabetes developed shortly before presentation of the dog to the veterinarian. The reader is referred to page 818 for more information on serum fructosamine.

A thorough evaluation of the dog's overall health is recommended once the diagnosis of diabetes mellitus has been established to identify any disease that may be causing or contributing to the carbohydrate intolerance (e.g., hyperadrenocorticism), that may result from the carbohydrate intolerance (e.g., bacterial cystitis), or that may mandate a modification of therapy (e.g., pancreatitis). The minimum laboratory evaluation should include a CBC, a serum biochemistry panel, measurement of serum pancreatic lipase immunoreactivity, and urinalysis with bacterial culture. Serum progesterone concentration should be determined if diabetes mellitus is diagnosed in an intact bitch, regardless of her cycling history. If available, abdominal ultrasound is indicated to assess for pancreatitis, adrenomegaly, pyometritis in an intact bitch, and abnormalities affecting the liver and urinary tract (e.g., changes consistent with pyelonephritis or cystitis). Measurement of baseline serum insulin concentration or an insulin response test is not routinely done. Additional tests may be warranted after the history is obtained, the physical examination is performed, or ketoacidosis is identified. Potential clinical pathologic abnormalities are listed in Box 49.4.

BOX 49.4

Clinicopathologic Abnormalities Commonly Found in Dogs and Cats With Uncomplicated Diabetes Mellitus

Complete Blood Count

Typically normal
Neutrophilic leukocytosis, toxic neutrophils if pancreatitis or infection present

Biochemistry Panel

Hyperglycemia
Hypercholesterolemia
Hypertriglyceridemia (lipemia)
Increased alanine aminotransferase activity (typically <500 IU/L)
Increased alkaline phosphatase activity (typically <500 IU/L)

Urinalysis

Urine specific gravity typically > 1.025
Glycosuria
Variable ketonuria
Proteinuria
Bacteriuria

Ancillary Tests

Serum Spec cPL or fPL normal or increased if pancreatitis present
Serum lipase normal or increased if pancreatitis present
Serum trypsin-like immunoreactivity (TLI)
  Low if pancreatic exocrine insufficiency present
  Normal or increased if pancreatitis present
Baseline serum insulin concentration
  IDDM: low, normal
  NIDDM: low, normal, increased
  Insulin resistance induced: low, normal, increased

IDDM, Insulin-dependent diabetes mellitus; *NIDDM,* non–insulin-dependent diabetes mellitus; *Spec cPL,* canine pancreatic-specific lipase; *Spec fPL,* feline pancreatic-specific lipase.

Treatment

The primary goal of therapy is elimination of client-observed clinical signs of diabetes. Persistence of clinical signs and development of chronic complications (Box 49.5) are directly correlated with the severity and duration of hyperglycemia. In the diabetic dog, control of hyperglycemia can be established with insulin, diet, exercise, prevention or control of concurrent insulin antagonistic diseases, and discontinuation of medications that cause insulin resistance. The veterinarian should also guard against the dog developing hypoglycemia, which is most apt to occur as the result of overzealous insulin therapy. The veterinarian should balance the benefits of tight glucose control obtainable with aggressive insulin therapy against the risk of hypoglycemia.

The second goal is to minimize the impact of therapy on the owner's lifestyle. A recent study evaluated the psychological and social impact of diabetes and its treatment on the quality of life of owners of diabetic dogs (Niessen et al., 2012). The top 10 negative impact items were associated mostly with the owner's quality of life rather than the pet's quality of life (Table 49.2). Awareness of the impact of the

BOX 49.5

Complications of Diabetes Mellitus in Dogs and Cats

Common

Iatrogenic hypoglycemia
Persistent or recurring polyuria, polydipsia, weight loss
Cataracts (dog)
Lens-induced uveitis (dog)
Bacterial infection, especially involving the urinary tract
Chronic pancreatitis
Recurring ketosis, ketoacidosis
Hepatic lipidosis
Peripheral neuropathy (cat)
Systemic hypertension (dog)

Uncommon

Peripheral neuropathy (dog)
Diabetic nephropathy
  Significant proteinuria
  Glomerulosclerosis
Retinopathy
Exocrine pancreatic insufficiency
Gastric paresis
Intestinal hypomotility and diarrhea
Diabetic dermatopathy (i.e., superficial necrolytic dermatitis)

TABLE 49.2

Top 10 Negative Psychological and Social Impacts of Diabetes Mellitus and Its Treatment on the Quality of Life of Owners of a Diabetic Dog

ITEM	MEAN ITEM WEIGHTED IMPACT SCORE
Worry about pet's diabetes	-5.92
Interferes with visiting family and friends	-5.68
Worry about the dog developing cataracts	-5.58
Worry about boarding the dog	-5.18
Worry about dog developing hypoglycemia	-4.95
Having to fit the dog's needs into their social life	-4.82
Cost of treating the diabetes	-4.11
Worry about future ability to care for the dog	-4.07
Having to fit the dog's needs into their work schedule	-3.88
Restricting the owners vacation and work activities	-3.88

The quality-of-life survey was completed by 101 owners originating from the United Kingdom, United States, Canada, Australia, and Europe.
From Niessen SJM et al: Evaluation of a quality-of-life tool for dogs with diabetes mellitus, *J Vet Intern Med* 26:953, 2012.

treatment regimen, home monitoring and frequency of evaluations by the veterinarian on the client, and simplifying the overall management of the diabetic dog as much as possible without negatively impacting control of glycemia is important for the long-term success of treating diabetes.

OVERVIEW OF INSULIN PREPARATIONS

Types of insulin typically used for home treatment of diabetes in dogs and cats include intermediate-acting insulin (NPH, lente) and long-acting basal insulin (protamine zinc insulin [PZI], insulin glargine, insulin detemir; Table 49.3). NPH (Humulin N, Novolin N) is a recombinant human insulin; lente (Vetsulin, Caninsulin) is a purified pork-source insulin that is a mixture of three parts short-acting amorphous insulin and seven parts long-acting microcrystalline insulin; and PZI (Pro-Zinc, IDEXX) is a recombinant human insulin. Porcine-source lente and protamine zinc insulin are approved by the FDA for treatment of diabetes in dogs and cats, respectively.

NPH insulin, insulin glargine, and insulin detemir are U100 insulin preparations (i.e., 100 units of insulin per mL of solution), and porcine-source lente and protamine zinc insulin and are U40 insulin preparations (i.e., 40 units of insulin per mL of solution). The appropriate insulin syringe should be used for the insulin preparation being administered (i.e., U40 or U100 insulin syringe for a U40 or U100 insulin preparation). Insulin pens are also available for NPH insulin, porcine-source lente insulin, insulin glargine, and insulin detemir. The manufacturer of porcine lente insulin recommends vigorous shaking of the insulin vial until a homogeneous milky suspension is obtained before withdrawal of the insulin into the syringe.

Recombinant DNA technology has been applied for the production of insulin analogs with faster and slower absorption characteristics than are seen with native human insulin preparations. Rapid-acting insulin analogs, including insulin lispro (Humalog), insulin aspart (Novolog), and insulin glulisine (Apidra®) and are typically administered to human patients with diabetes three times a day before each of the three main meals (breakfast, lunch, and dinner), are used to control postprandial hyperglycemia, and are referred to as *prandial insulin preparations*. The role, if any, of these extremely short-acting insulins for the home treatment of diabetic dogs remains to be determined. A recent study documented similar effectiveness of insulin lispro and regular crystalline insulin for the treatment of DKA in dogs (Sears et al., 2012).

Insulin glargine (Lantus) and insulin detemir (Levemir) are long-acting basal insulin analogs that have a slow, sustained absorption from the subcutaneous site of insulin deposition, are designed to inhibit hepatic glucose secretion, are administered once a day at bedtime, and are used

TABLE 49.3

Commonly Used Insulin Preparations for Treating Diabetes in Dogs and Cats

		ADMINISTRATION		TYPICAL DURATION OF EFFECT (h)			
INSULIN	**ORIGIN**	**INDICATIONS**	**ROUTE**	**FREQUENCY**	**DOG**	**CAT**	**COMMON PROBLEMS**
Regular crystalline	Recombinant human	Treat DKA	IV	Continuous infusion	—	—	Rapid decrease in blood glucose concentration
			IM	Hourly initially	4-6	4-6	
			SC	q6-8h	6-8	6-8	May cause hypokalemia
		Treat diabetes at home	SC	q8h	6-8	6-8	
Lispro	Recombinant human analog	Treat DKA	IV	Continuous infusion	—	—	Rapid decrease in blood glucose concentration; may cause hypokalemia
NPH	Recombinant human	Treat diabetes at home	SC	q12h	6-12	6-10	Short duration of effect in dogs and cats
Lente	100% pork	Treat diabetes at home	SC	q12h	8-14	6-12	Short duration of effect in cats
		Good initial insulin for dogs					
PZI	Recombinant human	Treat diabetes at home Good initial insulin for cats	SC	q12h	10-16	10-14	Duration of effect too long for q12h therapy in some dogs Unpredictable timing of glucose nadir in some dogs
Glargine	Recombinant human analog	Treat diabetes at home Good initial insulin for cats	SC	q12-24h	8-24	8-24	Duration of effect too long for q12h therapy in some cats and dogs; weak glucose-lowering effect and unpredictable timing of glucose nadir in some dogs
Detemir	Recombinant human analog	Treat diabetes at home	SC	q12-24h	8-24	8-24	Duration of effect too long for q12h therapy in some cats and dogs; insulin dosage requirements considerably lower than those seen with other insulin preparations

DKA, Diabetic ketoacidosis; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.

in conjunction with rapid-acting prandial insulin analogs in diabetic humans. Insulin glargine has been modified by replacing the amino acid asparagine with glycine at position A21 of the A chain, and two arginines have been added to the C-terminus of the B chain of insulin—modifications that shift the isoelectric point from a pH of 5.4 toward a neutral pH. This shift makes insulin glargine more soluble at a slightly acidic pH and less soluble at a physiologic pH than native human insulin. The solution in the bottle of glargine is acidic, which keeps glargine soluble and suspended in the solution (i.e., the solution is clear, and the bottle does not need to be rolled before insulin is drawn up into the syringe). Because of this dependency on pH, glargine should not be diluted or mixed with anything that may change the pH of the solution. Glargine forms microprecipitates in the subcutaneous tissue at the site of injection from which small amounts of insulin glargine are slowly released and absorbed into the circulation. Insulin detemir is also a long-acting basal insulin analog in which the amino acid threonine has been removed at B30 and a 14-carbon fatty acid (myristic acid) has been bound to the lysine amino acid at position B29 of the B chain of the insulin molecule. Prolonged action results from a combination of strong self-association at the injection site and binding to albumin, which reduces free insulin detemir concentrations in the circulation. Insulin detemir is a clear, colorless, aqueous neutral solution that does not need to be shaken before drawing up the insulin into the syringe. The manufacturer recommends tht insulin detemir not be mixed or diluted with other insulin preparations. Insulin detemir can be diluted using the Insulin Diluting Medium for NovoRapid® (insulin aspart) and Levemir®(detemir) supplied by Novo Nordisk.

STORAGE AND DILUTION OF INSULIN

Freezing and heating the insulin bottle will inactivate insulin in the bottle. Historically, shaking the bottle of NPH, lente, or PZI insulin was believed to inactivate the insulin, but recent studies performed by the pharmaceutical company have shown that shaking the bottle of lente insulin does not impact insulin action, provides more uniform dispersal of insulin throughout the solution than rolling the bottle, and is currently recommended. Similar recommendations have not yet been reported for NPH and PZI insulins. Although keeping the bottle of insulin at "room temperature" does not inactivate insulin, we routinely instruct clients to store the insulin bottle in the door of the refrigerator to maintain a consistent environment. Some veterinarians advocate replacing insulin with a new bottle every 1 to 2 months to prevent problems caused by loss of activity or sterility. This practice can create financial hardship for some clients and may not be necessary. The shelf life of a bottle of insulin that has been stored appropriately is longer than manufacturer recommendations. We have not appreciated a clinically significant loss of insulin action with time when insulin preparations, including glargine and detemir, are maintained in a constant environment (i.e., refrigerator) and handled appropriately. Routinely purchasing a new bottle of insulin every month may not be necessary, especially if the diabetic dog is doing well. However, development of cloudiness or discoloration suggest contamination, change in pH of the solution (glargine), and/or loss of insulin activity. The bottle of insulin should be discarded and replaced with a new bottle of insulin. Similarly, loss of insulin activity in the bottle should always be considered whenever clinical signs recur, regardless of the quantity of insulin remaining in the bottle.

Dilution of insulin is a common practice, especially in very small dogs and cats. Only diluting solutions provided by the respective company should be used. Although studies evaluating the shelf-life of diluted insulin have not been published, we recommend replacing diluted insulin preparations every 4 to 8 weeks. Even when these guidelines are observed, insufficient amounts of insulin are administered when diluted insulin is used in some dogs and cats, despite appropriate dilution and insulin administration techniques—inadequacies that are corrected when full-strength insulin is used. It is important to remember that insulin glargine is pH-dependent and should not be diluted with solutions that may change the pH of the solution.

INITIAL INSULIN RECOMMENDATIONS FOR DIABETIC DOGS

Once the diagnosis of diabetes is established, dogs should be considered insulin-dependent and treatment with insulin should be initiated. In our opinion, porcine-source lente insulin (Vetsulin, Caninsulin) is the initial insulin of choice for treating newly diagnosed diabetic dogs (see Table 49.3). Recombinant human NPH insulin is also effective, but problems with the short duration of effect are more common with NPH insulin than lente insulin. Studies to date suggest that the median dosage of lente and NPH insulin required to attain glucose control in most diabetic dogs is approximately 0.5 U/kg/injection, with a range of 0.2 to 1 U/kg. One important goal in the initial regulation of the diabetic dog is avoidance of symptomatic hypoglycemia, especially in the home environment. For this reason, our starting insulin dosage is always on the low end of the range (i.e., approximately 0.25 U/kg), and we prefer to start with twice-a-day insulin administration because an overwhelming majority of diabetic dogs require lente and NPH insulin twice a day.

Published experiences with insulin glargine in diabetic dogs is limited. In a study by Fracassi et al. (2012), insulin glargine administered twice a day was effective in improving or maintaining control of glycemia in the majority of diabetic dogs enrolled in the study. By week 24 of the study, 58% and 33% of dogs had attained good or moderate glycemic control, respectively. Insulin dosages required to attain glycemic control were similar to insulin dosages reported with NPH, lente, and PZI insulin (Table 49.4). The timing of the glucose nadir was variable, suggesting that short and especially prolonged duration of action of insulin glargine occurs in diabetic dogs (Fig. 49.2). The authors speculated that the published success rate of other types of insulins (i.e., NPH and lente) was somewhat better than insulin glargine. Our experiences with insulin glargine in dogs have been mixed

TABLE 49.4

Comparison of Insulin Preparation Dosages Required to Attain Control of Glycemia in Diabetic Dogs

INSULIN PREPARATION	NUMBER OF DOGS	INSULIN DOSAGE (U/kg/injection) MEDIAN	RANGE	STUDY
NPH	54	0.8* 0.4+	0.4-1.9 0.3-0.8	Lorenzen, 1992
Lente	35	0.8	0.3-1.4	Monroe et al., 2005
PZI	17	0.9	0.4-1.5	Della-Maggiore et al., 2012
Glargine	12	0.6	0.1-1.1	Fracassi et al., 2012
Detemir	13	0.2	NR	Ford, 2010
Detemir	15	0.3	0.1-0.6	UCD, 2013**

NR: not reported
*Dogs weighing < 15 kg
+Dogs weighing ≥ 15 kg
**UCD, 2013: Insulin dosage required to attain glycemic control in 15 of 24 diabetic dogs treated with insulin detemir at UC Davis veterinary hospital; glycemic control could not be attained using detemir in 9 of the 24 dogs.

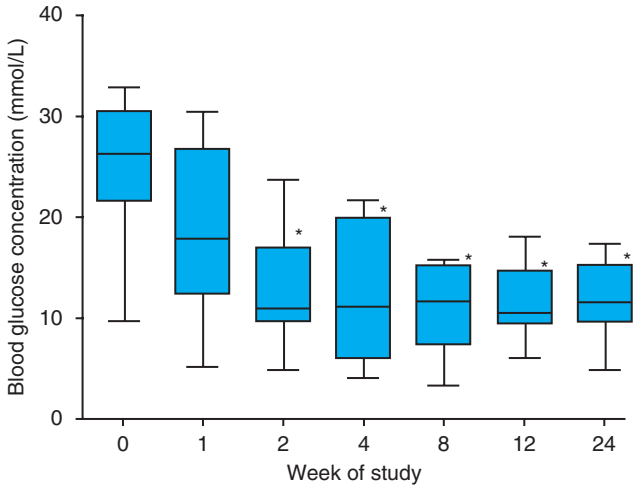


FIG 49.2
Box plots of 12-hour mean blood glucose concentrations in the blood glucose curves for 12 dogs with diabetes mellitus treated by various doses of insulin glargine administration twice daily for 24 weeks. Twelve-hour mean blood glucose concentration is the mean of the seven blood glucose concentrations measured during a 12-hour period. The horizontal line represents the median, the box represents the interquartile range (i.e., 25%-75%), the T-bars represent the main body of data. *=P <0.05. (From Fracassi F et al: Use of insulin glargine in dogs with diabetes mellitus, *Vet Rec* 170:52, 2012.).

and somewhat disappointing. We have been unable to attain good glycemic control in the majority of diabetic dogs treated with insulin glargine. We do not consider insulin glargine a first choice insulin for the treatment of diabetes in dogs but do consider using insulin glargine in diabetic dogs with problems of short duration of effect of NPH and lente insulin and problems with prolonged duration of effect of insulin detemir (see page 826).

Published experiences with insulin detemir in diabetic dogs are also limited. Insulin detemir is currently the longest acting insulin preparation for use in diabetic dogs, with a potential for duration of effect to be 16 hours or longer. The prolonged duration of effect combined with twice a day administration is responsible for lower dosage requirements and a greater likelihood for hypoglyemia with insulin detemir, compared with NPH or lente insulin (see Table 49.4). In an unpublished study, insulin detemir was effective in improving control of glycemia in 13 diabetic dogs managed with home blood glucose monitoring during a 4 to 24 month (median, 10 month) period (Ford et al., 2010). Ten of 13 dogs were previously treated with NPH or lente insulin with poor results. The mean and median insulin dosage on the last week of evaluation was 0.45 and 0.22 U/kg/injection, respectively. Biochemical hypoglycemia (blood glucose < 60 mg/dL; 3.4 mmol/L) was identified in approximately 2% of all blood glucose measurements and occurred on average 7.5 times per dog during the study. Our experiences with insulin detemir in dogs have been mixed but better than our experiences with insulin glargine. The absorption of insulin detemir from the subcutaneous site of injection is variable. In some diabetic dogs the absorption is slow and sustained, resulting in relatively flat blood glucose curves. In other dogs the absorption is similar to that seen with intermediate-acting insulin preparations like lente, resulting in "U"-shaped blood glucose curves. The most common problem with insulin detemir has been hypoglycemia when insulin detemir is given twice a day. We do not consider insulin detemir a first choice insulin for the treatment of diabetes in dogs but consider it the insulin of choice in diabetic dogs with problems of short duration of effect of NPH and lente insulin. Our starting dosage for insulin detemir is 0.1 U/kg twice a day.

Although recombinant human PZI, insulin glargine, and insulin detemir are effective in controlling glycemia in some

diabetic dogs, problems with consistency of effect, variable and unpredictable timing of the glucose nadir, and prolonged duration of effect preclude recommending these insulin preparations for use in the newly diagnosed diabetic dog. However, these insulin preparations should be considered when problems caused by short duration of insulin effect develop with lente or NPH insulin.

DIET

Diet plays an important role in management of the diabetic dog. What diet is ultimately fed is dictated, in part, by the weight of the dog, concurrent disease, and owner and dog preferences. Correction of obesity is the most beneficial step that can be taken to improve control of glycemia. Obesity causes insulin resistance in dogs and is an important factor accounting for variations in response to insulin therapy in diabetic dogs. Weight loss improves insulin resistance in obese diabetic dogs. Weight loss usually requires a combination of the following: restricting caloric intake, feeding low-calorie-dense diets, and increasing caloric expenditure through exercise. The reader is referred to Chapter 51 for more information on treating obesity.

Increasing the fiber content of the diet is beneficial for treating obesity and improving control of glycemia in diabetic dogs. Most major pet food companies offer diets designed for diabetic dogs that contain a mixture of soluble and insoluble fiber sources that slow glucose absorption from the gut and help minimize postprandial hyperglycemia (Box 49.6). Many diets designed for weight loss contain higher levels of insoluble fiber than diabetic diets and lower fat content to decrease the caloric density of the food. These diets may be fed to obese diabetic dogs to promote weight loss. High-fiber diets should not be fed to thin or emaciated diabetic dogs until control of glycemia is established and a normal body weight is attained with a higher-calorie-dense, lower-fiber diet designed for maintenance. Complications of feeding diabetic diets containing high fiber content are listed in Box 49.7. Most of these problems will resolve by changing the type or quantity of fiber consumed (i.e., a change in the diet).

Concurrent disease in which diet is an important aspect of therapy also dictates the type of diet to be fed. For example, diabetic dogs with concurrent chronic pancreatitis or exocrine pancreatic insufficiency (pancreatic acinar atrophy) should be fed a low-fat, low-fiber, highly digestible diet. Diabetic dogs with chronic kidney disease should be fed a lower-protein diet designed for kidney failure. Diabetic dogs with concurrent inflammatory bowel disease may need a hypoallergenic diet to help control inflammation and clinical signs. Whenever possible, dietary therapy for all disorders should be "blended," but if this is not possible, dietary therapy for the most serious disorder should take priority.

EXERCISE

Exercise plays an important role in maintaining glycemic control in the diabetic dog by helping to promote weight loss and by eliminating the insulin resistance induced by obesity.



BOX 49.6

Recommendations for Dietary Treatment of Diabetes Mellitus in Dogs and Cats

- Correct obesity and maintain body weight in an acceptable range (see Chapter 51).
  - Control daily caloric intake.
  - Increase daily exercise.
  - Avoid excessive amounts of insulin.
- Maintain consistency in the timing and caloric content of meals.
  - Feed within the time frame of insulin action.
  - Feed one half the daily caloric intake at the time of each insulin injection with q12h insulin therapy or at the time of the insulin injection and 6 to 10 hours later with q24h insulin therapy.
- Minimize the impact of food on postprandial blood glucose concentrations.
  - Avoid monosaccharides and disaccharides, propylene glycol, and corn syrup.
  - Let "nibbler" cats and dogs nibble throughout the day and night; ensure that other pets do not have access to the food.
  - Increase the fiber content of the diet (dogs).
  - Feed high-protein, low-carbohydrate diets (cats).

Examples of Veterinary Diets for Diabetic Dogs	Examples of Veterinary Diets for Diabetic Cats
Hill's Prescription Diet w/d	High-protein, low-carbohydrate diets:
Hill's Prescription Diet r/d (obese diabetic dog)	Purina DM
Purina DCO	Hill's Prescription Diet MD
Purina OM (obese diabetic dog)	Royal Canin Diabetic
Royal Canin Diabetic	Fiber-containing diets:
Royal Canin Calorie Control CC High Fiber (obese diabetic dog)	Hill's Prescription Diet w/d
Iams Glucose and Weight Control Plus	Hill's Prescription Diet r/d (obese diabetic cat)
	Purina OM (obese diabetic cat)
	Royal Canin Calorie Control (obese diabetic cat)



BOX 49.7

Common Complications Associated With Feeding Diets Containing Increased Quantities of Fiber

- Inapetence caused by poor palatability or boredom with food
- Increased frequency of defecation
- Constipation and obstipation (insoluble fiber)
- Soft stools and diarrhea (soluble fiber)
- Increased flatulence (soluble fiber)
- Weight loss
- Hypoglycemia

Exercise also has a glucose-lowering effect by increasing the mobilization of insulin from its injection site, presumably resulting from increased blood and lymph flow, by increasing blood flow (and therefore insulin delivery) to exercising muscles, and by stimulating glucose transporters in muscle

cells. The daily routine for diabetic dogs should include exercise, preferably at the same time each day and not around the time of peak insulin effect. Strenuous and sporadic exercise can cause severe hypoglycemia and should be avoided. If it is unavoidable, the insulin dose should be decreased in dogs subjected to sporadic strenuous exercise on those days of anticipated increased exercise. The reduction in insulin dose required to prevent hypoglycemia is variable and determined by trial and error. Reducing the insulin dose by 50% initially is recommended, with further adjustments based on the occurrence of symptomatic hypoglycemia and the severity of polyuria and polydipsia that develop during the ensuing 24 to 48 hours, or based on results of blood glucose testing by clients who monitor blood glucose concentrations in their diabetic dog using a portable blood glucose monitor (PBGM). Regardless, clients must be aware of the signs of hypoglycemia and must have a source of glucose readily available to give to their dog should any of these signs develop.

IDENTIFICATION AND CONTROL OF CONCURRENT PROBLEMS

Concurrent disease and insulin-antagonistic drugs can interfere with tissue responsiveness to insulin, resulting in insulin resistance and poor control of diabetes. Concurrent disease and insulin-antagonistic drugs typically cause insulin resistance by altering insulin metabolism (prereceptor problem), by decreasing the concentration or binding affinity of insulin receptors on the cell membrane (receptor problem), by interfering with the insulin receptor signaling cascade (postreceptor problem), or through a combination of these. Depending on the cause, insulin resistance may be mild and easily overcome by increasing the dose of insulin (e.g., obesity); may be severe, causing sustained and marked hyperglycemia regardless of the type and dose of insulin administered (e.g., hyperadrenocorticism); or may fluctuate in severity over time (e.g., chronic pancreatitis; Box 49.8). Some causes of insulin resistance, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids), are readily apparent at the time diabetes is diagnosed. Other causes of insulin resistance are not readily apparent and require an extensive diagnostic evaluation to be identified. In general, any concurrent inflammatory, infectious, hormonal, or neoplastic disorder can cause insulin resistance and can interfere with the effectiveness of insulin therapy. Identification and treatment of concurrent disease play integral roles in the successful management of the diabetic dog. A thorough history and physical examination and a complete diagnostic evaluation are imperative for the newly diagnosed diabetic dog (see the section on diagnosis).

PROTOCOL FOR IDENTIFYING INITIAL INSULIN REQUIREMENTS

Diabetic dogs require several days to equilibrate to changes in insulin dose or preparation. Therefore newly diagnosed diabetic dogs are typically hospitalized for no longer than 48 hours to finish the diagnostic evaluation of the dog, begin insulin therapy, and evaluate the initial glycemic response to the insulin. The intent is to identify low blood glucose concentrations (i.e., blood glucose < 80 mg/dL) in those dogs that are unusually sensitive to the actions of insulin and to modify the insulin dose in those dogs that remain hyperglycemic during the first few days of insulin therapy. The objective during this first visit is *not* to establish perfect glycemic control before sending the dog home. Rather, the objectives are to begin to reverse the metabolic derangements induced by the disease, to allow the dog to equilibrate to the insulin and the change in diet, to teach the client how to administer insulin, and to give the client a few days to become accustomed to treating the diabetic dog at home. Additional adjustments in insulin therapy are made on subsequent evaluations once the client and the pet have become accustomed to the treatment regimen. Glycemic control is attained when clinical signs of diabetes have resolved; the pet is healthy and interactive in the home; its body weight is stable (unless the dog is undergoing weight loss to correct obesity); the client is satisfied with the progress of therapy; and, if possible, blood glucose concentrations range between 100 and 250 mg/dL throughout the day. The goals of therapy are explained to the client; changes in insulin dose and possibly in insulin type are common and should be anticipated by the client. If the dog remains poorly controlled, the dose of insulin is gradually increased by 1 to 5 U/injection (depending on the size of the dog) each week until control is attained. This gradual increase in dose helps prevent hypoglycemia. Control of glycemia can be established in most dogs using insulin doses in the range of 1 U of insulin/kg or less (median, 0.5 U/kg) administered twice each day. If the insulin dose exceeds 1 U/kg/injection without adequate glycemic control, further investigations are indicated to determine the reason

BOX 49.8

Recognized Causes of Insulin Resistance in Diabetic Dogs and Cats

Disorders Typically Causing Severe Insulin Resistance	Disorders Typically Causing Mild or Fluctuating Insulin Resistance
Hyperadrenocorticism	Obesity
Acromegaly (cat)	Infection
Diestrus in intact female dog (causes increase in serum progesterone and growth hormone)	Chronic inflammation
	Chronic pancreatitis
	Chronic inflammatory bowel disease
Progesterone-secreting adrenocortical carcinoma	Disease of the oral cavity
	Chronic kidney disease
Diabetogenic drugs (most notably glucocorticoids and progestins)	Hepatobiliary disease
	Cardiac disease
	Hypothyroidism
	Hyperthyroidism
	Pancreatic exocrine insufficiency
	Hyperlipidemia
	Neoplasia
	Glucagonoma
	Pheochromocytoma

for treatment failure (see the section on complications of insulin therapy). If hypoglycemia is noted clinically or biochemically at any time, the insulin dosage should be decreased and further adjustments in the insulin dose made as needed to attain glycemic control.

Many factors affect the dog's glycemic control from day to day, including variations in insulin administration and absorption, dietary indiscretions and caloric intake, amount of exercise, and variables that affect insulin responsiveness (e.g., stress, concurrent inflammation, infection). As a consequence, the insulin dosage required to maintain glycemic control typically changes with time. Initially, a fixed dose of insulin is administered at home and changes are made only after the client consults with the veterinarian. As the insulin dose range required to maintain glycemic control becomes apparent, and as confidence is gained in the client's ability to recognize signs of hypoglycemia and hyperglycemia, the client is eventually allowed to make *slight* adjustments in the insulin dose at home on the basis of clinical observations of the pet's well-being and ideally results of home blood glucose monitoring.

Techniques for Monitoring Diabetic Control

The basic objective of insulin therapy is to eliminate the clinical signs of diabetes mellitus while avoiding or delaying the onset of common complications associated with the disease (see Box 49.5). Blindness caused by cataract formation is inevitable for most diabetic dogs but can be delayed if good glycemic control can be established and wide fluctuations in the blood glucose concentration avoided (see page 828). Complications to avoid include poor haircoat and unthrifty appearance, weight loss, hypoglycemia, recurring ketosis, and recurrence of polyuria and polydipsia. The devastating chronic complications of human diabetes (e.g., diabetic nephropathy, atherosclerosis) require years to develop and become clinically relevant and are uncommon in diabetic dogs, in part, because diabetes is diagnosed in older dogs. As such, the need to establish nearly normal blood glucose concentrations is not necessary in diabetic dogs. Most clients are happy and most dogs are healthy and relatively asymptomatic if most blood glucose concentrations are kept between 100 mg/dL and 250 mg/dL.

HISTORY AND PHYSICAL EXAMINATION

The most important initial parameters for assessing control of glycemia are the client's subjective opinion of severity of clinical signs and overall health of the pet, findings on physical examination, and stability of body weight. If the client is happy with the results of treatment, the physical examination is supportive of good glycemic control, and the body weight is stable, the diabetic dog is usually adequately controlled. Measurement of serum fructosamine concentrations can add further objective evidence for the status of glycemic control (discussed in greater detail later). Poor control of glycemia should be suspected and additional diagnostics (e.g., serial blood glucose curve) or a change in insulin therapy considered if the client reports clinical signs suggestive of hyperglycemia or hypoglycemia, if the physical examination identifies problems consistent with poor control of glycemia (e.g., thin appearance, poor haircoat), or if the dog is losing weight.

SINGLE BLOOD GLUCOSE DETERMINATION

Measuring a single blood glucose concentration is helpful only if hypoglycemia is identified. Documenting hypoglycemia supports insulin overdosage and the need to decrease the insulin dose, especially if glycemic control is poor. In contrast, documenting an increased blood glucose concentration does not, *by itself,* confirm poor control of glycemia. Stress or excitement can cause marked hyperglycemia, which does not reflect the dog's responsiveness to insulin and can lead to the erroneous belief that the diabetic dog is poorly controlled. If a discrepancy exists between the history, physical examination findings, and blood glucose concentration, or if the dog is fractious, aggressive, excited, or scared and the blood glucose concentration is known to be unreliable, serum fructosamine concentration should be measured for further evaluation of the status of glycemic control. In addition, a single blood glucose concentration is not reliable for evaluating the effects of a given type and dose of insulin in a poorly controlled diabetic dog (see the section on serial blood glucose curve).

SERUM FRUCTOSAMINE CONCENTRATION

Fructosamines are glycated proteins that result from an irreversible, nonenzymatic, insulin-independent binding of glucose to serum proteins. The extent of glycosylation of serum proteins is directly related to the blood glucose concentration; the higher the average blood glucose concentration during the preceding 2 to 3 weeks, the higher the serum fructosamine concentration and vice versa. Serum fructosamine concentration is not affected by acute increases in the blood glucose concentration, as occurs with stress- or excitement-induced hyperglycemia, but can be affected by concurrent hypoalbuminemia, hypoproteinemia, hypertriglyceridemia, hyperthyroidism (cats), hypothyroidism, azotemia, prolonged storage at room temperature, and interfering substances such as hemolysis (Table 49.5). Serum fructosamine concentrations can be measured during the routine evaluation of glycemic control in a diabetic dog; to clarify the effect of stress or excitement on blood glucose concentrations; to clarify discrepancies between the history, physical examination findings, and serial blood glucose concentrations; and to assess the effectiveness of changes in insulin therapy.

Fructosamine is measured in serum, which should be frozen and shipped on cold packs overnight to the laboratory. Although freezing does not cause a significant change in results, prolonged storage of serum at room temperature or in the refrigerator can decrease serum fructosamine results. Each laboratory should furnish its own reference

TABLE 49.5

Sample Handling, Methodology, and Normal Values for Serum Fructosamine Concentrations Measured in Our Laboratory

	FRUCTOSAMINE
Blood sample	1-2 mL; allow to clot, obtain serum
Sample handling	Freeze until assayed
Methodology	Automated colorimetric assay using nitroblue tetrazolium chloride
Factors affecting results	Hypoalbuminemia (decreased), hyperlipidemia (mild decrease—dogs), hemolysis-decrease, zotemia (mild decrease—dogs), hyperthyroidism (decreased—cats), hypothyroidism (increased—dogs), obesity (mild increase—cats), storage at room temperature (decreased)
Normal range	225-365 µmol/L (dogs) 190-365 µmol/L (cats)
Interpretation in Diabetic Dogs and Cats	
Excellent control	350-400 µmol/L
Good control	400-450 µmol/L
Fair control	450-500 µmol/L
Poor control	>500 µmol/L
Prolonged hypoglycemia	<300 µmol/L
DDiabetic remission (cats)	<300 µmol/L

range. In our laboratory the reference range for serum fructosamine in dogs is 225 to 365 µmol/L—a range determined in healthy dogs with persistently normal blood glucose concentrations. Interpretation of serum fructosamine in a diabetic dog must take into consideration the fact that hyperglycemia is common, even in well-controlled diabetic dogs. Most clients are happy with the pet's response to insulin treatment if serum fructosamine concentrations can be kept between 350 and 450 µmol/L. Values greater than 500 µmol/L suggest inadequate control of the diabetic state, and values greater than 600 µmol/L indicate serious lack of glycemic control. Serum fructosamine concentrations in the lower half of the reference range (i.e., <300 µmol/L) or below the reference range should raise concern about significant periods of hypoglycemia in the diabetic dog or concurrent problems that decrease the serum fructosamine concentration. Increased serum fructosamine concentrations (i.e., >500 µmol/L) suggest poor control of glycemia and a need for insulin adjustments but do not identify the underlying problem.

Serum fructosamine concentrations should not be used as the sole indicator of status of glycemic control but rather should be interpreted in conjunction with the history, findings on physical examination, and stability of body weight. A disconnect between interpretation of the serum fructosamine concentration and the clinical picture or, more commonly, results of blood glucose concentrations may occur in some diabetic dogs. When a low serum fructosamine concentration is identified in a dog with suspected poor control of the diabetic state, reasons for a low fructosamine test result (see Table 49.5) or an increase in serum glucose concentrations should be considered, and vice versa when a high serum fructosamine concentration is identified in a dog with suspected good control of the diabetic state. Whenever information used to assess glycemic control conflicts, we rely most heavily on history, physical examination findings, and stability of body weight when deciding whether a change in insulin therapy is indicated.

URINE GLUCOSE MONITORING

Occasional monitoring of urine for glycosuria and ketonuria is helpful in diabetic dogs that have problems with recurring ketosis or hypoglycemia to identify ketonuria or persistent negative glycosuria, respectively. The client is instructed not to adjust daily insulin doses on the basis of morning urine glucose measurements, except to decrease the insulin dose in dogs with recurring hypoglycemia and persistent negative glycosuria. Many diabetic dogs develop complications because clients were misled by morning urine glucose concentrations and increase the insulin dose, which eventually results in insulin overdosing, hypoglycemia, and glucose counter regulation (see page 825). Persistent glycosuria throughout the day and night suggests inadequate control of the diabetic state and the need for a more complete evaluation of diabetic control using other techniques discussed in this section.

SERIAL BLOOD GLUCOSE CURVES

If an adjustment in insulin therapy is deemed necessary after a review of the history, physical examination findings, and changes in body weight, a serial blood glucose curve should be generated to provide guidance in making the adjustment, unless blood glucose measurements are unreliable because of stress, aggression, or excitement. The serial blood glucose curve provides guidelines for making adjustments in insulin therapy. Evaluation of a serial blood glucose curve is mandatory during the initial regulation of the diabetic dog and is necessary in the dog in which clinical manifestations of hyperglycemia or hypoglycemia have developed. Reliance on history, physical examination findings, and body weight to determine when a blood glucose curve is needed helps reduce the frequency of performing glucose curves, thereby minimizing the animal's aversion to these evaluations and improving the chances of obtaining meaningful results when a blood glucose curve is needed. Insulin therapy is adjusted

according to interpretation of a single serial blood glucose curve, and the impact of the change is initially assessed by client perceptions of clinical response. If problems persist, the blood glucose curve can be repeated. If possible, performing blood glucose curves on multiple, consecutive days should be avoided because it promotes stress-induced hyperglycemia. Information gained from a prior serial blood glucose curve should never be assumed to be reproducible on subsequent curves. Lack of consistency in the results of serial blood glucose curves is a source of frustration for many veterinarians and is a direct reflection of all the variables that affect the blood glucose concentration in diabetic dogs. Daily self-monitoring of blood glucose concentrations and adjustments in insulin dose are used in human patients with diabetes to minimize the effects of these variables on control of glycemia. A similar approach for diabetic dogs and cats is becoming more common with the advent of home blood glucose monitoring of diabetic dogs and cats by their owners (see next section).

When a blood glucose curve is generated, the insulin and feeding schedule used by the client should be maintained and the dog dropped off at the hospital early in the morning. Owners of diabetic dogs who are finicky eaters should feed their pet at their home, not at the hospital. Inappetence can profoundly alter the results of a serial blood glucose curve (Fig. 49.3). The first blood sample for blood glucose measurement is obtained when the dog enters the hospital, and subsequent blood samples are typically obtained every 2 hours throughout the day for glucose determination. Glucose measurements should be done more frequently than every 2 hours if the blood glucose is dropping quickly or hypoglycemia is identified. If there are concerns regarding the client's technique for administering insulin, the client can administer insulin (using his or her own insulin and syringe) in the hospital *after* the initial blood glucose is obtained or can demonstrate his or her technique using sterile saline after arriving to pick up the pet at the end of the day. The veterinarian or a veterinary technician should closely evaluate the entire insulin administration procedure. By measuring blood glucose concentration every 2 hours throughout the day, the clinician will be able to determine if the insulin is effective and identify the glucose nadir, time of peak insulin effect, approximate duration of insulin effect, and range of blood glucose concentrations in that particular dog. Identifying the glucose nadir and the time of the glucose nadir in relation to the time of insulin administration is critical for assessing the duration of insulin effect. If the glucose nadir has not been identified by the time of the next insulin injection, the glucose curve should be continued, the scheduled insulin injection aborted, and the dog fed its evening meal (see the discussion of the prolonged duration of insulin effect, p. 826). Obtaining only one or two blood glucose concentrations during the day has not been reliable for evaluating the effect of a given insulin dose (Fig. 49.4). Persistent poor control of the diabetic state often stems from misinterpretation of the effects of insulin based on assessment of only one or two blood glucose concentrations.

Changes in blood glucose concentrations are typically assumed to be comparable following the morning and evening administration of insulin so most dogs receive the same dose of insulin morning and evening (Mori et al., 2013). This assumption is fine as long as the dog is doing

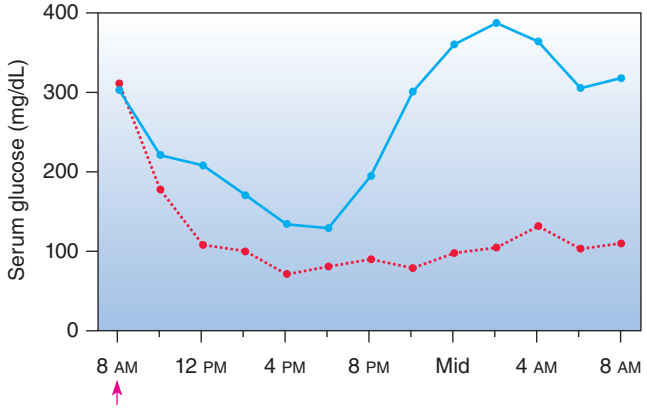


FIG 49.3
Mean blood glucose concentrations in eight diabetic dogs after administration of NPH insulin (↑) and the feeding of equally sized meals at 8 AM and 6 PM *(blue line)* or feeding of nothing *(red line)* during the 24 hours of blood sampling.

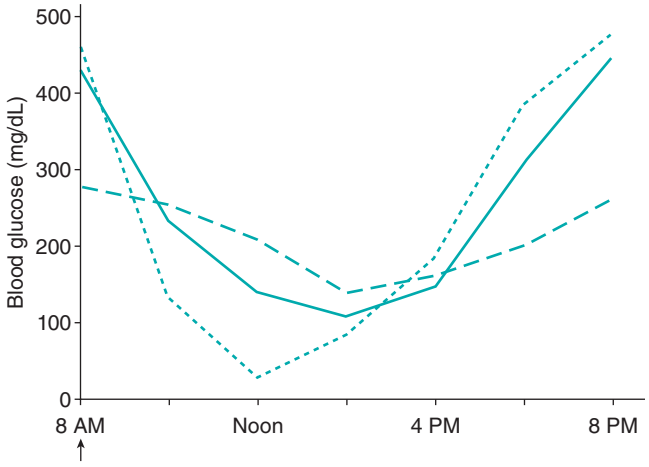


FIG 49.4
Blood glucose concentration curve in a Dachshund receiving 0.8 U of recombinant human lente insulin per kilogram of body weight twice a day *(solid line)*, a Miniature Poodle receiving 0.6 U of recombinant human lente insulin per kilogram of body weight twice a day *(dashed line)*, and a Terrier-mix receiving 1.1 U of recombinant human lente insulin per kilogram of body weight twice a day *(dotted line)*. Insulin and food were given to each dog at 8 AM. Interpretation of the blood glucose curves suggests a short duration of insulin effect in the Dachshund, insulin underdosing in the Miniature Poodle, and the Somogyi response in the Terrier-mix. Blood glucose concentrations were similar in all dogs at 2 PM and 4 PM; glucose results at these times do not establish the diagnosis in any of the dogs.

well. However, different blood glucose results during the day versus the night should be suspected if polyuria and polydipsia persist despite blood glucose concentrations that are close to acceptable during the day, especially if polyuria and polydipsia are worse at night. For these cases, obtaining a 24-hour blood glucose curve or use of a continuous glucose monitoring device should be considered.

Blood glucose concentrations are typically determined by either a point-of-care glucose analyzer or handheld PBGM device. The accuracy of commercially available PBGM devices designed for use in human diabetics varies considerably when used in diabetic dogs, compared with results using standard reference methods (i.e., glucose oxidase and hexokinase methods) (Cohn et al., 2000; Cohen et al., 2009; Wess and Reusch., 2000). Blood glucose values determined by most PBGM devices designed for use in human diabetics are typically lower than actual glucose values determined by reference methods and the difference between the actual glucose value and value obtained from the PBGM increases as hyperglycemia worsens. This bias may result in an incorrect diagnosis of hypoglycemia or the misperception that glycemic control is better than it actually is. Failure to consider this rror could result in insulin underdosage and the potential for persistence of clinical signs despite apparently acceptable blood glucose results. One exception is the AlphaTRAK® by Abbott Laboratories, a PBGM device designed for use in diabetic dogs and cats. Accuracy of this PBGM device is very good, but glucose values may be higher or lower than glucose values measured by reference methodologies on the same blood sample, forcing the veterinarian to accept the blood glucose concentration at face value (Cohen et al., 2009). Haematocrit may also affect the results of PBGMs. In one study, results of the AlphaTRAK® were less accurate compared with a laboratory reference method in blood samples with a lower haematocrit (<30%) but not an increased haematocrit (>50%), whereas results from a PBGM for use in humans was less accurate with increased haematocrit but not a decreased haematocrit (Paul et al., 2011).

Home Blood Glucose Monitoring

Hyperglycemia induced by stress, aggression, or excitement is the single biggest problem affecting accuracy of the serial blood glucose curves (Fig. 49.5). The biggest factors causing stress-induced hyperglycemia are frequent hospitalizations and multiple venipunctures. An alternative to hospital-generated blood glucose curves is to have the client generate the blood glucose curve at home using the ear or metacarpal, metatarsal or foot pad prick technique and a PBGM device that allows the client to touch the drop of blood on the ear or foot pad with the end of the glucose test strip. There are several excellent online sites that demonstrate home blood glucose monitoring techniques for the owner of a diabetic dog (e.g., Abbott Laboratories website for the AlphaTRAK2®). This technique should be considered for diabetic dogs in which the reliability of blood glucose results generated in the veterinary hospital is questionable. Home blood glucose monitoring is also becoming a routine monitoring technique

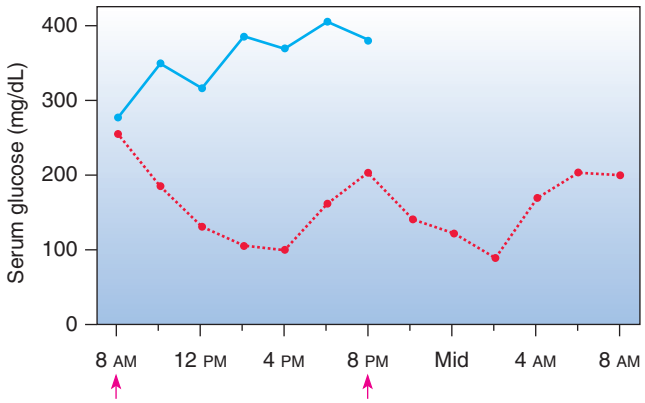


FIG 49.5
Blood glucose concentration curves in a fractious Terrier-mix. The same dose of NPH insulin was given for each curve. One glucose curve *(blue line)* was obtained with the dog in an agitated state, requiring physical restraint each time a blood specimen was obtained; blood for the other glucose curve *(red line)* was obtained through a jugular catheter with minimal to no restraint and with the dog in a quiet state. ↑, Insulin administration and food.

used by clients. The biggest problem has been overzealous owners who monitor blood glucose concentrations too frequently and begin to interpret results and adjust the insulin dose without consulting their veterinarian, a practice that ultimately leads to insulin overdosage. The reader is referred to page 835 for more information on home blood glucose monitoring.

Continuous Glucose-Monitoring Systems

Continuous glucose-monitoring (CGM) systems are frequently used to monitor glucose concentrations in diabetic humans and are beginning to be used in diabetic dogs and cats. CGM systems measure interstitial fluid glucose concentrations rather than blood glucose concentrations. The correlation between interstitial and blood glucose concentrations is good. A frequently used CGM system (Guardian REAL-time, Medtronic, Northridge, Calif) measures interstitial glucose with a small, flexible sensor inserted through the skin into the subcutaneous space and secured to the skin. Interstitial glucose is detected via the glucose oxidase reaction, and detection occurs entirely at the electrode within the sensor component. Glucose results are transmitted by a wireless transmitter to a pager-sized monitor. The interstitial fluid glucose concentration is recorded and stored every 5 minutes, and the data can be downloaded to a computer for analysis (Fig. 49.6). Calibration of the CGM system is required at initiation and once every 12 hours. The working glucose range for the CGM system is 40 to 400 mg/dL. Studies to date suggest that the primary advantage of continuous glucose monitoring is detection of hypoglycemic periods that are not detected with serial blood glucose curves and a PBGM device. (See Suggested Readings for more information on continuous glucose monitoring.)

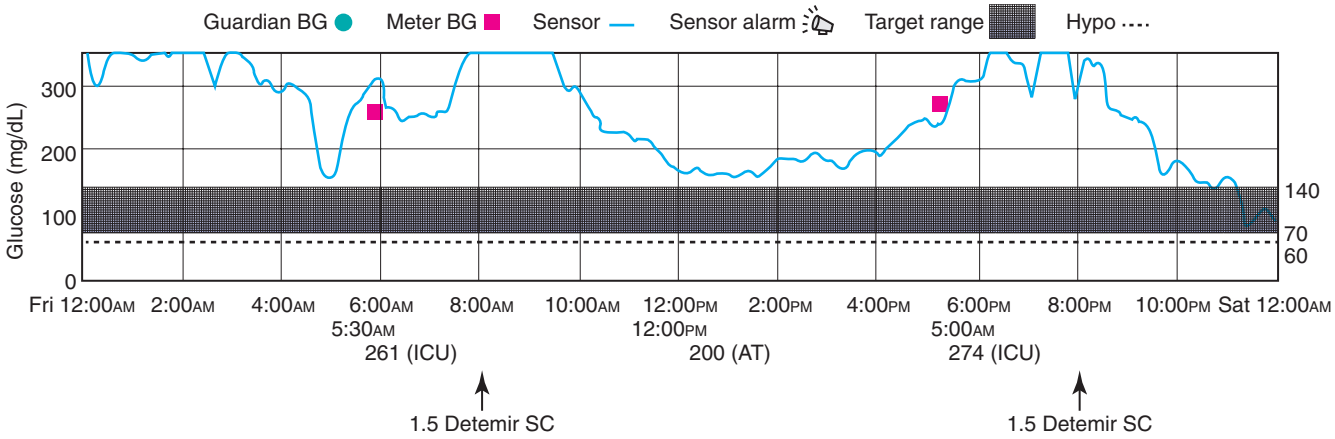


FIG 49.6
Example of results of continuous glucose monitoring using the Guardian EAL-Time monitor in a female-spayed Miniature Schnauzer with persistent polyuria, polydipsia and weight loss despite various doses of insulin detemir twice daily. Hypoglycemia and possible glucose counter-regulation was suspected but blood glucose concentrations obtained by venipuncture were always increased. Stress-induced hyperglycemia was believed to be interfering with glucose results. Results of continuous glucose monitoring with minimal blood sampling documented efficacy of insulin detemir and the occurrence of hypoglycemia in the dog. (From Feldman EC et al: *Canine and feline endocrinology,* ed 4, St Louis, 2015, Elsevier Saunders.)

Interpreting the Serial Blood Glucose Curve

An overview of how to interpret results of a serial blood glucose curve is provided in Fig. 49.7. The *ideal* goal is to maintain the blood glucose concentration between 80 mg/dL and 250 mg/dL during the time period between insulin injections, although many diabetic dogs do well despite blood glucose concentrations consistently in the high 100s to low 300s. The goal of insulin therapy is to have the highest blood glucose concentration less than 300 mg/dL, the glucose nadir between 80 and 130 mg/dL, and the mean of all blood glucose values measured that day at less than 250 mg/dL. Typically, the highest blood glucose concentrations occur at the time of each insulin injection, but this is not always so. If the blood glucose nadir is greater than 130 mg/dL, the insulin dose may need to be increased, and if the nadir is less than 60 mg/dL, the insulin dose should be decreased.

Duration of insulin effect can be assessed if the glucose nadir is greater than 80 mg/dL and no rapid decrease in blood glucose concentration is noted after insulin administration. Assessment of duration of insulin effect may not be valid when blood glucose decreases to less than 60 mg/dL or decreases rapidly because of the potential induction of glucose counterregulation (i.e., secretion of glucagon, epinephrine, and cortisol), which can falsely decrease the apparent duration of insulin effect (see p. 825). A rough approximation of the duration of effect of insulin can be gained by examining the time of the glucose nadir. For most well-controlled diabetic dogs, the initial blood glucose concentration near the time of insulin administration is less than 300 mg/dL, and the glucose nadir occurs approximately 8 hours after injection of insulin. An initial blood glucose concentration greater than 300 mg/dL, combined with a glucose nadir occurring less than 8 hours after insulin administration and subsequent blood glucose concentrations increasing to greater than 300 mg/dL, is supportive of a short duration of insulin effect. A glucose nadir that occurs 12 hours or longer after insulin administration is supportive of a prolonged duration of insulin effect. Dogs may develop hypoglycemia (blood glucose < 60 mg/dL) and initiate glucose counterregulation if the duration of insulin effect is greater than 14 hours and insulin is administered twice a day (Fig. 49.8).

Role of Serum Fructosamine in Aggressive, Excitable, or Stressed Dogs

Blood glucose curves are unreliable in aggressive, excitable, or stressed dogs because of problems related to stress-induced hyperglycemia. Hyperglycemia presumably develops as a result of increased catecholamine and glucocorticoid secretion and can significantly increase the blood glucose concentration despite insulin administration. In these dogs home blood glucose monitoring by the client may provide accurate blood glucose results. If home blood glucose monitoring is not available, the clinician must make an educated guess as to where the problem lies (e.g., wrong type of insulin, low dose), make an adjustment in therapy, and rely on changes in serum fructosamine to assess the benefit of the change in treatment. The reader is referred to page 818 for more information on the use of serum fructosamine in diabetic dogs and cats with stress-induced hyperglycemia.

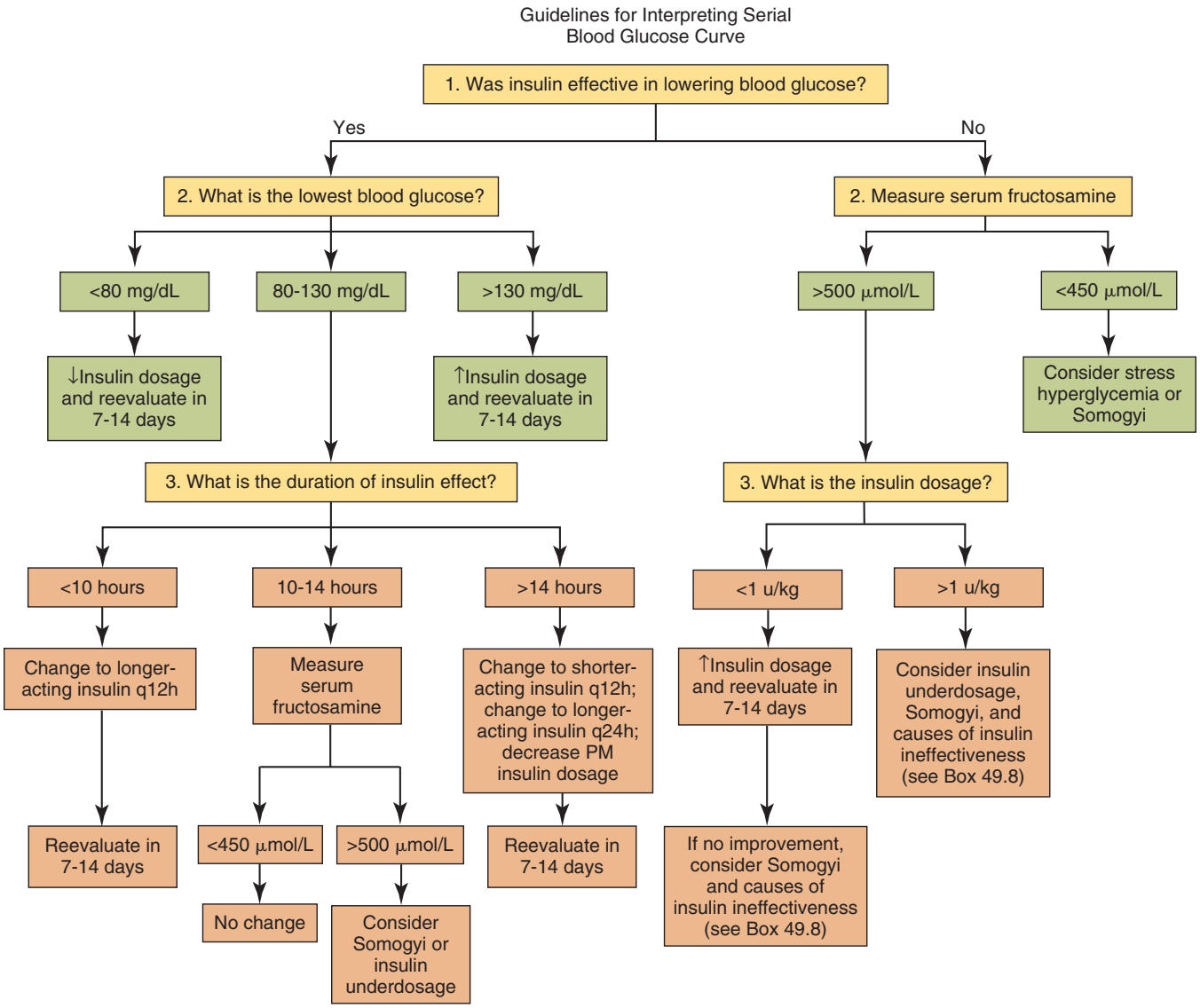


FIG 49.7
Algorithm for interpreting results of a blood glucose concentration curve.

INSULIN THERAPY DURING SURGERY

Generally, elective surgery should be delayed in diabetic dogs until the animal's clinical condition is stable and the diabetic state is controlled with insulin. Exceptions are those situations in which surgery is required to eliminate insulin resistance (e.g., ovariohysterectomy in a diestrus bitch) or to save the animal's life. The surgery itself does not pose a greater risk in a stable diabetic dog than in a nondiabetic dog. The concern is the interplay between insulin therapy and the lack of food intake during the perioperative period. The stress of anesthesia and surgery also causes the release of diabetogenic hormones, which promote ketogenesis. Insulin must be administered during the perioperative period to prevent severe hyperglycemia and to minimize ketone formation. To compensate for the lack of food intake and prevent hypoglycemia, the amount of insulin administered during the perioperative period is decreased and IV dextrose is administered when needed.

We use the following protocol during the perioperative period in dogs and cats undergoing surgery. The day before surgery the dog or cat is given its normal dose of insulin and fed as usual. Food is withheld after 10 PM. On the morning of the procedure, the blood glucose concentration is measured before the dog or cat is given insulin. If the blood glucose concentration is less than 100 mg/dL, insulin is not given and an IV infusion of 5% dextrose is initiated. If the blood glucose concentration is between 100 and 200 mg/dL, one quarter of the animal's usual morning dose of insulin is given and an IV infusion of dextrose is initiated. If the blood glucose concentration is greater than 200 mg/dL, one half of the usual morning dose of insulin is given, but the IV dextrose infusion is withheld until the blood glucose

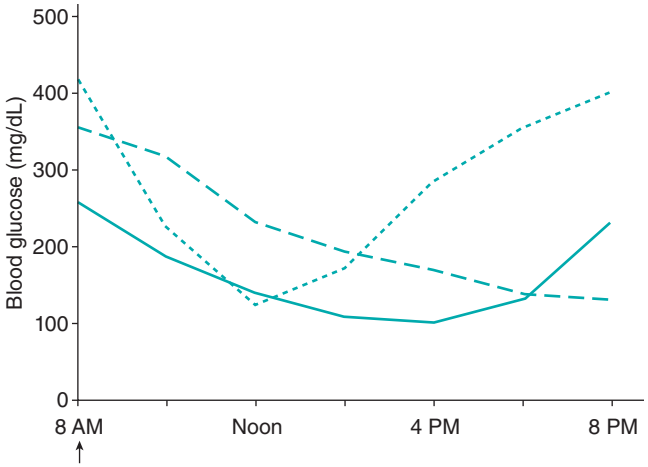


FIG 49.8
Blood glucose concentration curves obtained from three diabetic dogs treated with recombinant human lente insulin twice a day, illustrating a difference between dogs in the duration of insulin effect. The insulin is effective in lowering the blood glucose concentration in all dogs, and the blood glucose nadir is between 100 and 175 mg/dL for the dogs. However, the duration of insulin effect is approximately 12 hours *(solid line)* in one dog with good control of glycemia (ideal duration of effect), approximately 8 hours *(dotted line)* in one dog with persistently poor control of glycemia (short duration of effect), and longer than 12 hours *(dashed line)* in one dog with a history of good days and bad days of glycemic control (prolonged duration of effect)—a history suggestive of the Somogyi response (see Fig. 49.9).

concentration is less than 150 mg/dL. In all three situations the blood glucose concentration is measured every 30 to 60 minutes during the surgical procedure. The goal is to maintain the blood glucose concentration at between 150 and 250 mg/dL during the perioperative period. A 5% dextrose infusion is administered intravenously as needed to correct or prevent hypoglycemia. When the blood glucose concentration exceeds 300 mg/dL, the dextrose infusion should be discontinued and the blood glucose concentration evaluated 30 and 60 minutes later. If the blood glucose concentration remains greater than 300 mg/dL, regular crystalline insulin is administered intramuscularly at approximately 20% of the dose of the long-acting insulin used at home. Subsequent doses of regular crystalline insulin should be given no more frequently than every 4 hours (every 6 hours if administered subcutaneously), and the dose should be adjusted on the basis of the effect of the first insulin injection on the blood glucose concentration.

On the day after surgery the diabetic dog or cat can usually be returned to the routine schedule of insulin administration and feeding. An animal that is not eating can be maintained with IV dextrose infusions and regular crystalline insulin injections given subcutaneously every 6 to 8 hours. Once the animal is eating regularly, it can be returned to its normal insulin and feeding schedule.

COMPLICATIONS OF INSULIN THERAPY

Hypoglycemia

Hypoglycemia is a common complication of insulin therapy. Signs of hypoglycemia are most apt to occur after sudden large increases in the insulin dose, with excessive overlap of insulin action in dogs receiving insulin twice a day, after prolonged inappetence, during unusually strenuous exercise, following sudden improvement in concurrent insulin resistance, and in insulin-treated cats that have undergone diabetic remission. In these situations severe hypoglycemia may occur before glucose counterregulation (i.e., secretion of glucagon, epinephrine, and cortisol) is able to compensate for and reverse hypoglycemia. The occurrence and severity of clinical signs are dependent on the rate of blood glucose decline and the severity of hypoglycemia. In many diabetic dogs, signs of hypoglycemia are not apparent to clients, and hypoglycemia is identified during evaluation of a serial blood glucose curve or is suspected when a low serum fructosamine concentration is identified. Clinical signs and treatment of hypoglycemia are discussed on page 806. If clinical signs of hypoglycemia have occurred, insulin therapy should be stopped until hyperglycemia and glycosuria recur. Urine glucose testing by the owner with the dog in the home environment is useful for identifying when glycosuria recurs. The adjustment in the insulin dose is somewhat arbitrary; as a general rule of thumb, the insulin dose initially should be decreased by 25% to 50% and subsequent adjustments in the dose based on clinical response and results of blood glucose measurements. Failure of glycosuria to recur after a hypoglycemic episode suggests diabetic remission or impaired glucose counterregulation.

Recurrence of Clinical Signs

Recurrence or persistence of clinical signs is perhaps the most common complication of insulin therapy in diabetic dogs. This is usually caused by problems with client technique in administering insulin; problems with insulin therapy related to the insulin type, dose, or frequency of administration; or problems with responsiveness to insulin caused by concurrent inflammatory, infectious, neoplastic, or hormonal disorders (i.e., insulin resistance).

Problems with client administration and insulin activity

Failure to administer an appropriate dose of biologically active insulin will result in recurrence or persistence of clinical signs. Common reasons include administration of biologically inactive (e.g., outdated, previously heated or frozen) insulin, administration of diluted insulin, use of inappropriate insulin syringes for the concentration of insulin (e.g., U100 syringe with U40 insulin), and problems with the insulin administration technique (e.g., failure to correctly read the insulin syringe, inappropriate injection technique). These problems are identified by evaluating the client's insulin administration technique and by administering new undiluted insulin and measuring several blood glucose concentrations throughout the day.

Problems with the insulin treatment regimen

The most common problems with the insulin treatment regimen in the dog include insulin underdosage, insulin overdosage causing hypoglycemia and glucose counterregulation, short duration of effect of lente or NPH insulin, prolonged duration of effect of insulin glargine and insulin detemir, and once-daily insulin administration. Discrepancies in the parameters used to assess glycemic control, resulting in an erroneous belief that the diabetic dog is poorly controlled, should also be considered. This is usually caused by erroneously high blood glucose concentrations induced by stress that suggest insulin ineffectiveness or presence of a concurrent unrecognized disorder that also causes polyuria and polydipsia such as early renal insufficiency. When evaluating a diabetic dog for suspected insulin ineffectiveness, it is important that all parameters used to assess glycemic control be critically analyzed, most notably the owner's perceptions of how their dog is doing in the home environment, findings on physical examination, and changes in body weight. If the history, physical examination, change in body weight, and serum fructosamine concentration suggest poor control of the diabetic state, a diagnostic evaluation to identify the cause is warranted, beginning with evaluation of the owner's insulin administration technique and the biologic activity of the insulin preparation. The insulin treatment regimen should be critically evaluated for possible problems and appropriate changes made in an attempt to improve insulin effectiveness, especially if the history and physical examination do not suggest a concurrent disorder causing insulin resistance.

Insulin underdosing

Control of glycemia can be established in most dogs with less than 1 U of insulin/kg of body weight (median, 0.5 U/kg) administered twice daily. An inadequate dose of insulin in conjunction with once-daily insulin therapy is a common cause for persistence of clinical signs. In general, insulin underdosing should be considered if the insulin dose is less than 1 U/kg and the dog is receiving insulin twice a day. If insulin underdosing is suspected, the dose of insulin should be gradually increased by 1 to 5 U/injection (depending on the size of the dog) per week. The effectiveness of the change in therapy should be evaluated by client perception of clinical response and measurement of serial blood glucose concentrations or serum fructosamine concentration. Although some dogs require insulin dosages as high as 1.5 U/kg to attain control of glycemia, other causes of insulin ineffectiveness, most notably occult hypoglycemia inducing glucose counterregulation and concurrent insulin resistance, should be considered once the insulin dose exceeds 1 U/kg/injection, the insulin is being administered every 12 hours, and control of glycemia remains poor.

Insulin overdosing and glucose counterregulation (Somogyi response). The Somogyi response results from a normal physiologic response to impending hypoglycemia induced by excessive insulin. When the blood glucose concentration declines to less than 60 mg/dL, or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones, most notably epinephrine and glucagon, increase the blood glucose concentration, minimize signs of hypoglycemia, and may cause marked hyperglycemia within 12 hours of glucose counterregulation. The hyperglycemia that occurs after hypoglycemia is due, in part, to an inability of the diabetic dog to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration in conjunction with insufficient concentrations of circulating insulin derived from the injected insulin. By the next morning the blood glucose concentration can be extremely elevated (>400 mg/dL), and the morning urine glucose concentration is consistently 1 to 2 g/dL as measured with urine glucose test strips. Unrecognized short duration of insulin effect, combined with insulin dose adjustments based on morning urine glucose concentrations, is historically the most common cause for the Somogyi response in dogs. Currently, the most common event seen with the Somogyi response involves clients who monitor their pet's blood glucose concentration at home and adjust the insulin dose (i.e., increase the dose) without consulting their veterinarian. The increasing use of longer-acting insulin preparations (i.e., insulin glargine, insulin detemir) that have the potential to last longer than 12 hours may dampen the severity of the post-hypoglycemic hyperglycemia historically affiliated with the Somogyi response, presumably because insulin derived from the injected insulin is still present in the circulation. The diabetogenic hormonal response to hypoglycemia is still intact, and persistently increased concentrations of these hormones will still negatively impact control of glycemia, especially if hypoglycemia and the diabetogenic hormonal response reoccur frequently.

Clinical signs of hypoglycemia typically are mild or not recognized by the client; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces the Somogyi response is variable and unpredictable. The Somogyi response should be suspected in poorly controlled diabetic dogs in which insulin dosage exceeds 1 U/kg body weight/injection but can also occur at insulin dosages less than 0.5 U/kg/injection. Toy and miniature breeds of dogs are especially susceptible to development of the Somogyi response with lower than expected doses of insulin.

Diagnosis of the Somogyi response requires demonstration of hypoglycemia (<60 mg/dL) followed by hyperglycemia (>300 mg/dL) after insulin administration (Fig. 49.9). The Somogyi response should also be suspected when the blood glucose concentration decreases rapidly regardless of the glucose nadir (e.g., a drop from 400 to 100 mg/dL in 2-3 hours). If the duration of insulin effect is greater than 12 hours, hypoglycemia often occurs at night after the evening dose of insulin, and the serum glucose concentration is typically greater than 300 mg/dL the next morning. Unfortunately, the diagnosis of the Somogyi response can be elusive, in part, because the glucose-lowering effects of the insulin vary from day to day, and on any given day hypoglycemia is

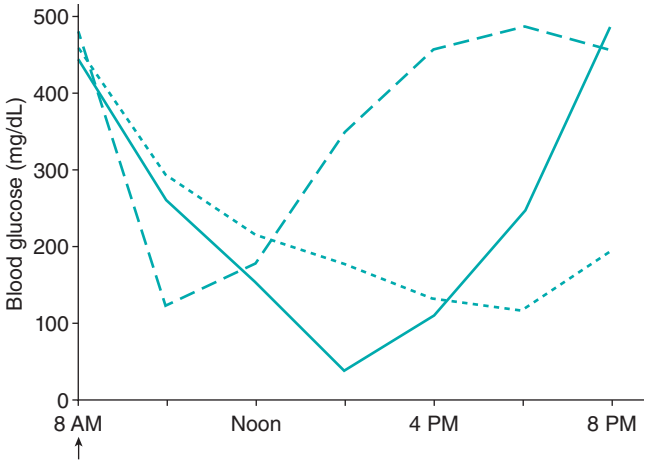


FIG 49.9
Blood glucose concentration curves obtained from three poorly controlled diabetic dogs treated with recombinant human lente insulin twice a day, illustrating the typical blood glucose curves suggestive of the Somogyi response. In one dog *(solid line)* the glucose nadir is less than 80 mg/dL and is followed by a rapid increase in blood glucose concentration. In another dog *(dashed line)* a rapid decrease in blood glucose concentration occurs within 2 hours of insulin administration and is followed by a rapid increase in blood glucose concentration; the rapid decrease in blood glucose stimulates glucose counterregulation, despite maintaining the blood glucose nadir above 80 mg/dL. In one dog *(dotted line)* the blood glucose curve is not suggestive of the Somogyi response, per se. However, the insulin injection causes blood glucose to decrease by approximately 300 mg/dL during the day, and the blood glucose concentration at the time of the evening insulin injection is considerably lower than the 8 am blood glucose concentration. If a similar decrease in blood glucose occurs with the evening insulin injection, hypoglycemia and the Somogyi response would occur at night and would explain the high blood glucose concentration in the morning and the poor control of the diabetic state.

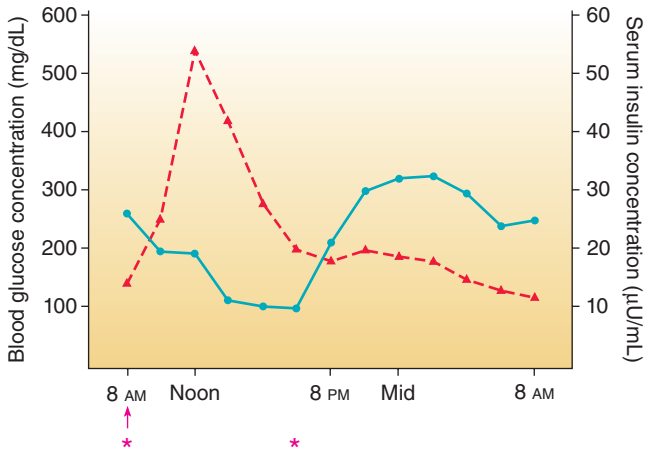


FIG 49.10
Mean blood glucose *(blue line)* and serum insulin *(red line)* concentrations in eight dogs with diabetes mellitus treated with beef/pork-source NPH insulin subcutaneously once daily. The duration of NPH effect is too short, resulting in prolonged periods of hyperglycemia beginning shortly after the evening meal. ↑, Insulin injection; *, equally sized meals consumed.

not always identified. Serum fructosamine concentrations are unpredictable but are usually increased (>500 μmol/L); these results confirm poor glycemic control but do not identify the underlying cause.

Establishing the diagnosis may require several days of hospitalization and serial blood glucose curves—an approach that eventually leads to problems with stress-induced hyperglycemia. An alternative, preferable approach consists of arbitrarily gradually reducing the insulin dose by 1 to 3 U (depending on the size of the dog and the dose of insulin) and having the client evaluate the dog's clinical response over the ensuing 2 to 5 days, specifically as it relates to changes in polyuria and polydipsia. If the severity of polyuria and polydipsia worsens after an initial reduction in the insulin dose, another cause for the insulin ineffectiveness should be pursued. However, if the client reports no change or improvement in polyuria and polydipsia, continued gradual reduction of the insulin dose should be pursued until polyuria and polydipsia worsen again, which identifies an inadequate dose of insulin for the dog. Alternatively, glycemic regulation of the diabetic dog could be started over with an insulin dose of 0.25 U/kg given twice daily.

Short duration of insulin effect

For most dogs the duration of effect of lente and NPH insulin is 10 to 14 hours, and twice-daily insulin administration is effective in controlling blood glucose concentrations. However, in some diabetic dogs the duration of effect of lente and NPH insulin is less than 10 hours—a duration that is too short to prevent periods of hyperglycemia and persistence of clinical signs (Fig. 49.10). Serum fructosamine concentrations are variable but usually greater than 500 μmol/L. A diagnosis of short duration of insulin effect is made by demonstrating an initial blood glucose concentration greater than 300 mg/dL combined with a glucose nadir above 80 mg/dL that occurs less than 8 hours after insulin administration and recurrence of hyperglycemia (>300 mg/dL) within 12 hours of the insulin injection (see Fig. 49.8). Treatment involves a change to longer-acting insulin (Fig. 49.11). Although PZI, insulin glargine, and insulin detemir all have the potential to be effective in diabetic dogs, our preference is to start with insulin detemir at an initial dosage of 0.1 U/kg administered twice a day. The most common problem with insulin detemir is a prolonged duration of effect (>14 hours), which can create issues with hypoglycemia and glucose counterregulation when insulin detemir is given twice a day. Regardless, most diabetic dogs require insulin detemir twice a day to attain diabetic control, and the insulin dosage can be quite small to compensate for prolonged duration of effect in dogs with this problem.

Prolonged duration of insulin effect

In some diabetic dogs the duration of effect of lente or NPH insulin is greater than 12 hours, and twice-daily insulin

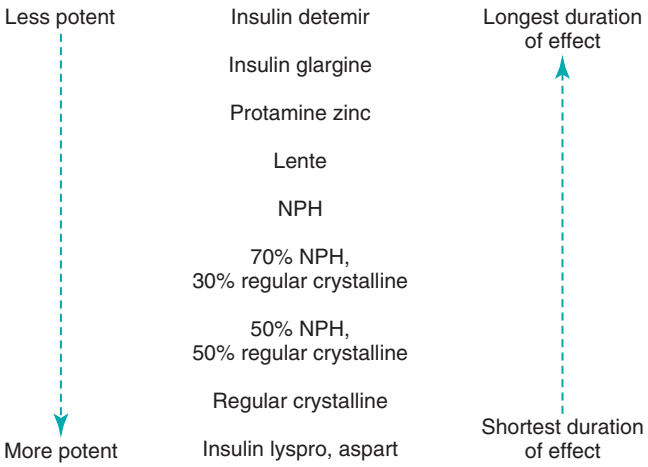


FIG 49.11
Categorization of types of commercial insulin based on potency and duration of effect. An inverse relationship exists between potency and duration of effect.

administration creates problems with hypoglycemia and glucose counterregulation. In these dogs the glucose nadir after the morning administration of insulin typically occurs near or after the time of the evening insulin administration, and the morning blood glucose concentration is usually greater than 300 mg/dL (see Fig. 49.8). Gradually decreasing blood glucose concentrations measured at the time of sequential insulin injections is another indication of prolonged insulin effect. The effectiveness of insulin in lowering the blood glucose concentration is variable from day to day, presumably because of varying concentrations of diabetogenic hormones, the secretion of which was induced by prior hypoglycemia. Serum fructosamine concentrations are variable but usually greater than 500 µmol/L. An effective treatment depends, in part, on the duration of effect of the insulin. An extended blood glucose curve should be generated after administration of insulin once in the morning and feeding of the dog at normal times of the day. This will allow the clinician to evaluate the effect of the evening meal on postprandial blood glucose concentrations and to estimate whether insulin from the morning injection is still present in the blood and capable of preventing a postprandial increase in blood glucose. If postprandial blood glucose increases (typically ≥ 75 mg/dL) within 2 hours of feeding, the duration of effect is close to 12 hours, and manipulation of the insulin dose, timing of the meals in relation to the timing of insulin injections, or both should be tried before a switch is made to longer-acting insulin. Failure of the blood glucose to increase 2 hours or longer after the evening meal is eaten suggests a prolonged duration of effect (i.e., 14 hours or longer). Switching to a longer-acting insulin (e.g., insulin detemir) administered once a day can be tried initially (see Fig. 49.11).

Inadequate insulin absorption

Slow or inadequate absorption of insulin from the subcutaneous site is uncommon in diabetic dogs treated with NPH or lente insulin. Impaired absorption of insulin may occur as a result of thickening of the skin and inflammation of the subcutaneous tissues caused by chronic injection of insulin in the same area of the body. Rotation of the injection site will help prevent this problem.

Allergic reactions to insulin

Allergic reactions to insulin have been poorly documented in diabetic dogs. Pain on injection of insulin is usually caused by inappropriate injection technique, inappropriate site of injection, a reaction to the cold temperature of insulin stored in the refrigerator, the acidic pH of insulin glargine, or issues with behavior and not an adverse reaction to insulin, per se. Chronic injection of insulin in the same area of the body may cause inflammation and thickening of the skin and subcutaneous tissues, and may be caused by an immune reaction to insulin or some other protein (e.g., protamine) in the insulin bottle. Inflammation and thickening of the skin and subcutaneous tissues may impair insulin absorption, resulting in recurrence of clinical signs of diabetes. Rarely, diabetic dogs will develop acute focal subcutaneous edema and swelling at the site of an insulin injection. Insulin allergy is suspected in these animals. Treatment includes switching to a less antigenic insulin and to a more purified insulin preparation. Systemic allergic reactions to insulin in dogs have yet to be identified.

Concurrent disorders causing insulin resistance

Insulin resistance is a condition in which a normal amount of insulin produces a subnormal biologic response. Insulin resistance may result from problems occurring before the interaction of insulin with its receptor, at the receptor, or at steps distal to the interaction of insulin and its receptor. In dogs, receptor and postreceptor abnormalities are usually attributable to obesity, circulating acute phase proteins and inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interleukin-1, interleukin-6) that interfere with insulin signal transduction or a disorder causing excessive or deficient secretion of an insulin-antagonistic hormone, such as cortisol, growth hormone, progesterone, or thyroid hormone. No insulin dose clearly defines insulin resistance. For most diabetic dogs control of glycemia can usually be attained using 1.0 U or less of lente or NPH insulin per kilogram of body weight given twice daily (see Table 49.4). Insulin resistance should be suspected if control of glycemia is poor despite an insulin dosage in excess of 1.5 U/kg, when excessive amounts of insulin (i.e., insulin dosage >1.5 U/kg) are necessary to maintain the blood glucose concentration below 300 mg/dL), and when control of glycemia is erratic and insulin requirements are constantly changing in an attempt to maintain control of glycemia. Failure of the blood glucose concentration to decrease below 300 mg/dL during a serial blood glucose curve is suggestive of, but not definitive for, the presence of insulin resistance. An insulin resistance–type blood glucose curve can also result from other problems with insulin therapy (see Box 49.8), and a decrease in the blood glucose concentration below 300 mg/dL can occur with disorders causing relatively mild insulin resistance (e.g., obesity, inflammation). Serum fructosamine

concentrations are typically greater than 500 µmol/L in dogs with insulin resistance and can exceed 700 µmol/L if resistance is severe. Unfortunately, an increased serum fructosamine concentration is merely indicative of poor glycemic control not insulin resistance, per se.

The severity of insulin resistance is dependent, in part, on the underlying etiology. Insulin resistance may be mild and easily overcome by increasing the dosage of insulin or may be severe, causing marked hyperglycemia regardless of the type and dosage of insulin administered. Some causes of insulin resistance are readily apparent at the time diabetes is diagnosed, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids). Other causes of insulin resistance are not readily apparent and require an extensive diagnostic evaluation to be identified. In general, any concurrent inflammatory, infectious, hormonal, neoplastic, or organ system disorder can cause insulin resistance and interfere with the effectiveness of insulin therapy. In our experience, the most common concurrent disorders interfering with insulin effectiveness in diabetic dogs include diabetogenic drugs (glucocorticoids), severe obesity, hyperadrenocorticism, diestrus, chronic pancreatitis, chronic kidney disease, inflammatory bowel disease, oral cavity disease, infections of the urinary tract, hyperlipidemia, and insulin-binding antibodies in dogs receiving beef insulin. Obtaining a complete history and performing a thorough physical examination is the most important initial step in identifying these concurrent disorders. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum canine pancreatic-specific lipase (cPL), serum progesterone concentration (intact female dog), abdominal ultrasound, and urinalysis with bacterial culture should be obtained to further screen for concurrent illness. Additional tests will be dependent on results of the initial screening tests (Box 49.9).

Treatment and reversibility of insulin resistance is dependent on the etiology. Insulin resistance is reversible with treatable disorders, for example, sodium levothyroxine treatment in a diabetic dog with concurrent hypothyroidism or ovariohysterectomy in an intact female diabetic dog in diestrus. In contrast, insulin resistance often persists with disorders that are difficult to treat such as chronic recurring pancreatitis. In some situations, measures can be taken to prevent insulin resistance, such as avoidance of glucocorticoids in diabetic dogs and an ovariohysterectomy at the time diabetes mellitus is diagnosed in an intact female dog.

BOX 49.9

Diagnostic Tests to Consider for Evaluation of Insulin Resistance in Diabetic Dogs and Cats

- Complete blood count, serum biochemistry panel, urinalysis
- Bacterial culture of the urine
- Serum canine/feline pancreatic-specific lipase (Spec cP/fPL) (pancreatitis)
- Serum trypsin-like immunoreactivity (TLI) (exocrine pancreatic insufficiency)
- Adrenocortical function tests
  - Urine cortisol/creatinine ratio (spontaneous hyperadrenocorticism)
  - Low-dose dexamethasone suppression test (spontaneous hyperadrenocorticism)
  - Adrenocorticotropic hormone (ACTH)–stimulation test (iatrogenic hyperadrenocorticism)
- Thyroid function tests
  - Baseline serum total and free thyroxine (hypothyroidism and hyperthyroidism)
  - Serum thyroid-stimulating hormone (TSH; hypothyroidism)
- Serum progesterone concentration (diestrus in intact female dog)
- Fasting serum triglyceride concentration (hyperlipidemia)
- Plasma growth hormone or serum insulin-like growth factor 1 concentration (acromegaly)
- Serum insulin concentration 24 hours after discontinuation of insulin therapy (insulin antibodies)
- Abdominal ultrasonography (adrenomegaly, adrenal mass, pancreatitis, pancreatic mass)
- Thoracic radiography (cardiomegaly, neoplasia)
- Computed tomography or magnetic resonance imaging (pituitary mass)

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Complications resulting from diabetes or its treatment are common in diabetic dogs and include blindness and anterior uveitis resulting from cataract formation, hypoglycemia, chronic pancreatitis, recurring infection, poor glycemic control, and ketoacidosis (see Box 49.5). Many clients are hesitant to treat their newly diagnosed diabetic dog because of knowledge regarding chronic complications experienced in humans with diabetes and concern that a similar fate awaits their pet. However, clients should be assured that the devastating effects of human diabetes (e.g., nephropathy, vasculopathy, coronary artery disease) require 10 to 20 years or longer to occur and therefore are uncommon in diabetic dogs.

Cataracts

Cataract formation is the most common and one of the most important long-term complications of diabetes mellitus in the dog. A retrospective cohort study on the development of cataracts in 132 diabetic dogs referred to a university referral hospital that found cataract formation in 14% of dogs at the time diabetes was diagnosed, and a time interval for 25%, 50%, 75%, and 80% of the study population to develop cataracts at 60, 170, 370, and 470 days, respectively (Beam et al., 1999). The pathogenesis of diabetic cataract formation is thought to be related to altered osmotic relationships in the lens induced by the accumulation of sorbitol and galactitol—sugar alcohols produced following reduction of glucose and galactose by the enzyme aldose reductase in the lens are potent hydrophilic agents, which cause an influx of water

into the lens, leading to swelling and rupture of lens fibers and the development of cataracts. Cataract formation is an irreversible process once it begins, and it can occur rapidly. Diabetic dogs that are poorly controlled and have problems with wide fluctuations in blood glucose concentrations seem especially at risk for rapid development of cataracts. Good glycemic control and minimal fluctuation in the blood glucose concentration prolongs the onset of cataract formation. Once blindness occurs as a result of cataract formation, the need for stringent blood glucose control is reduced.

Blindness may be eliminated by removing the abnormal lens. Vision is restored in approximately 80% of diabetic dogs that undergo cataract removal. Factors that affect the success of surgery include the degree of glycemic control preceding surgery, the presence of retinal disease, and the presence of lens-induced uveitis. Acquired retinal degeneration affecting vision is more of a concern in older diabetic dogs than diabetic retinopathy. Fortunately, acquired retinal degeneration is unlikely in an older diabetic dog with vision immediately before cataract formation. If available, electroretinography should be performed before surgery to evaluate retinal function.

Lens-Induced Uveitis

During embryogenesis the lens is formed within its own capsule, and its structural proteins are not exposed to the immune system. Therefore immune tolerance to the crystalline proteins does not develop. During cataract formation and reabsorption, lens proteins are exposed to the local immune system, resulting in inflammation and uveitis. Uveitis that occurs in association with a reabsorbing, hypermature cataract may decrease the success of cataract surgery and must be controlled before surgery. Treatment of lens-induced uveitis focuses on decreasing inflammation and preventing further intraocular damage. Topical ophthalmic glucocorticoids (e.g., prednisone acetate) are the most commonly used drug for the control of ocular inflammation. However, systemic absorption of topically applied glucocorticoids may cause insulin resistance and interfere with glycemic control of the diabetic state, especially in toy and miniature breeds. An alternative is the topical administration of nonsteroidal antiinflammatory agents such as diclofenac (Voltaren) or flurbiprofen ophthalmic (Ocufen). Although not as potent an antiinflammatory agent as glucocorticoids, nonsteroidal antiinflammatory drugs should not interfere with glycemic control.

Diabetic Neuropathy

Although a common complication in the diabetic cat (see p. 833), diabetic neuropathy is infrequently recognized in the diabetic dog. Subclinical neuropathy is probably more common than is severe neuropathy resulting in clinical signs. Clinical signs consistent with diabetic neuropathy are most commonly recognized in dogs that have been diabetic for a long time (i.e., 5 years or longer), although diabetic neuropathy has been diagnosed in dogs shortly after the diagnosis of diabetes has been established. Clinical signs and physical examination findings include pelvic limb paresis, abnormal gait, knuckling, decreased muscle tone, muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. Diabetic neuropathy in the dog is primarily a distal polyneuropathy, characterized by segmental demyelination and axonal degeneration. Electrodiagnostic abnormalities include spontaneous sharp waves and fibrillation potentials and decreased M-wave amplitude on electromyogram and decreased motor and sensory nerve conduction velocities. No specific treatment for diabetic neuropathy is known besides meticulous metabolic control of the diabetic state.

Diabetic Nephropathy

Diabetic nephropathy has occasionally been reported in the dog. Diabetic nephropathy is a microvascular disease involving the capillary and precapillary arterioles, and is manifested mainly by thickening of the capillary basement membrane. Histopathologic findings include membranous glomerulonephropathy, glomerular and tubular basement membrane thickening, an increase in the mesangial matrix material, and the presence of subendothelial deposits, glomerular fibrosis, and glomerulosclerosis. Glucose plays a central role in the development of microvascular damage. Clinical signs depend on the severity of glomerulosclerosis and the functional ability of the kidney to excrete metabolic wastes. Initially, diabetic nephropathy is manifested as proteinuria, primarily albuminuria. As glomerular changes progress, glomerular filtration becomes progressively impaired, resulting in the development of azotemia and eventually uremia. With severe fibrosis of the glomeruli, oliguric and anuric kidney failure may develop.

Monitoring urine for the presence of microalbuminuria is used as an early marker for development of diabetic nephropathy in diabetic humans. Microalbuminuria occurs in diabetic dogs, and increased urine albumin:creatine ratios precede increased urine protein:creatinine ratios. In one study, 11 (55%) of 20 diabetic dogs had an increase in the urine albumin:creatinine ratio, and only 6 of these 11 dogs also had an increase in urine protein:creatinine ratio, suggesting that monitoring urine albumin:creatinine ratio may be of value as an early marker for kidney disease in diabetic dogs (Mazzi et al., 2008). However, the predictive value of microalbuminuria for diabetic nephropathy and the clinical relevance of microalbuminuria in diabetic dogs remains to be clarified. Diabetic nephropathy is a significant chronic complication in diabetic humans that takes years to progress to chronic end-stage kidney disease; a time line that may explain why clinically relevant diabetic nephropathy is uncommon in diabetic dogs. Regardless, proteinuria, kidney function, and systemic blood pressure should be monitored in diabetic dogs that have developed microalbuminuria. No specific treatment for diabetic nephropathy is known, apart from meticulous metabolic control of the diabetic state, conservative medical management of kidney disease, administration of angiotensin-converting enzyme (ACE) inhibitors to minimize proteinuria, and control of systemic hypertension.

Systemic Hypertension

Diabetes mellitus and hypertension commonly coexist in dogs. Struble et al. (1998) found the prevalence of hypertension to be 46% in 50 insulin-treated diabetic dogs in which hypertension was defined as systolic, diastolic, or mean blood pressure greater than 160, 100, or 120 mm Hg, respectively. The development of hypertension was associated with the duration of diabetes and an increased albumin/creatinine ratio in the urine. Diastolic and mean blood pressure values were higher in dogs with longer duration of disease. A correlation between control of glycemia and blood pressure was not identified. Systemic hypertension may result from existing subclinical kidney disease or develop secondary to the effects of diabetes on vascular compliance, glomerular function, or some other mechanism. Treatment for hypertension should be initiated if the systolic blood pressure is consistently greater than 160 mm Hg.

Prognosis

The prognosis for dogs diagnosed with diabetes mellitus depends, in part, on owner commitment to treating the disorder, ease of glycemic regulation, presence and reversibility of concurrent disorders, avoidance of chronic complications associated with the diabetic state, and minimizing the impact of treatment on the quality of life of the owner (see Table 49.2). In a large study involving insured dogs in Sweden, the median survival time after the first diabetes mellitus claim (686 dogs) was 57 days and for dogs surviving at least one day (463 dogs) was 2.0 years (Fall et al., 2007). For dogs surviving at least 30 days after the first diabetes mellitus claim (347 dogs), the proportion of dogs surviving 1, 2, and 3 years was 40%, 36%, and 33%, respectively. However, survival times will vary between countries and between socioeconomic regions within a country, and survival time is somewhat skewed because dogs are often 8 to 12 years old at the time of diagnosis, and a relatively high mortality rate exists during the first 6 months because of concurrent life-threatening or uncontrollable disease (e.g., ketoacidosis, acute pancreatitis, kidney failure). In our experience, diabetic dogs that survive the first 6 months can easily maintain a good quality of life for longer than 5 years with proper care by the owners, timely evaluations by the veterinarian, and good client-veterinarian communication.

DIABETES MELLITUS IN CATS

Etiology, Classification, and Diabetic Remission

Type 1 diabetes mellitus with an underlying immune-mediated etiology appears to be rare in cats. Although lymphocytic infiltration of islets has been described in diabetic cats, this histologic finding is not common, and β-cell and insulin autoantibodies have not been identified in newly diagnosed diabetic cats.

Type 2 diabetes predominates in cats and is characterized by insulin resistance and dysfunctional β cells. Common histologic findings in the pancreatic islets include islet-specific amyloidosis, β-cell vacuolar degeneration, and a reduction in the number of pancreatic islets, insulin-containing β cells in the islet, or both. Genetics undoubtedly plays a role in Burmese cats in Australia, New Zealand, and the United Kingdom, but the role of genetics in other breeds remains to be determined. Additional risk factors for type 2 diabetes mellitus include male neutered cat, inactivity (indoor cat), increasing age, insulin-resistant medications (e.g., glucorticoids) and disease (e.g., hypersomatotropism), and perhaps most important – obesity.

Adipose tissue produces two important adipokines: adiponectin, an adipokine that enhances insulin sensitivity and has antiinflammatory properties, and leptin, an adipokine involved in appetite suppression, energy expenditure, and modulation of insulin sensitivity (Hoenig, 2012). Obesity results in a decrease in circulating adiponectin and causes leptin resistance. Adipose tissue also secretes a number of proinflammatory cytokines (e.g., TNF-α, IL-6) that negatively influence insulin signaling and cause insulin resistance (Hoenig et al., 2006). All of these actions promote the development of diabetes, and all of these actions are potentially reversible with weight loss.

Islet amyloidosis also plays an important role in the development of type 2 diabetes in cats. Islet-amyloid polypeptide (IAPP), or amylin, is the principal constituent of amyloid in adult cats with diabetes, is stored in β-cell secretory granules, and is co-secreted with insulin by the β cell. Stimulants of insulin secretion also stimulate the secretion of amylin. Chronic increased secretion of insulin and amylin, as occurs with obesity and other insulin-resistant states, results in aggregation and deposition of amylin in the islets as amyloid (Fig. 49.12). IAPP-derived amyloid fibrils are cytotoxic and may lead to a decline in β-cell function and β-cell apoptosis (Costes et al., 2013). Loss of β-cell function may be present before amyloid depositions are visible in the islets.

If deposition of amyloid is progressive, as occurs with a sustained demand for insulin secretion in response to persistent insulin resistance, islet cell destruction progresses and eventually leads to diabetes mellitus. The severity of islet amyloidosis and β-cell destruction determines, in part, whether the diabetic cat is insulin-dependent or not and whether diabetic remission is possible. Total destruction of the islets results in insulin-dependent diabetes mellitus (IDDM) and the need for insulin treatment for the rest of the cat's life. Partial destruction of the islets may or may not result in clinically evident diabetes, insulin treatment may or may not be required to control glycemia, and diabetic remission may or may not occur once treatment is initiated. If amyloid deposition is progressive, the cat will progress from subclinical diabetes to noninsulin dependent diabetes (NIDDM; i.e., glycemia can be controlled with correction of insulin resistance and diet) and ultimately to IDDM. The difference between IDDM and NIDDM is primarily a difference in severity of loss of β cells and severity and reversibility of concurrent insulin resistance.

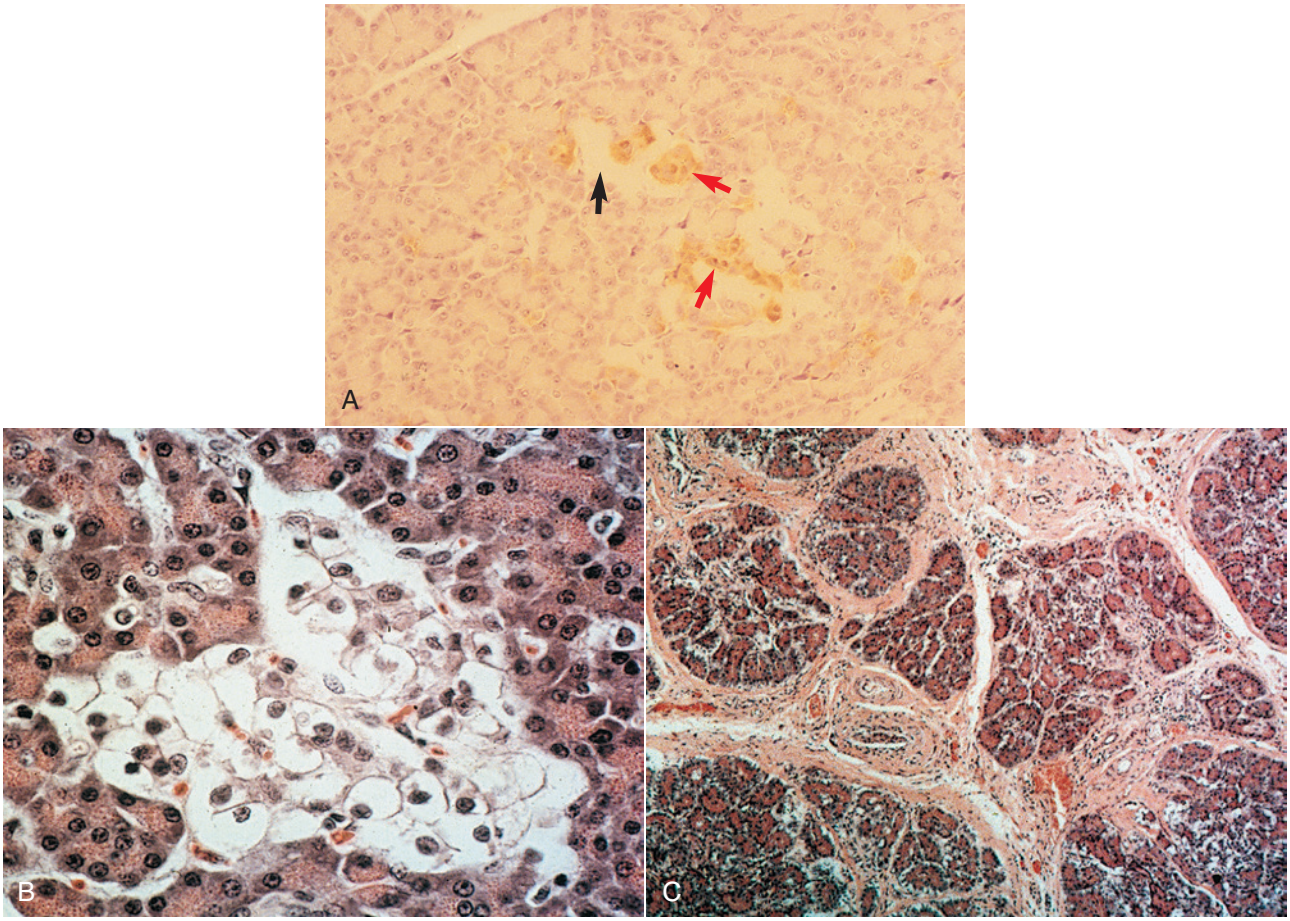


FIG 49.12
(A) Severe islet amyloidosis *(black arrow)* in a cat with initial non–insulin-dependent diabetes mellitus (NIDDM) that progressed to insulin-dependent diabetes mellitus (IDDM). A pancreatic biopsy specimen was obtained while the animal was in the IDDM state. Residual β cells containing insulin *(red arrows)* are also present. (Immunoperoxidase stain, ×100.) **(B)** Severe vacuolar degeneration of islet cells. Pancreatic tissue was evaluated at necropsy 28 months after diabetes was diagnosed and 20 months after the cat progressed from NIDDM to IDDM, requiring insulin to control blood glucose concentrations. The cat died from metastatic exocrine pancreatic adenocarcinoma. (Hematoxylin and eosin stain; ×500.) **(C)** Severe chronic pancreatitis with fibrosis in a diabetic cat with IDDM. The cat was euthanized because of persistent problems with lethargy, inappetence, and poorly controlled diabetes mellitus. (Hematoxylin and eosin stain; ×100.) (**A** from Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

Glucose toxicity also plays an important role in diabetic cats, especially as it relates to diabetic remission. Diabetic remission is defined as a scenario in which diabetes mellitus is correctly diagnosed in a cat, insulin treatment is initiated in conjunction with adjustments in diet and discontinuation of insulin antagonistic medications (most notably glucocorticoids) and, weeks to months later, hyperglycemia resolves and insulin is discontinued without recurrence of hyperglycemia. Blood glucose concentrations should remain in the reference range for at least 4 weeks before diabetes is considered to be in remission.

Cats that experience diabetic remission are in a subclinical diabetic state that becomes clinical when the cat is exposed to a concurrent insulin-antagonistic drug or disease, most notably glucocorticoids and chronic inflammation (Fig. 49.13). Unlike healthy cats, those that experience diabetic remission have a reduced population of β cells, dysfunctional β cells, or both, and this impairs the ability of the pancreas to compensate for concurrent insulin resistance. An inadequate insulin response results in hyperglycemia. Persistent hyperglycemia can, in turn, cause hypoinsulinemia by suppressing the function of remaining β cells and can induce insulin resistance by promoting downregulation of glucose transport systems, causing a defect in posttransport insulin action. This phenomenon is referred to as *glucose toxicity*. β cells have an impaired response to stimulation by

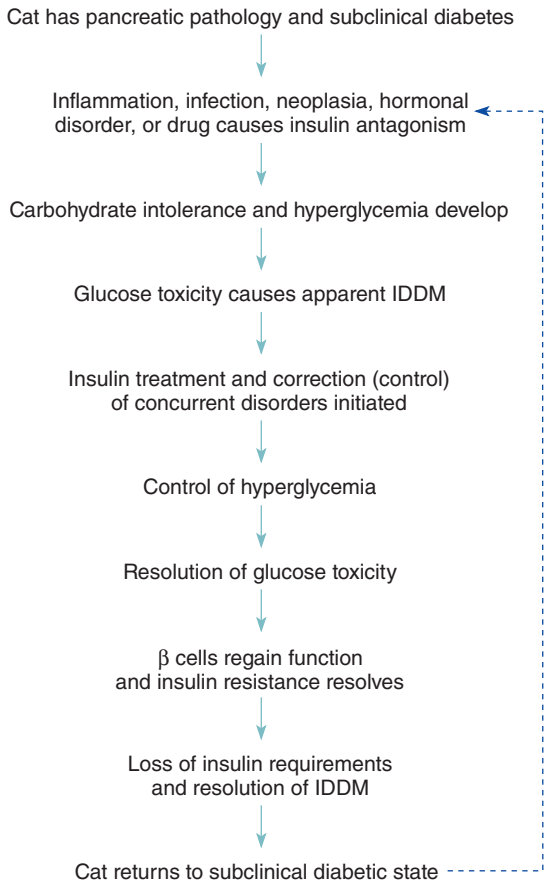


FIG 49.13
Sequence of events in the development and resolution of an insulin-requiring diabetic episode in cats with transient diabetes. (From Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

insulin secretagogues, thereby mimicking type 1 IDDM. The effects of glucose toxicity are potentially reversible upon correction of the hyperglycemic state. The clinician makes a correct diagnosis of diabetes mellitus; insulin therapy, discontinuation of insulin antagonistic drugs, and treatment of insulin-antagonistic disorders improve hyperglycemia and insulin resistance; glucose toxicity resolves; β-cell function improves; insulin secretion returns; and an apparent IDDM state resolves (Nelson et al., 1999). Diabetic remission usually occurs during the first 2 to 3 months of treatment, but we have seen cats undergo remission up to a year or longer after initiating insulin treatment. Cats that experience diabetic remission have impaired glucose tolerance. Approximately 30% of cats relapse, usually within 5 to 6 months of discontinuing insulin. The future requirement for insulin treatment depends on the underlying abnormality in the islets. If the abnormality is progressive (e.g., amyloidosis), eventually enough β cells will be destroyed and IDDM will develop.

Glucose toxicity is a secondary event that only becomes apparent after hyperglycemia has occurred. The cellular mechanisms by which chronic hyperglycemia affects insulin secretion and insulin sensitivity are poorly understood, although oxidative stress and inflammatory cytokines are believed to play a role (Zini et al., 2009a). Reversal of glucose toxicity is an important mechanism to explain diabetic remission. The key to diabetic remission lies in the ability to correct insulin resistance and attain and maintain good glycemic control of the diabetic state. Factors involved in diabetic remission are listed in Box 49.10. Published remission rates vary, but most veterinary internists report rates between 25% and 50%. A recent study among primary care veterinarians in the southern United States under "everyday conditions" reported an approximate remission rate of 26% (Smith et al., 2012).

BOX 49.10

Factors Involved in Diabetic Remission in Cats

Recently diagnosed diabetic cat
Correction of glucose toxicity
Maintaining good glycemic control
Using long-acting insulin preparations twice daily
Feeding low carbohydrate diets
Avoiding insulin resistant medications (e.g., glucocorticoids)
Nature and reversibility of concurrent disorders
Frequent evaluations
  Intensity of home blood glucose monitoring
  Ability to attain blood glucose targets

Clinical Features

SIGNALMENT AND RISK FACTORS

Although diabetes mellitus may be diagnosed in cats of any age, most diabetic cats are 7 to 15 years of age at the time of diagnosis. Diabetes mellitus occurs predominantly in neutered male cats. Studies with a large cohort of cats performed in in Sweden and the United Kingdom identified Burmese, Russian Blue, Norwegian Forest, and Abyssinian cats at increased risk for diabetes mellitus. Additional risk factors included age, increasing body weight, indoor confinement, and possibly dry cat food in normal weight cats.

HISTORY

The history in virtually all diabetic cats includes polydipsia, polyuria, polyphagia, and weight loss. A common complaint of cat owners is the constant need to change the litter and an increase in the size of the litter clumps. Additional clinical signs include lethargy; decreased interaction with family members; lack of grooming behavior and development of a dry, lusterless, unkempt, or matted haircoat; and decreased jumping ability, rear limb weakness, or development of a plantigrade posture (Fig. 49.14; Video 49.1). If the client does not notice clinical signs associated with uncomplicated diabetes, a diabetic cat may be at risk for developing DKA. The time sequence from the onset of initial clinical signs to the development of DKA is unpredictable.

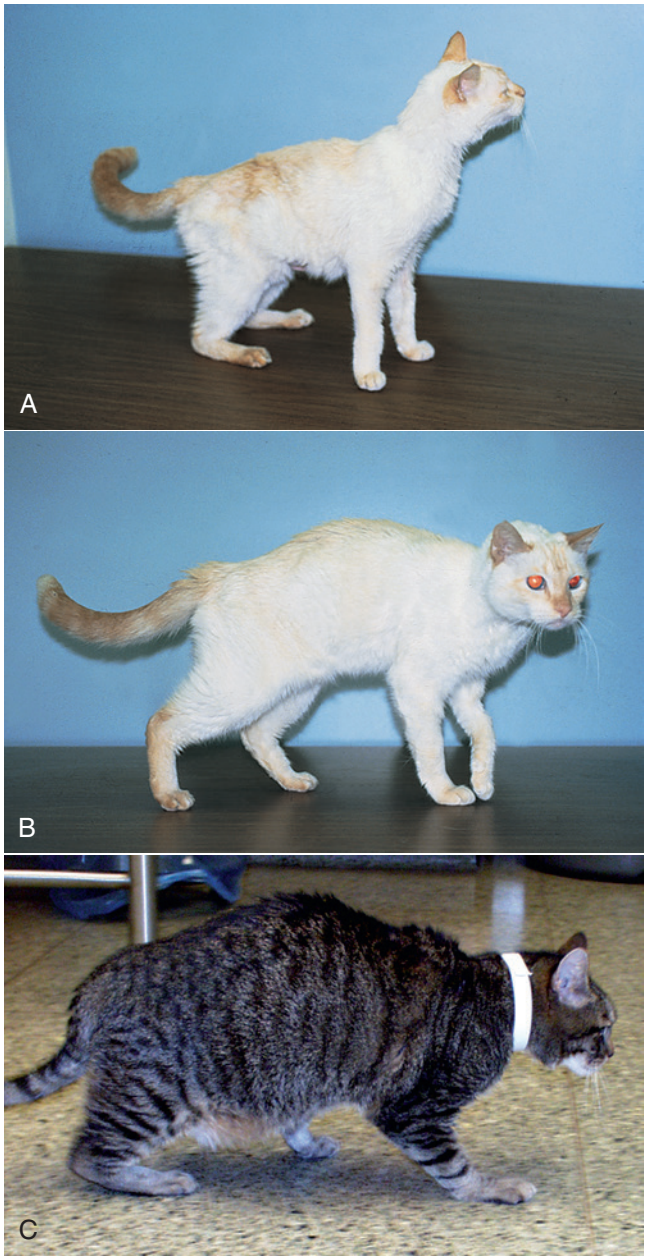


FIG 49.14
(A) Plantigrade posture in a cat with diabetes mellitus and exocrine pancreatic insufficiency. **(B)** Resolution of hindlimb weakness and plantigrade posture after glycemic control is improved by adjustment of insulin therapy and initiation of pancreatic enzyme replacement therapy. **(C)** Severe diabetic neuropathy in a cat with diabetes mellitus. Note the palmigrade and plantigrade posture. The more severe and the more chronic the neuropathy, the less likely the neuropathy will improve after diabetic control is improved.

PHYSICAL EXAMINATION

Physical examination findings depend on the presence and severity of DKA and the nature of other concurrent disorders. The nonketotic diabetic cat has no classic physical examination findings. Many diabetic cats are obese but otherwise in good physical condition. Cats with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., hyperthyroidism) is present. Newly diagnosed and poorly controlled diabetic cats often stop grooming and develop a dry, lusterless haircoat. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Impaired ability to jump, weakness in the rear limbs, ataxia, or a plantigrade posture (i.e., the hocks touch the ground when the cat walks) may be evident if the cat has developed diabetic neuropathy (see Video 49.1). Distal muscles of the rear limbs may feel hard on digital palpation, and cats may object to palpation or manipulation of the rear limbs, presumably because of pain associated with the neuropathy. Additional abnormalities may be identified in the ketoacidotic diabetic cat.

Diagnosis

Establishing the diagnosis of diabetes mellitus is similar for cats and dogs and is based on identification of appropriate clinical signs, persistent hyperglycemia, and glycosuria (see p. 811). Transient, stress-induced hyperglycemia is a common problem in cats and can cause the blood glucose concentration to increase to above 300 mg/dL. Unfortunately, stress is a subjective state that cannot be accurately measured, is not always easily recognized, and may evoke inconsistent responses among individual cats. Glycosuria usually does not develop in cats with transient stress-induced hyperglycemia but can be present if stress is prolonged (i.e., hours). For this reason, the presence of appropriate clinical signs, persistent hyperglycemia, and glycosuria should always be documented when a diagnosis of diabetes mellitus is established in cats. If the clinician is in doubt, the stressed cat can be sent home with instructions for the client to monitor the urine for the presence of glucose in the nonstressed home environment. Alternatively, a serum fructosamine concentration can be measured. A documented increase in the serum fructosamine concentration supports the presence of sustained hyperglycemia; however, a serum fructosamine concentration in the upper end of the reference range can occur in symptomatic diabetic cats if diabetes developed shortly before presentation of the cat to the veterinarian.

Clinical signs develop when hyperglycemia causes glycosuria and are the same regardless of the functional status of pancreatic islets. Information used to establish the diagnosis of diabetes mellitus does not provide information on the status of pancreatic islet health, the presence of glucose toxicity, the ability of the cat to secrete insulin, or the severity and reversibility of concurrent insulin resistance. Unfortunately, measurements of baseline serum insulin concentration or serum insulin concentrations after administration of an insulin secretagogue have not been consistent aids in assessing the function of the islets. Identification of a baseline serum insulin concentration greater than 15 μU/mL (reference range, 5-20 μU/mL [40-145 pmol/L]) in a newly diagnosed, untreated diabetic cat supports the presence of functional β cells and partial destruction of the islets; however, low or undetectable serum insulin concentrations do not rule out partial β-cell loss and the potential for

diabetic remission because of the suppressive effects of glucose toxicity on circulating insulin concentrations. An insulin assay validated for the cat should be used when measuring serum insulin concentrations in cats.

A thorough evaluation of the cat's overall health is recommended once the diagnosis of diabetes mellitus has been established. The minimal laboratory evaluation in any diabetic cat should include a CBC, a serum biochemical panel, a serum thyroxine concentration, and urinalysis with bacterial culture. If available, abdominal ultrasound should also be a routine part of the diagnostic evaluation to assess the liver, kidneys, adrenal glands, and especially the pancreas for chronic pancreatitis. Measurement of baseline serum insulin concentration or performance of an insulin secretory response test is not routinely done in cats because of problems encountered with glucose toxicity. Additional tests may be warranted after the history is obtained, the physical examination is performed, or ketoacidosis is identified. See Box 49.4 for a list of potential clinical pathologic abnormalities.

Treatment

The significant incidence of type 2 diabetes in cats raises interesting questions regarding the need for insulin treatment. Glycemic control can be maintained in some diabetic cats with dietary changes, correction of obesity, control of concurrent diseases, discontinuation of insulin-antagonistic drugs, or a combination of these. The ultimate differentiation between insulin-dependent and non–insulin-dependent diabetes is usually made retrospectively, after the clinician has had several weeks to assess the response of the cat to therapy and to determine the cat's need for insulin. The initial treatment strategy is based on the severity of clinical signs and physical abnormalities, the presence or absence of ketonuria and ketoacidosis, the general health of the cat, and client wishes. For most newly diagnosed diabetic cats, treatment includes insulin, adjustments in diet, and correction or control of concurrent insulin resistance.

INITIAL INSULIN RECOMMENDATIONS FOR DIABETIC CATS

Diabetic cats are notoriously unpredictable in their response to exogenous insulin, and all insulin preparations have the potential for short duration of effect in cats. No insulin preparation is consistently effective in maintaining control of glycemia, even with twice-daily administration. Insulin preparations used for the long-term management of diabetic cats include porcine lente insulin, recombinant human PZI, insulin glargine, and insulin detemir (see p. 812 and Fig. 49.11). Because short duration of insulin effect is common in cats, we prefer to start insulin therapy using insulin glargine (Lantus) or recombinant human PZI (ProZinc). Both insulin preparations are effective in controlling glycemia and inducing diabetic remission in diabetic cats. Studies to date suggest that the median dosage of insulin glargine and PZI required to attain glucose control in most diabetic cats is approximately 0.5 U/kg/injection, with a range of 0.2 to 0.8 U/kg. One important goal in the initial regulation of the diabetic cat is avoidance of symptomatic hypoglycemia, especially in the home environment. Considerable overlap in the insulin dosage range that causes hypoglycemia, establishes control of glycemia, and does not establish control of glycemia exists with all insulin preparations. Predicting an effective dosage of any insulin product that does not cause hypoglycemia in some diabetic cats is difficult, in part because of variability between cats in their response to insulin. For this reason, our starting insulin dosage is always on the low end of the range, typically 0.25 U/kg per injection (½ to 2 U/injection), and we prefer to start with twice-a-day insulin administration because the overwhelming majority of diabetic cats require insulin glargine and PZI twice a day. The most common problem with insulin glargine and PZI is a prolonged duration of effect (>12 hours). This can create problems with hypoglycemia when these insulin preparations are administered twice a day, problems that can be minimized by starting with an insulin dose at the lower end of the effective range.

DIET

The general principles for dietary therapy are listed in Box 49.6. Obesity, feeding practices, and content of the diet warrant discussion in diabetic cats. Obesity is common in diabetic cats and results from excessive caloric intake typically caused by free-choice feeding of dry cat food. Obesity causes reversible insulin resistance that resolves as obesity is corrected. Control of glycemia often improves, and some diabetic cats experience diabetic remission after weight reduction. Correction of obesity is difficult in cats because it requires restriction of daily caloric intake without a corresponding increase in caloric expenditure (i.e., exercise). Typical weight-reducing diets recommended for obese diabetic cats include diets with increased protein and decreased carbohydrate content, and low-calorie-dense diets with decreased fat and increased fiber content. The reader is referred to Chapter 51 for more information on correction of obesity in cats.

The eating habits of cats vary considerably, from eating everything at the time food is offered to grazing throughout the day and night. The primary goal of dietary therapy is to minimize the impact of a meal on postprandial blood glucose concentrations. Consuming the same number of calories in multiple small amounts throughout a 12-hour period should have less impact than consuming the calories at a single large meal. Half of the cat's total daily caloric intake should be offered at the time of each insulin injection and should remain available to the cat to consume when it wishes. Attempts to force a grazing cat to eat the entire meal at one time usually fail and are not warranted as long as the cat has access to the food during the ensuing 12 hours.

Cats are carnivores and, as such, have higher dietary protein requirements than omnivores such as humans and dogs. Hepatic glucokinase and hexokinase activity is lower in cats, compared with that in carnivores with omnivorous eating habits. This suggests that diabetic cats may be predisposed to developing higher postprandial blood glucose

concentrations after consumption of diets containing a high carbohydrate load and vice versa. Dietary studies in diabetic cats have documented improved control of glycemia with diets containing increased protein and decreased carbohydrate content, and low-calorie-dense fiber-containing diets. The central theme in these dietary studies has been restriction of carbohydrate absorption by the gastrointestinal tract, either by delaying intestinal glucose absorption (fiber) or decreasing carbohydrate ingestion (low-carbohydrate-containing diets). Intuitively, the most effective means to minimize gastrointestinal absorption of carbohydrates in the diabetic cat is to feed diets that contain minimal amounts of carbohydrate. Currently, we initially use diets with high protein and low carbohydrate content. If problems with palatability, satiation, azotemia, or chronic pancreatitis become an issue, or if poor control of glycemia persists despite adjustments in insulin therapy, a switch to one of the low-calorie-dense fiber-containing diets designed for diabetic cats, or a switch to a more appropriate diet that addresses concurrent problems (e.g., a kidney diet in an azotemic cat or a moderate-protein, highly digestible diet for chronic pancreatitis) should be considered. Diets with high fat and low carbohydrate content (e.g., growth diets) are not recommended because of concerns related to the impact of high dietary fat content on obesity, hepatic lipidosis, chronic pancreatitis, and insulin resistance—the latter induced by increased circulating concentrations of nonesterified fatty acids, β-hydroxybutyric acid, and triglycerides.

IDENTIFICATION AND CONTROL OF CONCURRENT PROBLEMS

Identification and correction of concurrent disorders that cause insulin resistance and interfere with the success of insulin therapy is critical to the successful treatment of diabetes in cats. Examples include obesity; chronic pancreatitis and other chronic inflammatory diseases; infection; and insulin-resistant disease such as hyperthyroidism, hyperadrenocorticism, and acromegaly. In diabetic cats with partial loss of β cells, correction of insulin resistance may result in diabetic remission. An evaluation of the diabetic cat for concurrent problems is indicated at the time diabetes is diagnosed and whenever control of glycemia deteriorates in a previously well-controlled cat. The initial evaluation should include a thorough history, physical examination, CBC, serum biochemistry panel, serum thyroxine concentration, urinalysis with culture, and (if available) abdominal ultrasound.

ORAL HYPOGLYCEMIC DRUGS

Oral hypoglycemic drugs work by stimulating pancreatic insulin secretion (e.g., sulfonylureas), enhancing tissue sensitivity to insulin (e.g., metformin, thiazolidinediones), or slowing postprandial intestinal glucose absorption (α-glucosidase inhibitors). Only the sulfonylurea drug glipizide was marginally effective in diabetic cats and was used as an alternative treatment for owners who initially refused to administer insulin. The current recommendation in this situation is to feed diets containing increased protein and decreased carbohydrate content to the cat rather than administer glipizide.

Newer antidiabetic medications for the treatment of type 2 diabetes in humans have focused on incretins. Incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gastrointestinal hormones released in response to food intake that increase glucose-dependent insulin secretion, inhibit glucagon secretion, slow gastric emptying, induce satiation, and promote weight loss in humans. A recent pilot study evaluating the effect of a GLP-1 analogue (Exenatide Extended) in newly diagnosed diabetic cats concurrently treated with insulin glargine and a low-carbohydrate diet achieved diabetic remission or good metabolic control in 40% and 89% of the diabetic cats compared with 20% and 58% in control diabetic cats, respectively (Riederer et al., 2016). Exenatide Extended was safe in cats, did not result in weight gain, and stimulated insulin secretion. What role, if any, incretin medications may have for the treatment of diabetic cats remains to be determined. These medications are presumably not indicated in dogs because dogs do not develop type 2 diabetes.

Adjusting Insulin Treatment and Blood Glucose Monitoring

Stress hyperglycemia and diabetic remission are two important considerations when monitoring and adjusting insulin in the diabetic cat. Cats have the propensity to develop stress-induced hyperglycemia caused by frequent visits to the veterinary hospital for blood samplings. Once stress-induced hyperglycemia develops, it is a perpetual problem and blood glucose measurements can no longer be considered accurate. Veterinarians must remain wary of stress hyperglycemia in diabetic cats and should take steps to prevent its development. Micromanaging diabetic cats is not recommended, and blood glucose curves should be done only when the clinician perceives a need to change insulin therapy.

In a newly diagnosed diabetic cat, we will initially do an abbreviated blood glucose curve, measuring blood glucose at the time of the insulin injection and 3 or 4 more measurements during the day, making sure hypoglycemia has not occurred, and then send the cat home to be treated by the client. During this time period, we also talk to the client about diabetic remission and home blood glucose monitoring. We initially rely on the client's perception of response one week after initiating insulin treatment to determine if an increase in the insulin dose is indicated. If the client believes the cat is doing well, we will not adjust the insulin dose and evaluate a blood glucose curve a week later. If the client has seen minimal to no improvement in clinical signs, we will increase the insulin dose one half to one unit per injection (depending on the size of the cat) and evaluate a blood glucose curve one week later. The subsequent frequency of monitoring and obtaining blood glucose curves depends on

the response of the cat to insulin. Most clients of diabetic cats are happy with the response to insulin treatment if blood glucose concentrations range between 80 and 280 mg/dL throughout the day, and the average blood glucose concentration is less than 250 mg/dL.

The frequency of glucose monitoring is at the discretion of the client. If home blood glucose monitoring is not an option, a more conservative, hands-off approach to monitoring and adjusting insulin is taken. In this scenario, micromanaging the diabetic cat is not recommended, and blood glucose curves are usually done when the clinician perceives a need to change insulin therapy. Determination of good versus poor control of glycemia should be based on the client's subjective opinion of the presence and severity of clinical signs and the overall health of the pet, the ability of the cat to jump, grooming behavior, findings on physical examination, and stability of body weight. Generation of a blood glucose curve is reserved for when problems with control are perceived.

Home Blood Glucose Monitoring and Diabetic Remission

A more intensive approach to treating diabetic cats involves frequent home blood glucose monitoring by the client and adjusting the insulin dose based on glucose results, an approach that has the potential to be more aggressive in maintaining control of blood glucose concentrations, increasing the chance for diabetic remission, and potentially delaying the onset of diabetic neuropathy. The key to diabetic remission lies in the ability to correct insulin resistance and attain and maintain good glycemic control of the diabetic state. Home blood glucose monitoring relies on obtaining capillary blood samples by pricking the inner aspect of the pinna or the metacarpal or metatarsal pads using a lancet or needle and a PBGM device that allows the client to touch the drop of blood to with the end of the glucose test strip (Fig. 49.15). The ear and pad prick technique decreases the need for physical restraint during sample collection, thereby minimizing the cat's discomfort and stress. Accuracy of blood



FIG 49.15
Ear prick technique for measuring blood glucose concentration. **(A)** A hot washcloth is applied to the pinna for 2 to 3 minutes to increase circulation to the ear. **(B)** A spot is identified on the periphery of the outer side of the pinna, a small coating of petrolatum jelly is applied, and the spot is pricked with the lancet device supplied with the portable blood glucose meter. Gauze should be placed between the pinna and the digit holding the pinna to prevent pricking of the finger if the blade of the lancet accidentally passes through the pinna. Petrolatum jelly is applied to help the blood form into a ball on the pinna as it seeps from the site that is lanced. **(C)** Digital pressure is applied in the area of the lanced skin to promote bleeding. The glucose test strip is touched to the drop of capillary blood that forms and is removed once enough blood has been drawn into the test strip to activate the meter.

glucose results are similar when blood for glucose determination is obtained by the ear and pad prick technique and venipuncture. However, blood glucose results obtained by PBGM devices designed for use in humans with diabetes may overestimate but more commonly underestimate the actual blood glucose values obtained with reference methods. This inherent error must be considered when blood glucose results obtained by these PBGM devices are interpreted. One exception is the AlphaTRAK2®(Abbott Laboratories). Accuracy of this portable glucometer is very good in cats, but glucose values may be higher or lower than glucose values measured by benchtop methods on the same blood sample, forcing the veterinarian and client to accept the blood glucose concentration at face value. There are several excellent online sites that demonstrate home blood glucose monitoring techniques for the owner of a diabetic cat (e.g., Abbott Laboratories website for the AlphaTRAK2®). The clinician or technician should allow ample time to teach the technique to clients willing to give it a try and provide advice regarding how often to measure blood glucose concentration and when to monitor blood glucose concentration in relation to the time of insulin injection. Use of the ear and pad prick technique in cats has produced excellent results. Stress is often significantly reduced, and the accuracy of blood glucose measurements is improved. Problems with at-home monitoring of blood glucose concentrations include overzealous clients who start monitoring blood glucose concentrations too frequently, insulin overdosing and hypoglycemia caused by clients who interpret blood glucose results and adjust the insulin dose independent of input from the veterinarian, difficulty obtaining blood from the ear or pads, and cats who do not tolerate manipulation and pricking of the ear or pads.

Role of Serum Fructosamine in Stressed Diabetic Cats

The use of serum fructosamine concentrations for assessing control of glycemia is discussed on page 818. Serum fructosamine concentrations are not affected by acute transient increases in blood glucose concentration. Unlike blood glucose measurements, evaluation of serum fructosamine concentrations in fractious or stressed diabetic cats provides reliable objective information on the status of glycemic control during the previous 2 to 3 weeks. In fractious or stressed cats, the clinician must make an educated guess as to where the problem lies (e.g., wrong type of insulin, low insulin dose), make an adjustment in therapy, and rely on owner perception and changes in serum fructosamine to assess the benefit of the change in treatment. Serum fructosamine concentrations can be measured before and 2 to 3 weeks after insulin therapy is changed to assess the effectiveness of the change. If changes in insulin therapy are appropriate, the client should observe improvement in the severity of polyuria and polydipsia, and serum fructosamine concentration should decrease by more than 50 µmol/L. If the serum fructosamine concentration is the same or has increased, then the change was ineffective in improving glycemic control, another change in therapy based on an educated guess should be performed, and serum fructosamine should be measured again 2 to 3 weeks later.

INSULIN THERAPY DURING SURGERY

Approaches to managing the diabetic cat and dog during surgery are similar and are discussed on page 813.

COMPLICATIONS OF INSULIN THERAPY

Complications of insulin therapy are similar for diabetic dogs and cats and are discussed on page 824. The most common complications of insulin therapy in the diabetic cat are recurring hypoglycemia and diabetic remission; incorrect assessment of glycemic control caused by stress-induced hyperglycemia; insulin overdose; short duration of effect of NPH, lente, and, less commonly, PZI, insulin glargine, and insulin detemir; prolonged duration of effect of PZI, insulin glargine, and insulin detemir; and insulin resistance caused by concurrent inflammatory and hormonal disorders, most notably chronic pancreatitis. Evaluation of a serial blood glucose curve is usually required to identify the underlying problem. A common mistake when insulin glargine or insulin detemir is evaluated in a poorly controlled diabetic cat is that only one or two blood glucose concentrations are measured during the day under the assumption that insulin glargine and insulin detemir have a slow, sustained absorption that results in a relatively flat blood glucose curve (Fig. 49.16, *A*). Unfortunately, the absorption pattern and the duration of effect of insulin glargine and insulin detemir are unpredictable in diabetic cats (see Fig. 49.16, *B*), and interpretation of only one or two blood glucose concentrations can be misleading. A complete serial blood glucose curve as discussed on page 819 should always be done in a diabetic cat with persistence of clinical signs and poor diabetic control, regardless of the type of insulin being administered.

Stress Hyperglycemia

Transient hyperglycemia is a well-recognized problem in fractious, scared, and otherwise stressed cats. Hyperglycemia develops as a result of increased catecholamine concentrations. Blood glucose concentrations typically exceed 200 mg/dL in affected cats, and values in excess of 300 mg/dL are common. Stress hyperglycemia can significantly increase blood glucose concentrations in diabetic cats despite the administration of insulin—an effect that compromises the clinician's ability to accurately judge the effectiveness of the insulin injection. Frequent hospitalizations and venipunctures for monitoring blood glucose concentrations are the most common cause of stress hyperglycemia. Blood glucose concentrations can remain greater than 400 mg/dL throughout the day despite administration of insulin. Failure to recognize the effect of stress on blood glucose results may lead to the erroneous perception that the diabetic cat is poorly controlled. Insulin therapy is invariably adjusted, often by increasing the insulin dose, and another blood glucose curve is obtained 1 to 2 weeks later with essentially the same results. A vicious cycle ensues, which eventually

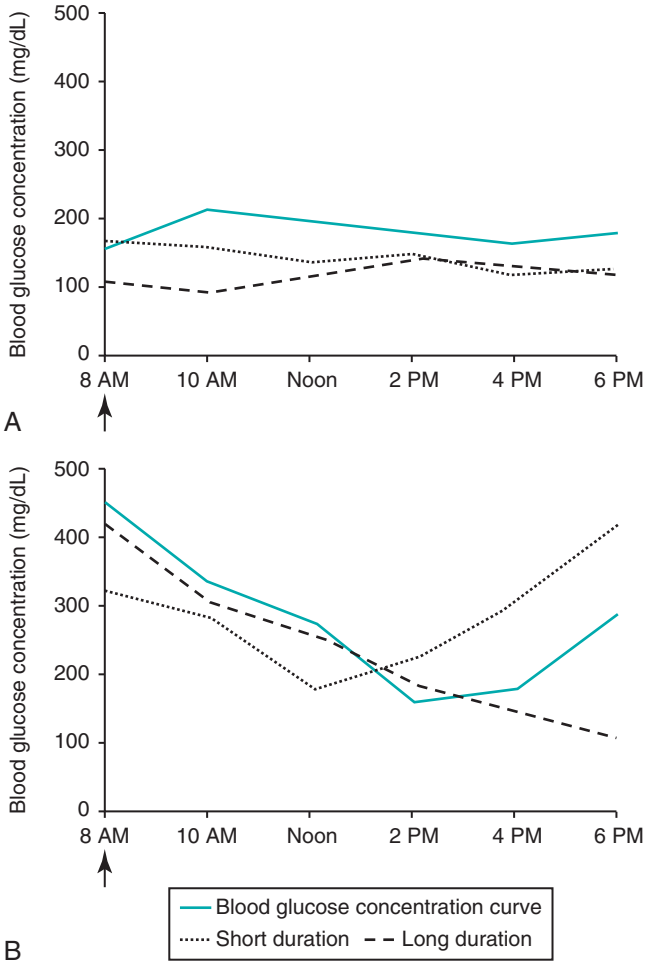


FIG 49.16
Blood glucose concentration curves in six diabetic cats weighing approximately 4 to 5 kg and receiving 1 or 2 units of insulin glargine twice a day, illustrating differences in the effect of insulin glargine on blood glucose results. The three cats in Fig. 49.16, *A* are well regulated and have relatively flat blood glucose curves, with most blood glucose concentrations remaining between 100 and 200 mg/dL, suggesting a slow sustained absorption of insulin glargine. The cats in Fig. 49.16, *B* are not well regulated, and the glycemic effect of insulin glargine is variable, ranging from short duration *(dotted line)* to prolonged duration *(dashed line)* of effect.

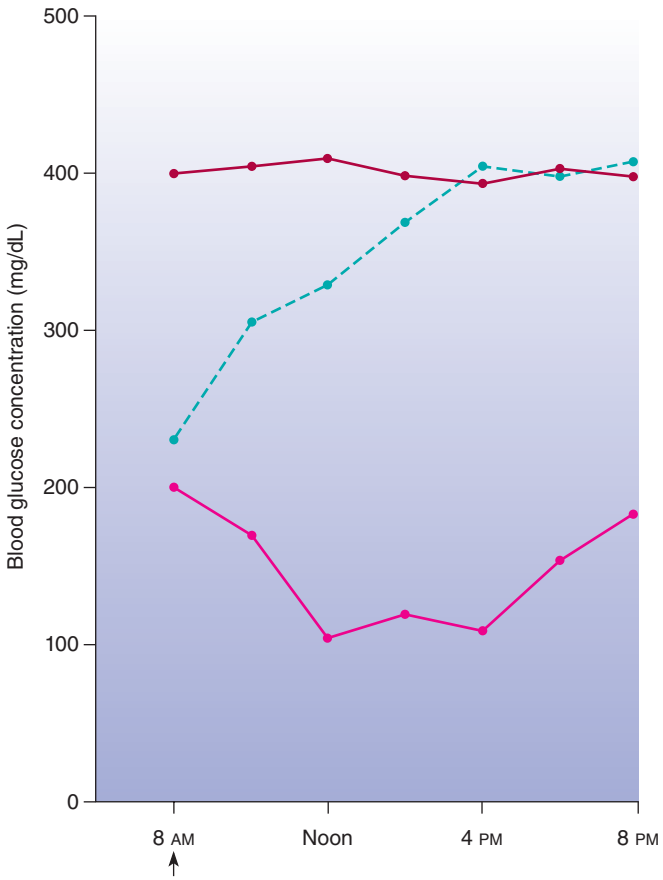


FIG 49.17
Blood glucose concentration curves in a 5.3-kg male cat receiving 2 U of recombinant human ultralente insulin *(pink line)* 2 weeks after initiation of insulin therapy, 2 U of recombinant human ultralente insulin *(blue line)* 2 months later, and 6 U of recombinant human ultralente insulin *(red line)* 4 months later. The insulin dose had been gradually increased on the basis of the blood glucose concentration curves. The client reported minimal clinical signs regardless of the insulin dose; at the 4-month recheck the cat had maintained its body weight, and results of the physical examination were normal. The cat became progressively more fractious during each hospitalization, supporting the existence of stress-induced hyperglycemia as the reason for the discrepancy between blood glucose values and other parameters used to evaluate glycemic control. Subcutaneous insulin injection and food. (From Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

culminates in symptomatic hypoglycemia, glucose counter-regulatory response, and referral for evaluation of insulin ineffectiveness.

Failure to identify the presence of stress hyperglycemia and its impact on the interpretation of blood glucose measurements is one of the most important reasons that the status of glycemic control in diabetic cats is misinterpreted. Stress hyperglycemia should be suspected if the cat is visibly upset or aggressive, or struggles during restraint and the venipuncture process. However, stress hyperglycemia can also be present in diabetic cats that are easily removed from the cage and do not resist the blood-sampling procedure. These cats are scared, but rather than becoming aggressive, they remain crouched in the back of the cage, often have dilated pupils, and usually are flaccid when handled. Stress hyperglycemia should also be suspected if a disparity exists between assessment of glycemic control based on results of the history, physical examination, and stability of body weight versus assessment of glycemic control based on results of blood glucose measurements; or when the initial blood glucose concentration measured in the morning is in an acceptable range (i.e., 150-250 mg/dL), but subsequent blood glucose concentrations increase steadily throughout the day (Fig. 49.17). Once stress hyperglycemia develops, it

is a perpetual problem, and blood glucose measurements can no longer be considered accurate. If stress hyperglycemia is suspected, reliance on home monitoring of blood glucose or evaluation of sequential serum fructosamine concentrations in conjunction with the history, physical examination, and stability of body weight should be used to assess control of glycemia.

Hypoglycemia and Diabetic Remission

Hypoglycemia is a common complication of insulin therapy and is discussed on page 806. In diabetic cats symptomatic hypoglycemia is most apt to occur after sudden large increases in the insulin dose, after sudden improvement in concurrent insulin resistance, with excessive duration of insulin action in cats receiving long-acting basal insulin preparations twice a day, after prolonged inappetence, and in insulin-treated cats that have undergone diabetic remission. In these situations severe hypoglycemia may occur before glucose counterregulation (i.e., secretion of glucagon and catecholamines) is able to compensate for and reverse low blood glucose concentrations. The initial treatment approach for symptomatic hypoglycemia is to discontinue insulin until hyperglycemia recurs and then reduce the ensuing insulin dose by 25% to 50%. If hypoglycemia remains a recurring problem despite reductions in the insulin dose, prolonged duration of insulin effect or diabetic remission should be considered. Diabetic remission should be suspected if hypoglycemia remains a persistent problem despite administration of small doses of insulin (i.e., 1 U or less per injection) and administration of insulin once a day; if blood glucose concentrations are consistently below 200 mg/dL before insulin administration; if serum fructosamine concentration is less than 300 µmol/L (reference interval in cats, 190-365 µmol/L); or if urine glucose test strips are consistently negative. Insulin therapy should be discontinued and periodic urine or blood glucose testing at any time of the day or night should be performed in the home environment to identify recurrence of glycosuria or hyperglycemia.

Insulin Underdosing

Insulin underdosing is discussed on page 825. Control of glycemia can be established in most diabetic cats by using less than 1 U of a long-acting insulin/kg of body weight/injection (median, 0.5 U/kg) administered twice daily. In general, insulin underdosing should be considered if the insulin dose is less than 1 U/kg/injection and the cat is receiving insulin twice a day. If insulin underdosing is suspected, the dose of insulin should be gradually increased by 0.5 to 1 U/injection per week. The effectiveness of the change in therapy should be evaluated by client perception of clinical response and measurement of blood glucose concentrations, preferably obtained in the home environment. Other causes of poor glycemic control should be ruled out before an increase in the insulin dose greater than 1 U/kg/injection is considered.

Short Duration of Insulin Effect

Short duration of insulin effect is discussed on page 826. Short duration of insulin effect is a common problem in diabetic cats despite twice-daily insulin administration. Short duration of effect is common with NPH and lente insulin but occurs with all insulins used to treat diabetic cats, including PZI, insulin glargine, and insulin detemir (see Table 49.3). A diagnosis of short duration of insulin effect is made by demonstrating an initial blood glucose concentration greater than 300 mg/dL combined with a glucose nadir above 80 mg/dL that occurs less than 8 hours after insulin administration and recurrence of hyperglycemia (>300 mg/dL) within 10 hours of the insulin injection (see Fig. 49.8). Treatment involves changing to a longer-acting insulin preparation (see Fig. 49.11).

Prolonged Duration of Insulin Effect

Prolonged duration of insulin effect is discussed on page 826. In diabetic cats problems with prolonged duration of insulin effect are most common with twice-daily administration of PZI, insulin glargine, and insulin detemir.

Inadequate Insulin Absorption

See page 827.

Concurrent Disorders Causing Insulin Resistance

Concurrent disorders causing insulin resistance are discussed on page 827. The most common concurrent disorders interfering with insulin effectiveness in cats include severe obesity, chronic inflammation such as chronic pancreatitis and gingivitis, chronic kidney disease, hyperthyroidism, acromegaly, and hyperadrenocorticism (see Box 49.8). Obtaining a complete history and performing a thorough physical examination are the most important steps in identifying these concurrent disorders. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum thyroxine concentration, urinalysis with bacterial culture, and (if available) abdominal ultrasound should be obtained to further screen for concurrent illness. Additional tests will depend on results of the initial screening tests (see Box 49.9).

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Chronic complications of diabetes mellitus are discussed on page 828. The most common complications in the diabetic cat are hypoglycemia; chronic pancreatitis; weight loss; poor grooming behavior causing a dry, lusterless, and unkempt haircoat; and peripheral neuropathy of the hindlimbs, causing weakness, inability to jump, a plantigrade stance, and ataxia (see Box 49.5). Diabetic cats are also at risk for ketoacidosis.

Diabetic Neuropathy

Diabetic neuropathy is the most important chronic complication of diabetes in cats. Clinical signs of a coexistent

neuropathy in the diabetic cat include weakness, impaired ability to jump, knuckling, a plantigrade posture with the cat's hocks touching the ground when it walks (see Fig. 49.14, Video 49.1), muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. Clinical signs may progress to include the thoracic limbs (palmigrade posture). Abnormalities on electrophysiologic testing are consistent with demyelination at all levels of the motor and sensory peripheral nerves and include decreased motor and sensory nerve conduction velocities in pelvic and thoracic limbs and decreased muscle action potential amplitudes. Electromyographic abnormalities are usually absent and, when identified, are consistent with denervation. Histologic examination of nerve biopsies from affected cats reveals endoneurial microvascular pathology, segmental demyelination, and axonal degeneration in myelinated nerve fibers that culminate in loss of myelinated fibers. The pathogenesis of diabetic peripheral neuropathy is considered multifactorial, with contributions from both metabolic and vascular factors. Currently, no specific therapy is available. Aggressive glucoregulation with insulin may improve nerve conduction and reverse posterior weakness and plantigrade posture (see Fig. 49.14). However, the response to therapy is unpredictable, and the risks of hypoglycemia increase with aggressive insulin treatment. Generally, the longer the neuropathy has been present and the more severe the neuropathy, the less likely it is that improving glycemic control will reverse the clinical signs of neuropathy. (See Suggested Readings for more information on diabetic neuropathy in cats.)

Prognosis

Variables that impact the prognosis are similar for diabetic cats and dogs and include owner commitment to treating the disorder, ease of glycemic regulation, presence and reversibility of concurrent disorders, avoidance of chronic complications associated with the diabetic state, and minimizing the impact of treatment on the quality of life of the owner (see p. 830). Median survival time from the time of diagnosis was 516 days (range, 1-3468 days) in 114 diabetic cats in Zurich, Switzerland (Callegari et al., 2013). In our experience, the mean survival time in diabetic cats is approximately 3 years from the time of diagnosis. However, survival times are somewhat skewed because cats are usually 8 to 15 years old at the time of diagnosis, and a high mortality rate exists during the first 6 months because of concurrent life-threatening or uncontrollable disease (e.g., pancreatitis, chronic kidney disease, acromegaly). In general, "younger" diabetic cats that survive the first 6 months can easily live longer than 5 years with the disease if properly treated.

DIABETIC KETOACIDOSIS

Etiology

Ketone bodies (i.e., acetoacetic acid, β-hydroxybutyric acid, acetone) are derived from oxidation of nonesterified or free fatty acids (FFAs) by the liver and are used as an energy source by many tissues during periods of glucose deficiency. Excessive production of ketone bodies as occurs in uncontrolled diabetes results in their accumulation in the circulation and development of the ketosis and acidosis of ketoacidosis.

The etiopathogenesis of DKA is complex and usually affected by concurrent clinical disorders. Virtually all dogs and cats with DKA have a relative or absolute deficiency of insulin. DKA develops in some diabetic dogs and cats even though they receive daily injections of insulin, and their circulating insulin concentrations may even be increased. The "relative" insulin deficiency in these animals is created by concurrent insulin resistance, which in turn is created by concurrent disorders such as pancreatitis, infection, or insulin-resistant hormonal disorder. Increased circulating concentrations of diabetogenic hormones, most notably glucagon, accentuate insulin deficiency by promoting insulin resistance; stimulate lipolysis, leading to ketogenesis; and stimulate hepatic gluconeogenesis, which worsens hyperglycemia.

Insulin deficiency and insulin resistance, together with increased circulating concentrations of diabetogenic hormones, play a critical role in the stimulation of ketogenesis. For the synthesis of ketone bodies to be enhanced, two major alterations in intermediary metabolism must occur: (1) enhanced mobilization of FFAs from triglycerides stored in adipose tissue, and (2) a shift in hepatic metabolism from fat synthesis to fat oxidation and ketogenesis. Insulin is a powerful inhibitor of lipolysis and FFA oxidation. A relative or absolute deficiency of insulin allows lipolysis to increase, thus increasing the availability of FFAs to the liver and in turn promoting ketogenesis. As ketones continue to accumulate in the blood, the body's buffering system becomes overwhelmed, and metabolic acidosis develops. As ketones accumulate in the extracellular space, the quantity eventually surpasses the renal tubular threshold for complete resorption, and they spill into the urine, contributing to the osmotic diuresis caused by glycosuria and enhancing the excretion of solutes (e.g., sodium, potassium, calcium, magnesium). Insulin deficiency per se also contributes to excessive renal losses of water and electrolytes. The result is excessive loss of electrolytes and water, leading to volume contraction, underperfusion of tissues, and the development of prerenal azotemia. The rise in blood glucose concentration raises plasma osmolality, and the resulting osmotic diuresis further aggravates the rise in plasma osmolality by causing water losses in excess of salt loss. The increase in plasma osmolality causes water to shift out of cells, leading to cellular dehydration. The metabolic consequences of DKA, which include severe acidosis, hyperosmolality, obligatory osmotic diuresis, dehydration, and electrolyte derangements, eventually become life-threatening.

Clinical Features

DKA is a serious complication of diabetes mellitus that occurs most commonly in dogs and cats with diabetes that has gone undiagnosed. Less commonly, DKA develops in an insulin-treated diabetic dog or cat receiving an inadequate

dose of insulin, often occurring in conjunction with an infectious, inflammatory, or insulin-resistant hormonal disorder. Because of the close association between DKA and newly diagnosed diabetes mellitus, the signalment of DKA in dogs and cats is similar to that of nonketotic diabetics.

The history and physical examination findings are variable, in part because of the progressive nature of the disorder and the variable time between the onset of DKA and client recognition of a problem. Polyuria, polydipsia, polyphagia, and weight loss develop initially but may be unnoticed or considered insignificant by the client. Systemic signs of illness (e.g., lethargy, anorexia, vomiting) ensue as ketonemia and metabolic acidosis develop and worsen, with the severity of these signs directly related to the severity of the metabolic acidosis and the nature of concurrent disorders that are often present. The time interval from onset of the clinical signs of diabetes to development of systemic signs of DKA is unpredictable and ranges from a few days to several months. Once ketoacidosis begins to develop, however, severe illness usually becomes evident within a week.

Common physical examination findings include dehydration, lethargy, weakness, tachypnea, tachycardia, and sometimes a strong odor of acetone on the breath. Slow, deep breathing may be observed in animals with severe metabolic acidosis. Gastrointestinal tract signs such as vomiting and abdominal pain are common in animals with DKA, in part because of the common concurrent occurrence of pancreatitis. Other intraabdominal disorders should be considered and diagnostic tests (e.g., abdominal ultrasound) performed to help identify the cause of the gastrointestinal signs. Additional physical examination findings associated with uncomplicated diabetes mellitus (e.g., hepatomegaly, cataracts, diabetic neuropathy) may be identified.

Diagnosis

The diagnosis of diabetes mellitus is based on appropriate clinical signs, persistent fasting hyperglycemia, and glycosuria. The concurrent documentation of ketonuria establishes a diagnosis of DK and documenting metabolic acidosis establishes the diagnosis of DKA. Commonly used nitroprusside reagent test strips for ketonuria (e.g., KetoDiastix) measure only acetoacetate and its byproduct acetone. β-hydroxybutyrate is not detected by conventional nitroprusside tests. If ketonuria is not present but DKA is suspected, serum or urine can be tested for acetone using Acetest tablets, blood can be tested for the presence of β-hydroxybutyrate using a quantitative enzymatic assay or a portable blood glucose and ketone analyzer (e.g., Precision Xtra, Abbott Diagnostics), or plasma from heparinized hematocrit tubes can be used to test for the presence of acetoacetate using urine reagent test strips used to document ketonuria.

Treatment of "Healthy" Dogs or Cats With Diabetic Ketosis or Diabetic Ketoacidosis

If systemic signs of illness are absent or mild, inappetence is not present, serious abnormalities are not readily identifiable on physical examination, and metabolic acidosis is mild (i.e., with total venous carbon dioxide [CO_2] or arterial bicarbonate concentration > 16 mEq/L), short-acting regular crystalline insulin can be administered subcutaneously three times daily at 8-hour intervals until the ketonuria resolves. Fluid therapy and intensive care usually are not needed. Because regular crystalline insulin is a potent insulin, the initial dosage (0.1-0.2 U/kg/injection) is lower than that recommended for longer-acting insulin preparations. To minimize hypoglycemia, the dog or cat should be fed one third of its daily caloric intake at the time of each insulin injection. Subsequent adjustments in the insulin dose are based on clinical response and results of blood glucose measurements. Urine ketone concentrations should be monitored and, if available, blood β-hydroxybutyrate concentrations should be monitored using a portable glucose and ketone meter (e.g., Precision Xtra®, Abbott). A decrease in the blood glucose concentration implies a decrease in ketone production. This, in combination with metabolism of ketones and loss of ketones in urine, will usually correct ketosis within 48 to 96 hours of initiating insulin therapy. Prolonged ketonemia and ketonuria is suggestive of a significant concurrent illness (e.g., chronic pancreatitis) or inadequate blood insulin concentrations to suppress lipolysis and ketogenesis. Once the ketosis has resolved, insulin therapy may be initiated using longer-acting insulin preparations. As a general rule of thumb, the initial dosage of the longer-acting insulin preparation is approximately the same as the dosage of regular crystalline insulin administered at the time the switch in insulin is made, with subsequent adjustments in the dosage based on the animal's response to the insulin.

Treatment of Sick Dogs or Cats With Diabetic Ketoacidosis

Aggressive therapy is called for if the dog or cat has systemic signs of illness (e.g., lethargy, anorexia, vomiting); physical examination reveals dehydration, depression, weakness, or a combination of these; or metabolic acidosis is severe (i.e., total venous CO_2 or arterial bicarbonate concentration < 12 mEq/L). The five goals of treatment of a severely ill, ketoacidotic, diabetic pet are (1) to provide adequate amounts of insulin to suppress lipolysis, ketogenesis, and hepatic gluconeogenesis; (2) to restore water and electrolyte losses; (3) to correct acidosis; (4) to identify the factors precipitating the present illness; and (5) to provide a carbohydrate substrate (i.e., dextrose) when necessary to allow continued administration of insulin without causing hypoglycemia (Box 49.11). Proper therapy does not mean forcing a return to a normal state as rapidly as possible. Because osmotic and biochemical problems can arise as a result of overly aggressive therapy as well as from the disease itself, rapid changes in various vital parameters can be as harmful as, or more harmful than, no change. If all abnormal parameters can be slowly returned toward normal over a period of 24 to 48 hours, therapy is more likely to be successful.

Critically important information for formulating the initial treatment protocol includes hematocrit and total

BOX 49.11

Initial Management of Dogs or Cats With Severe Diabetic Ketoacidosis

Fluid Therapy

Type: 0.9% saline if hyponatremia is severe (<130 mEq/L); isotonic crystalloid solution such as Ringer's, Ringer's lactate, Plasma-Lyte 148, or Normosol-R if serum sodium concentration ≥ 130 mEq/L

Rate: 60 to 100 mL/kg/24 h initially; adjust based on hydration status, urine output, persistence of fluid losses

Potassium supplement: Based on serum K^+ concentration (see Table 53.1); if unknown, initially add 40 mEq of KCl to each liter of fluids

Phosphate supplement: Administer if serum phosphorus concentration < 1.5 mg/dL; initial IV infusion rate is 0.01 to 0.03 mmol phosphate/kg/h in calcium-free intravenous fluids

Dextrose supplement: Not indicated until blood glucose concentration is less than 250 mg/dL, then begin 5% dextrose infusion

Bicarbonate Therapy

Indication: Administer if plasma bicarbonate concentration is less than 12 mEq/L or if total venous CO_2 concentration is less than12 mmol/L; if not known, do not administer unless animal is severely ill and then only once.

Amount: mEq HCO_3– = body weight (kg) × 0.4 × (12 – animal's HCO_3^-) × 0.5; if animal's HCO_3^- or total CO_2 concentration is unknown, use 10 in place of (12 – animal's HCO_3^-)

Administration: Add to intravenous fluids and give over 6 hours; do not give as bolus infusion

Retreatment: Only if plasma bicarbonate concentration remains less than 12 mEq/L after 6 hours of therapy

Insulin Therapy

Type: Regular crystalline insulin

Administration Technique

Intermittent intramuscular technique: Initial dose, 0.1 to 0.2 U/kg intramuscularly; then 0.1 U/kg intramuscularly hourly until blood glucose concentration is less than 250 mg/dL; then switch to regular insulin administered IM q4-6h or SC q6-8h

Low-dose intravenous infusion technique: To prepare infusion, add 2.2 U/kg (dogs) or 1.1 U/kg (cats) of regular insulin to 250 mL of 0.9% saline; run 50 mL through the drip set and discard; then administer via infusion or syringe pump through a line separate from that used for fluid therapy at an initial rate of 10 mL/h; adjust infusion rate according to hourly blood glucose measurements; switch to subcutaneous regular insulin q6-8h once blood glucose is less than 250 mg/dL, or continue insulin infusion at a decreased rate to prevent hypoglycemia until the insulin preparation is exchanged for a longer-acting product.

Goal: Gradual decline in blood glucose concentration, preferably around 50 mg/dL/h until concentration is less than 250 mg/dL

Ancillary Therapy

Concurrent pancreatitis is common in diabetic ketoacidosis; nothing by mouth and aggressive fluid therapy are usually indicated

Concurrent infections are common in diabetic ketoacidosis; use of broad-spectrum, parenteral antibiotics is usually indicated

Additional therapy may be needed, depending on the nature of concurrent disorders

Patient Monitoring

Blood glucose measurement q1-2h initially; adjust insulin therapy and begin dextrose infusion when decreases to below 250 mg/dL

Hydration status, respiration, pulse q2-4h; adjust fluids accordingly

Serum electrolyte and total venous CO_2 concentrations q6-12h; adjust fluid and bicarbonate therapy accordingly

Urine output, glycosuria, ketonuria q2-4h; adjust fluid therapy accordingly

Body weight, packed cell volume, temperature, and blood pressure q6-8h

Additional monitoring, depending on concurrent disease

plasma protein concentration; serum glucose, albumin, creatinine, and urea nitrogen concentrations; serum electrolytes; venous total CO_2 or arterial acid-base evaluation; and urine specific gravity. Abnormalities frequently associated with DKA are listed in Box 49.12. Once treatment for DKA is initiated, additional studies, such as CBC, serum biochemistry panel, urinalysis, urine culture, thoracic radiographs, and abdominal ultrasound, or diagnostic tests for pancreatitis, diestrus in the female dog, and hyperthyroidism in the cat are usually warranted to identify underlying concurrent disorders (see Box 49.8).

FLUID THERAPY

Initiation of appropriate fluid therapy should be the first step in the treatment of DKA, and in most cases it should precede the initiation of insulin therapy by 2 hours or longer to minimize the development of complications affiliated with insulin administration. Replacement of fluid deficiencies and maintenance of normal fluid balance are important to ensure adequate cardiac output, blood pressure, and blood flow to all tissues. Improvement in renal blood flow is especially critical. In addition to the general beneficial aspects of fluid therapy in any dehydrated animal, fluid therapy can correct

BOX 49.12

Common Clinicopathologic Abnormalities Identified in Dogs and Cats With Diabetic Ketoacidosis

Neutrophilic leukocytosis, signs of toxicity if septic
Hemoconcentration
Hyperglycemia
Hypercholesterolemia, lipemia
Increased alkaline phosphatase activity
Increased alanine aminotransferase activity
Increased blood urea nitrogen and serum creatinine concentrations
Hyponatremia
Hypochloremia
Hypokalemia
Metabolic acidosis (decreased total carbon dioxide concentration)
Hyperosmolality
Glycosuria
Ketonuria
Urinary tract infection

deficiencies in total body sodium and potassium, dampen the potassium-lowering effect of insulin treatment, and lower the blood glucose concentration in diabetic individuals, even in the absence of insulin administration. Unfortunately, fluid therapy alone does not suppress ketogenesis. For this reason, insulin is always required.

The type of parenteral fluid used initially will depend on the animal's electrolyte status, blood glucose concentration, and osmolality. Most sick dogs and cats with DKA have severe deficits in total body sodium, regardless of the measured serum concentration. Ringer's solution or Plasma-Lyte 148 (Baxter Healthcare Corp.) can be used for mild hyponatremia (serum sodium concentration of more than 130 mEq/L) and 0.9% (physiologic) saline for more severe hyponatremia (serum sodium concentration of less than 130 mEq/L) with appropriate potassium supplementation. Alternative isotonic crystalloid solutions that could be used include Ringer's lactated solution and Normosol-R® (Abbott Laboratories). Each of these solutions has a slightly different electrolyte composition; none contain as much sodium as 0.9% saline (see Tables 53.1 and 53.2). Most dogs and cats with severe DKA are sodium depleted and therefore not suffering from dramatic hyperosmolality. Hypotonic fluids (e.g., 0.45% saline) are rarely indicated in dogs and cats with DKA, even when severe hyperosmolality is present. Hypotonic fluids do not provide adequate amounts of sodium to correct the sodium deficiency, restore normal fluid balance, or stabilize blood pressure. Rapid administration of hypotonic fluids can cause a rapid decrease in the osmolality of extracellular fluid (ECF), which may result in cerebral edema, deterioration in mentation, and eventually coma. Hyperosmolality is best treated with isotonic fluids and the judicious administration of insulin. Fluid administration should be directed at gradually replacing hydration deficits over 24 hours while supplying maintenance fluid needs and matching ongoing losses. Rapid replacement of fluids is rarely indicated unless the dog or cat is in shock. Once the animal is out of this critical phase, fluid replacement should be decreased in an effort to correct the fluid imbalance in a slow but steady manner. As a general rule of thumb, a fluid rate of 1.5 to 2 times maintenance (i.e., 60-100 mL/kg q24h) is typically chosen initially, with subsequent adjustments based on frequent assessment of hydration status, urine output, severity of azotemia, and persistence of vomiting and diarrhea.

Potassium Supplementation

Most dogs and cats with DKA initially have normal or decreased serum potassium concentrations. During therapy for DKA the serum potassium concentration decreases because of rehydration (dilution), insulin-mediated cellular uptake of potassium (with glucose), continued urinary losses, and correction of acidemia (translocation of potassium into the intracellular fluid compartment; Fig. 49.18). Severe hypokalemia is the most common complication that develops during the initial 24 hours of treatment of DKA. Dogs and cats with hypokalemia require aggressive potassium replacement therapy to replace deficits and to prevent worsening, life-threatening hypokalemia after initiation of insulin therapy. The exception to potassium supplementation of fluids is hyperkalemia associated with oliguric kidney failure. Potassium supplementation should initially be withheld in these dogs and cats until glomerular filtration is restored, urine production increases, and hyperkalemia is resolving.

Ideally, the amount of potassium required should be based on actual measurement of the serum potassium concentration. If an accurate measurement of serum potassium is not available, potassium should be added to the liter of fluids to bring the potassium concentration to 40 mEq/L. For example, 0.9% saline solution does not contain potassium, and Ringer's solution contains 4 mEq of potassium per liter, thus these fluids should be supplemented with 40 mEq and 36 mEq of potassium, respectively. Subsequent adjustments in potassium supplementation should be based on measurement of serum potassium, preferably every 4 to 8 hours until the dog or cat is stable and serum electrolytes are in the reference range.

Phosphate Supplementation

Most dogs and cats with DKA have normal or decreased serum phosphorus concentrations on pretreatment testing. Within 24 hours of initiation of treatment for DKA, serum phosphorus concentration can decline to severe levels (i.e., <1 mg/dL) as a result of the dilutional effects of fluid therapy, the intracellular shift of phosphorus following the initiation of insulin therapy, and continuing renal and gastrointestinal loss (see Fig. 49.18). Hypophosphatemia primarily affects the hematologic and neuromuscular systems in dogs and cats. Hemolytic anemia is the most common problem and can be life-threatening if not recognized and treated. Weakness,

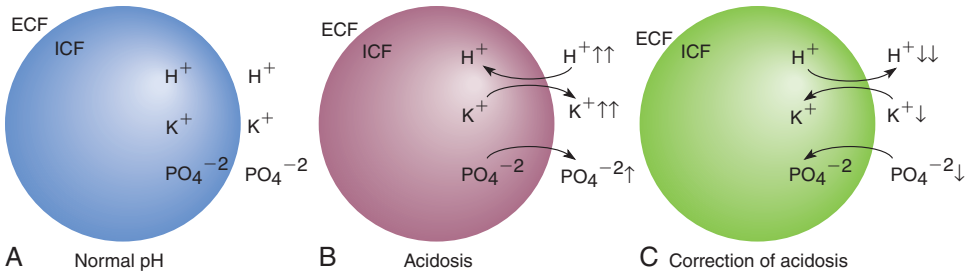


FIG 49.18
Redistribution of extracellular fluid *(ECF)* and intracellular fluid *(ICF)* hydrogen, potassium, and phosphate ions in response to a decrease in ECF pH (i.e., acidosis), an increase in ECF glucose and osmolality, and translocation of water from the ICF to the ECF compartment and subsequent correction of acidosis and the intracellular shift of glucose and electrolytes with insulin treatment. **(A)** Normal ECF pH. **(B)** ECF H^+ concentration increases during acidosis, causing H^+ to move into cells and down its concentration gradient. Increases in ECF glucose and osmolality cause extracellular shifts of water, K^+, and PO_4^{+2}. **(C)** ECF H^+ concentration decreases during correction of acidosis, causing H^+ to move out of the cells. Insulin administration and correction of acidemia cause an intracellular shift of glucose, K^+, and PO_4^{+2}, decreasing ECF K^+ and PO_4^{+2} concentrations. (From Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

ataxia, and seizures may be observed. Severe hypophosphatemia may be clinically silent in many animals.

Phosphate therapy is indicated if clinical signs or hemolysis is identified or if the serum phosphorus concentration decreases to less than 1.5 mg/dL. Phosphate is supplemented by IV infusion. Potassium and sodium phosphate solutions contain 3 mmol of phosphate and 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The recommended dosage for phosphate supplementation is 0.01 to 0.03 mmol of phosphate per kilogram of body weight per hour, preferably administered in calcium-free IV fluids (e.g., 0.9% sodium chloride). In dogs and cats with severe hypophosphatemia, it may be necessary to increase the dosage to 0.03 to 0.12 mmol/kg/h. Because the dose of phosphate necessary to replete an animal and the animal's response to therapy cannot be predicted, it is important to initially monitor the serum phosphorus concentration every 8 to 12 hours and adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, and calcification of soft tissues. Serum ionized calcium concentration should be measured at the same time as serum phosphorus concentration and the rate of phosphate infusion decreased if hypocalcemia is identified. Phosphorus supplementation is not indicated in dogs and cats with hypercalcemia, hyperphosphatemia, oliguria, or suspected tissue necrosis. If kidney function is in question, phosphorus supplementation should not be done until the status of kidney function and serum phosphorus concentration are known.

Magnesium Supplementation

Plasma total and ionized magnesium concentrations may be within or below the reference range at the time DKA is diagnosed in the dog or cat, often decrease during initial treatment of DKA, and typically normalize without treatment as DKA resolves. Clinical signs of hypomagnesemia do not usually occur until serum total and ionized magnesium concentrations are less than 1.0 and 0.4 mg/dL, respectively, and even at these low levels many dogs and cats remain asymptomatic. We do not routinely treat hypomagnesemia in dogs or cats with DKA unless problems with persistent lethargy, anorexia, weakness, or refractory hypokalemia or hypocalcemia are encountered after 24 to 48 hours of fluid and insulin therapy, and another cause for the problem cannot be identified. See Chapter 53 for information on the treatment of hypomagnesemia.

Bicarbonate Therapy

The clinical presentation of the dog or cat, in conjunction with the plasma bicarbonate or total venous CO_2 concentration, should be used to determine the need for bicarbonate therapy. Bicarbonate supplementation is not recommended when plasma bicarbonate (or total venous CO_2) is 12 mEq/L or greater, especially if the animal is alert. An alert dog or cat probably has a normal or near-normal pH in the cerebrospinal fluid (CSF). Acidosis in these animals is corrected through insulin and fluid therapy. Improvement in renal perfusion enhances urinary loss of ketoacids, and insulin therapy markedly diminishes the production of ketoacids. Acetoacetate and β-hydroxybutyrate are metabolically usable anions, and 1 mEq of bicarbonate is generated from each 1 mEq of ketoacid metabolized.

When the plasma bicarbonate concentration is 11 mEq/L or less (total venous $CO_2 < 12$ mEq/L), bicarbonate therapy should be initiated. Many of these animals have severe depression that may be a result of concurrent severe central nervous system acidosis. Metabolic acidosis should be corrected slowly, thereby avoiding major alterations in the pH of the CSF. Only a portion of the bicarbonate deficit is given

initially over a 6-hour period. The bicarbonate deficit (i.e., the milliequivalents of bicarbonate initially needed to correct acidosis to the critical level of 12 mEq/L over a period of 6 hours) is calculated by the following formula:

$$\text{mEq bicarbonate} = \text{body weight (kg)} \times 0.4 \times (12 - \text{animal's bicarbonate}) \times 0.5$$

If the serum bicarbonate concentration is not known, the following formula should be used:

$$\text{mEq bicarbonate} = \text{body weight (kg)} \times 2$$

The difference between the animal's serum bicarbonate concentration and the critical value of 12 mEq/L represents the treatable base deficit in DKA. If the animal's serum bicarbonate concentration is not known, the number 10 should be used for the treatable base deficit. The factor 0.4 corrects for the ECF space in which bicarbonate is distributed (40% of body weight). The factor 0.5 provides one half of the required dose of bicarbonate in the IV infusion. This technique allows a conservative dose to be given over a 6-hour period. Bicarbonate should not be given by bolus infusion. After 6 hours of therapy, the acid-base status should be reevaluated and a new dose calculated. Once the plasma bicarbonate level is greater than 12 mEq/L, further bicarbonate supplementation is not indicated.

INSULIN THERAPY

Insulin therapy is critical for the resolution of ketoacidosis. However, overzealous insulin treatment can cause severe hypokalemia, hypophosphatemia, and hypoglycemia during the first 24 hours of treatment—problems that can be minimized by appropriate fluid therapy, frequent monitoring of serum electrolytes and blood glucose concentrations, and modification of the initial insulin treatment protocol as indicated. Initiating appropriate fluid therapy should always be the first step in the treatment of DKA. Delaying insulin therapy for a minimum of 2 hours is recommended to allow the benefits of fluid therapy to begin to be realized before the glucose-, potassium-, and phosphorus-lowering effects of insulin therapy commence. Additional delays and decisions on the initial dosage of insulin administered are based on serum electrolyte results. If the serum potassium concentration is within the normal range after 2 hours of fluid therapy, insulin treatment should commence as described in the subsequent paragraphs. If hypokalemia persists, insulin therapy can be delayed an additional 2 hours to allow fluid therapy to replenish potassium, the initial insulin dose can be reduced to dampen the intracellular shift of potassium and phosphorus, or both can be done. However, in our opinion, insulin therapy should be started within 4 hours of initiation of fluid therapy.

The amount of insulin needed by an individual animal is difficult to predict. Therefore an insulin preparation with a rapid onset of action and a brief duration of effect is ideal for making rapid adjustments in the dose and frequency of administration to meet the needs of that particular dog or cat. Rapid-acting regular crystalline insulin meets these criteria and is recommended for the treatment of DKA. Rapid-acting insulin analogs (e.g., insulin lispro and insulin aspart) are also effective for treating DKA in, dogs and cats. The rapid-acting insulin analog lispro insulin (Humalog) is also effective when administered as a constant-rate infusion, as described later.

Insulin protocols for the treatment of DKA include the hourly intramuscular technique, the continuous low-dose IV infusion technique, and the intermittent intramuscular then subcutaneous technique. All three routes (IV, intramuscular, and subcutaneous) of insulin administration are effective in decreasing blood glucose and ketone concentrations. Successful management of DKA is *not* dependent on the route of insulin administration. Rather, it is dependent on proper treatment of each disorder associated with DKA.

Hourly Intramuscular Insulin Technique

Dogs and cats with severe DKA should receive an initial regular crystalline insulin loading dose of 0.1 to 0.2 U/kg followed by 0.1 U/kg every1 to 2 hours thereafter. The insulin dose can be reduced by 25% to 50% for the first 2 to 3 injections if hypokalemia is a concern. Insulin should be administered into the muscles of the rear legs to ensure that the injections are penetrating muscle rather than fat or subcutaneous tissue where insulin absorption may be impaired in the dehydrated dog or cat. Diluting regular insulin 1:10 with sterile saline or special diluents available from the insulin manufacturer and using 0.3 mL U100 insulin syringes are helpful when small doses of insulin are required. The blood glucose concentration should be measured every hour using a point-of-care chemistry analyzer or PBGM device, and the insulin dosage adjusted accordingly. The goal of initial insulin therapy is to *slowly* lower the blood glucose concentration to the range of 200 to 250 mg/dL, preferably over a 6- to 10-hour time period. An hourly decline of 50 mg/dL in the blood glucose concentration is ideal. This provides a steady moderate decline, with no major shifts in osmolality. A declining blood glucose concentration also ensures that lipolysis and the supply of FFAs for ketone production have been effectively turned off. Glucose concentrations, however, decrease much more rapidly than do ketone concentrations. In general, hyperglycemia is corrected within 12 hours, but ketosis may take 48 to 72 hours to resolve.

Once initial hourly insulin therapy brings the blood glucose concentration near 250 mg/dL, hourly administration of regular insulin should be discontinued and regular insulin given every 4 to 6 hours intramuscularly or, if hydration status is good, every 6 to 8 hours subcutaneously. The initial dose is usually 0.1 to 0.3 U/kg, with subsequent adjustments based on blood glucose concentrations. In addition, at this point the IV infusion solution should have enough 50% dextrose added to create a 5% dextrose solution (100 mL of 50% dextrose added to each liter of fluids). The blood glucose concentration should be maintained between 150 and 300 mg/dL until the dog or cat is stable and eating.

Usually, a 5% dextrose solution is adequate in maintaining the desired blood glucose concentration. If the blood glucose concentration dips below 150 mg/dL or rises above 300 mg/dL, the insulin dose can be lowered or raised accordingly. Dextrose helps minimize problems with hypoglycemia and allows insulin to be administered on schedule. Delaying the administration of insulin delays correction of the ketoacidotic state.

Constant Low-Dose Intravenous Insulin Infusion Technique

Constant IV infusion of regular crystalline insulin is also effective in decreasing blood glucose concentrations. To prepare the infusion, regular crystalline insulin (2.2 U/kg for dogs; 1.1 U/kg for cats) is added to 250 mL of 0.9% saline and is initially administered at a rate of 10 mL/h in a line separate from that used for fluid therapy. This provides an insulin infusion of 0.05 (cat) and 0.1 (dog) U/kg/h—an infusion rate that has been shown to produce plasma insulin concentrations between 100 and 200 μU/mL (700-1400 pmol/L) in dogs. Because insulin adheres to glass and plastic surfaces, approximately 50 mL of the insulin-containing fluid should be run through the drip set before it is administered to the animal. The rate of insulin infusion can be reduced for the initial 2 to 4 hours if hypokalemia is a concern. Two separate catheters are recommended for treatment: a peripheral catheter for insulin administration and a central catheter for fluid administration and blood sampling. An infusion or syringe pump should be used to ensure a constant rate of insulin infusion.

Adjustments in the infusion rate are based on hourly measurements of blood glucose concentration; an hourly decline of 50 mg/dL in the blood glucose concentration is ideal. Once the blood glucose concentration approaches 250 mg/dL, the insulin infusion can be discontinued and regular insulin given every 4 to 6 hours intramuscularly or every 6 to 8 hours subcutaneously, as discussed for the hourly intramuscular protocol. Alternatively, the insulin infusion can be continued (at a decreased rate to prevent hypoglycemia) until the insulin preparation is exchanged for a longer-acting product. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL, as discussed in the section on hourly intramuscular insulin technique.

Sears et al. (2012) evaluated the efficacy of the short-acting insulin analog lispro (Humalog®, Eli Lilly) for the treatment of DKA using an IV constant rate infusion technique. Treatment with IV constant rate infusion of lispro was safe and as effective as treatment with regular crystalline insulin. Use of lispro insulin is a viable option for treating DKA, especially if production of regular crystalline insulin is discontinued in the future.

Intermittent Intramuscular/Subcutaneous Insulin Technique

The intermittent intramuscular followed by intermittent subcutaneous insulin technique is less labor intensive than the other techniques for insulin administration, but the decrease in blood glucose can be rapid and the risk of hypoglycemia greater. The initial regular crystalline insulin dose is 0.2 U/kg, administered intramuscularly. Subsequent intramuscular injections are repeated every 4 hours. Usually, insulin is administered intramuscularly only once or twice. Once the animal is rehydrated, the insulin is administered subcutaneously rather than intramuscularly every 6 to 8 hours. Subcutaneous administration is not recommended initially because of potential problems with insulin absorption from subcutaneous sites of deposition in a dehydrated dog or cat. The dosage of intramuscular or subcutaneous insulin is adjusted according to blood glucose concentrations, which initially should be measured hourly beginning with the first intramuscular injection. An hourly decline of 50 mg/dL in blood glucose concentration is ideal. Subsequent insulin dosages should be decreased by 25% to 50% if this goal is exceeded. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dL, as discussed in the section on hourly intramuscular insulin technique.

Initiating Longer-Acting Insulin

Longer-acting insulin (e.g., Lente, PZI, glargine) should not be administered until the dog or cat is stable, eating, and maintaining fluid balance without any IV infusions, and is no longer acidotic, azotemic, or electrolyte-deficient. The initial dose of the longer-acting insulin is similar to the regular insulin dose that is being used just before the switch to a longer-acting insulin. Subsequent adjustments in the longer-acting insulin dose should be based on clinical response and measurement of blood glucose concentrations, as described on page 817.

CONCURRENT ILLNESS

Therapy for DKA frequently involves the management of concurrent, often serious, illness. Common concurrent illnesses in dogs and cats with DKA include bacterial infection; pancreatitis; congestive heart failure; chronic kidney disease; hepatobiliary disease; and insulin-antagonistic disorders, most notably hyperadrenocorticism (dog), hyperthyroidism (cat), and diestrus (intact female dog). It may be necessary in such animals to modify the therapy for DKA (e.g., fluid therapy in animals with concurrent heart failure) or to implement additional therapy (e.g., antibiotics), depending on the nature of the concurrent illness. Insulin therapy, however, should not be delayed or discontinued because of concurrent illness. Resolution of ketoacidosis can be achieved only through insulin therapy. If nothing is to be given per os, insulin therapy should be continued and the blood glucose concentration maintained with IV dextrose infusions. If a concurrent insulin-antagonistic disease is present, it may be necessary to eliminate the disease while the animal is still ill to improve insulin effectiveness and resolve the ketoacidosis (e.g., ovariohysterectomy in diestrual bitch).

Prognosis

DKA remains one of the most difficult metabolic therapeutic challenges in veterinary medicine. One must remain aware of all the complicating factors in treatment and remember that fluid therapy, insulin, and potassium supplementation are the cornerstones of successful management. Added to these factors are close supervision and monitoring of the animal and identification and treatment of concurrent disease that is invariably present. Reported in-hospital mortality rates for DKA range from 20% to 30%, primarily as a result of severe concurrent illness. During the past decade in our hospital, the mortality rate has decreased to approximately 5% and death has usually been attributed to underlying medical disorders (e.g., pancreatitis) that precipitated the DKA, client financial constraints, or both rather than to the metabolic complications of ketoacidosis. It is worth reiterating that a careful search should always be made, both at the time of initial history and physical examination and during therapy, for underlying problems that might have precipitated the episode of DKA or developed during treatment of DKA. In particular, pneumonia, sepsis, pancreatitis, and hormonal diseases causing insulin resistance are often silent at the time of presentation. Despite all precautions and diligent therapy, a fatal outcome cannot be avoided in some cases. Nevertheless, with logical therapy and careful monitoring, the goal of therapy for DKA (i.e., achieving a healthy diabetic dog or cat) is attainable. Diabetic remission is also possible in cats following resolution of DKA, especially in cats with concurrent pancreatic disease or cats being treated with glucocorticoids at the time DKA is diagnosed.

Diabetic Hyperosmolar Hyperglycemic State

Diabetic hyperosmolar hypyerglycemic state (HHS) is an uncommon complication of diabetes mellitus in the dog and cat. This syndrome is characterized by severe hyperglycemia (blood glucose concentration >600 mg/dL), hyperosmolality (>350 mOsm/kg), and dehydration in the absence of significant ketosis. Progressively worsening lethargy ultimately leads to obtundation and coma as hyperosmolality becomes more severe. Concurrent disorders such as kidney failure, congestive heart failure, infection, and pancreatitis are common. The onset of HHS may be insidious and preceded for days or weeks by the classic signs of diabetes mellitus. Progressive weakness, anorexia, and lethargy develop, usually in conjunction with a reduction in water intake. Physical examination often reveals the presence of profound dehydration. These pets are typically lethargic, extremely depressed, or actually comatose. There is a direct relationship between the severity of the hyperosmolality and the severity of neurologic signs. Hyperosmolality is a consistent finding in HHS and can exceed 400 mOsm/kg. Ketosis is usually absent in dogs and cats with HHS, although trace ketonuria may occur. Ketoacidosis is not a part of HHS but metabolic acidosis may be identified, usually in the form of lactic acidosis. The goals of therapy for HHS are similar to DKA (see page 841). Restoring intravascular volume and lost electrolytes using isotonic fluids has the highest priority. Osmolality is returned to normal by lowering the blood glucose concentration and by replacing water deficits. Initially, fluid therapy is used to lower the blood glucose concentration; insulin should not be administered until intravascular volume is restored, electrolyte derangements improved, and blood pressure stabilized. Careful and frequent monitoring of the dog's or cat's clinical and laboratory response to therapy is essential. The need for insulin treatment is not as critical with HHS as with DKA, in part because ketone production and its metabolic consequences are minimal to nonexistent with HHS. In addition, insulin can cause a rapid decrease in the blood glucose concentration and ECF osmolality, changes which promote cerebral edema. The techniques for insulin administration are similar to those discussed for DKA. However, the insulin dosage used for the hourly IM technique or the insulin infusion rate used for the constant low-dose insulin infusion technique should be decreased by 50% initially to dampen the decrease in the blood glucose concentration and avoid a rapid decrease in ECF osmolality. These animals are critically ill and require close supervision. The prognosis for recovery is guarded to poor.

INSULIN-SECRETING β-CELL NEOPLASIA

Etiology

Functional tumors arising from the β cells of the pancreatic islets are malignant tumors that secrete insulin independent of the typically suppressive effects of hypoglycemia. β-Cell tumors, however, are not completely autonomous and respond to provocative stimuli such as an increase in blood glucose by secreting insulin, often in excessive amounts. Immunohistochemical analysis of β-cell tumors has revealed a high incidence of multihormonal production, including pancreatic polypeptide, somatostatin, glucagon, serotonin, and gastrin. However, insulin has been identified as the most common product demonstrated within the neoplastic cells, and clinical signs are primarily those that result from insulin-induced hypoglycemia.

Insulin-secreting β-cell tumors are uncommon in dogs and rare in cats. Virtually all β-cell tumors in dogs are malignant, and most dogs have microscopic or grossly visible metastatic lesions at the time the disease is diagnosed. The most common metastatic sites are the regional lymphatics and lymph nodes, liver, and peripancreatic omentum. Pulmonary metastasis is uncommon and occurs late in the disease. In most dogs hypoglycemia recurs days to weeks after surgical excision of the tumor. The high prevalence of metastatic lesions at the time afflicted dogs are initially examined results, in part, from the typically protracted time it takes for clinical signs to develop and the interval between the time a client initially observes signs (e.g., collapsing episodes, seizures) and seeks assistance from a veterinarian. Most dogs are symptomatic for 1 to 3 months before they are brought to a veterinarian.

Clinical Features

SIGNALMENT

β-Cell tumors typically occur in middle-aged or older dogs (median age, 10 years) but can occur in dogs as young as 3 to 4 years of age. No sex-related predilection is seen. β-Cell tumors are most commonly diagnosed in large breeds of dogs such as the German Shepherd dog, Labrador Retriever, Golden Retriever, and mixed breed dogs but also occur in dogs as small as Pomeranians. β-Cell tumors have also been reported in Siamese and mixed-breed cats older than 10 years of age.

CLINICAL SIGNS

Clinical signs are caused by hypoglycemia and an increase in circulating catecholamine concentrations and include, weakness, seizures, collapsing episodes, tremors, ataxia and disorientation (Box 49.13). The severity of clinical signs depends on the duration and severity of hypoglycemia. Dogs with chronic hypoglycemia or with recurring episodes appear to tolerate low blood glucose concentrations (20-30 mg/dL) for prolonged periods without clinical signs, and only small additional changes in the blood glucose concentration are then required to produce symptomatic episodes. Fasting, excitement, exercise, and eating may trigger the development of clinical signs. Because of the compensatory counterregulatory mechanisms that are designed to increase blood glucose concentrations when hypoglycemia develops, clinical signs tend to be episodic and are generally observed for only a few seconds to minutes. If these counterregulatory mechanisms are inadequate, seizures occur as the blood glucose concentration continues to decrease. Seizures are often self-limiting, lasting from 30 seconds to a few minutes, and may stimulate further catecholamine secretion and the activation of other counterregulatory mechanisms that increase blood glucose concentrations above critical levels.

BOX 49.13

Clinical Signs Associated With Insulin-Secreting Tumors in Dogs

Seizures*
Weakness*
Collapse
Ataxia
Tremors, shaking
Muscle fasciculations
Nervousness
Abnormal behavior
Disorientation
Polyphagia
Weight gain
Posterior weakness (neuropathy)
Lethargy

*Common clinical signs.

PHYSICAL EXAMINATION

Physical examination findings in dogs with β-cell tumors are surprisingly unremarkable; dogs are usually free of visible or palpable abnormalities. Weakness and lethargy are the most common findings and are identified in approximately 30% and 20% of our cases, respectively. Collapsing episodes and seizures may occur during the examination but are uncommon. Weight gain is evident in some dogs and is a result of the anabolic effects of excess insulin in dogs with a normal or increased appetite.

Peripheral Neuropathy

Peripheral neuropathies have been observed in dogs with β-cell tumors and may cause paraparesis to tetraparesis; facial paresis to paralysis; hyporeflexia to areflexia; hypotonia; and muscle atrophy of the appendicular, masticatory, and/or facial muscles. Sensory nerves may also be affected. Onset of clinical signs may be acute (i.e., days) or insidious (i.e., weeks to months). Histopathologic findings in motor and sensory nerves include moderate to severe axonal necrosis, nerve fiber loss, and variable demyelination-remyelination. The pathogenesis of the polyneuropathy is not known. Proposed theories include metabolic derangements of the nerves induced by chronic and severe hypoglycemia or some other tumor-induced metabolic deficiency, an immune-mediated paraneoplastic syndrome resulting from shared antigens between tumor and nerves, or toxic factors produced by the tumor that deleteriously affect the nerves. Treatment is aimed at surgical removal of the β-cell tumor. Prednisone therapy (initially 0.5 mg/kg q12h) may also improve clinical signs. Prognosis for improvement in clinical signs is guarded to poor, although the occasional dog shows remarkable improvement in ambulation after removal of the tumor and reestablishment of a normal blood glucose concentration.

CLINICAL PATHOLOGY

Results of CBC and urinalysis are usually normal. The only abnormality consistently identified in serum biochemistry profiles is hypoglycemia. The remainder of the serum biochemistry profile is usually normal. Hypoalbuminemia, hypophosphatemia, hypokalemia, and increased alkaline phosphatase and ALT activities may occur, but these findings are considered nonspecific and not helpful in arriving at a definitive diagnosis. A correlation between increased liver enzyme activities and metastasis of β-cell tumors to the liver has not been established.

Serum fructosamine concentration is a marker of the average blood glucose concentration during the lifespan of the circulating protein. Serum fructosamine concentrations below the reference range support the existence of significant hypoglycemia and an insulin secreting tumor, assuming the history, physical examination and findings on routine bloodwork are consistent with the diagnosis of a β-cell tumor. A serum fructosamine concentration below the reference range may also occur with other disorders that cause prolonged periods of hypoglycemia or that interfere with the assay (see page 818).

Ninety percent of dogs seen at our hospital had a random blood glucose concentration less than 60 mg/dL (median, 38 mg/dL). Dogs with β-cell tumors occasionally have a blood glucose concentration of 60 to 75 mg/dL. Such a finding does not rule out hypoglycemia as a cause of episodic weakness or seizure activity. Fasting with hourly evaluations of the blood glucose concentration should be carried out to induce hypoglycemia in dogs with suspected β-cell tumor. The time required to induce hypoglycemia with fasting depends in part on the extent of disease at the time the dog is examined and ranges from a few hours to longer than 24 hours. Hypoglycemia (blood glucose < 60 mg/dL) usually occurs within 12 hours of withholding food. We have had a few dogs require longer than 24 hours of fasting before hypoglycemia became apparent and a couple of dogs that did not develop hypoglycemia after 30 hours of fasting, and the diagnosis of β-cell tumor was not established until 2 to 3 months after initial presentation.

Diagnosis

Diagnosis of a β-cell tumor requires initial confirmation of hypoglycemia, followed by documentation of inappropriate insulin secretion and identification of a pancreatic mass using ultrasonography, computed tomography (CT), or exploratory celiotomy. Given the potential differential diagnoses for hypoglycemia (see Box 49.2), a tentative diagnosis of a β-cell tumor can often be made on the basis of the history, physical examination findings, and an absence of abnormalities other than hypoglycemia shown by routine blood tests. Abdominal ultrasonography can be used to identify a mass in the region of the pancreas and to look for evidence of potential metastatic disease in the liver and surrounding structures (Fig. 49.19). Because of the small size of most β-cell tumors and similar echogenicity of the tumor and the adjacent normal pancreas, abdominal ultrasonographic findings are often interpreted as normal, although a pancreatic mass or a metastatic lesion can be found at surgery. A normal abdominal ultrasonographic finding does not rule out the diagnosis of a β-cell tumor. Because β-cell tumors are highly vascular compared with the pancreas, evaluation of the arterial phase of a contrast study during dual-phase CT angiography, if available, is recommended to identify the tumor and its metastatic sites before surgery is performed. Thoracic radiographs are of minimal value in documenting metastatic disease, primarily because identifiable metastatic nodules in the lung occur late in the disease.

The diagnosis of a β-cell tumor is established by evaluating the serum insulin concentration at a time when hypoglycemia is present. Hypoglycemia suppresses insulin secretion in normal animals, with the degree of suppression directly related to its severity. Hypoglycemia fails to have this same suppressive effect on insulin secretion if the insulin is synthesized and secreted from autonomous neoplastic cells because tumor cells that produce and secrete insulin are less responsive to hypoglycemia than are normal β cells. Invariably, the dog with a β-cell tumor will have an inappropriate excess of insulin relative to that needed for a particular blood glucose concentration. Confidence in identifying an inappropriate excess of insulin depends on the severity of the hypoglycemia; the lower the blood glucose concentration, the more confident the clinician can be in identifying inappropriate hyperinsulinemia, especially when the serum insulin concentration falls in the reference range. If the blood glucose concentration is low (preferably < 50 mg/dL) and the insulin concentration is in the upper half of the reference range or is increased, the animal has a relative or absolute excess of insulin that can best be explained by the presence of an insulin-secreting β-cell tumor.

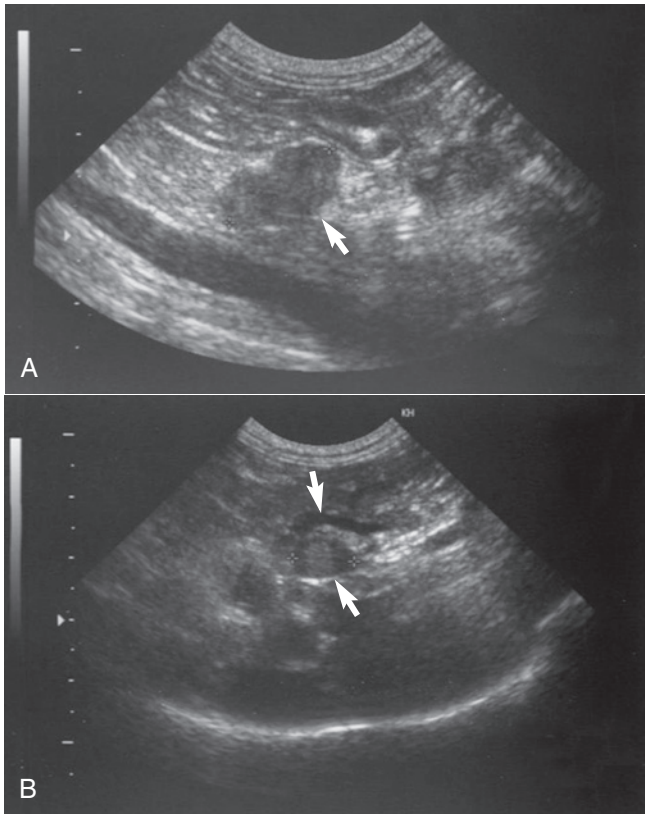


FIG 49.19
Ultrasonogram of the pancreas showing an islet β-cell tumor *(arrow)* **(A)** and an enlarged hepatic lymph node *(arrows)* **(B)** resulting from metastasis of the β-cell tumor to the liver in a 9-year-old Cocker Spaniel.

Most dogs with β-cell neoplasia are persistently hypoglycemic. If the blood glucose concentration is less than 60 mg/dL (preferably < 50 mg/dL), serum should be submitted to a commercial veterinary endocrine laboratory for determination of glucose and insulin concentration. The insulin assay must be validated for use in dogs (and cats), and interpretation of insulin results should be based on the reference interval established by the laboratory utilized. If the blood glucose concentration is greater than 60 mg/dL, fasting may be necessary to induce hypoglycemia. Blood glucose concentrations should be evaluated hourly during the fast, and blood obtained for glucose and insulin determination when the blood glucose concentration decreases

to less than 50 mg/dL. It is important to remember that blood glucose results obtained from PBGM devices are often lower than results obtained using benchtop methods. A blood sample for submission to a commercial laboratory for glucose and insulin determinations should not be obtained until the blood glucose measured on these devices is less than 50 mg/dL. Once hypoglycemia has been induced, the dog can be fed several small meals over the next 2 to 3 hours to minimize overstimulation of the tumor and rebound hypoglycemia.

Serum insulin concentrations must be evaluated simultaneously in relation to the blood glucose concentration. Finding a serum insulin concentration that exceeds the upper limit of the reference range in a dog with a corresponding blood glucose concentration less than 50 mg/dL in combination with appropriate clinical signs and clinicopathologic findings strongly supports the diagnosis of a β-cell tumor. A β-cell tumor is also possible if the serum insulin concentration is in the upper half of the reference range. Insulin values near the lower end of the reference range may be found in dogs with other causes of hypoglycemia as well as a β-cell tumor. Carefully reviewing the history, physical examination findings, and diagnostic test results in relation to the differentials for hypoglycemia (see Box 49.2) and, if necessary, repeating serum glucose and insulin measurements when hypoglycemia is more severe will usually reveal the cause of the hypoglycemia. Any serum insulin concentration that is below the reference range is consistent with insulinopenia and does not indicate the presence of a β-cell tumor. Similar guidelines are used for cats with a suspected β-cell tumor.

Treatment

OVERVIEW OF TREATMENT

Treatment options for a β-cell tumor include surgical exploration, medical treatment for chronic hypoglycemia, and both of these treatments combined. Surgery offers a chance to cure dogs with a resectable solitary mass. In dogs with nonresectable tumors or with obvious metastatic lesions, removal of as much abnormal tissue as possible frequently results in remission, or at least alleviation, of clinical signs and an improved response to medical therapy. Survival time is longer in dogs undergoing surgical exploration and tumor debulking followed by medical therapy compared with dogs that receive only medical treatment. Despite these benefits, surgery remains a relatively aggressive mode of treatment, in part because of the high prevalence of metastatic disease, the older age of many dogs at the time β-cell neoplasia is diagnosed, the potential for postoperative pancreatitis, and the unpredictable response to surgery as it relates to improvement in hypoglycemia and clinical signs. As a general rule, we are less inclined to recommend surgery in aged dogs (i.e., older than 12 years), dogs with extensive metastatic disease identified by diagnostic imaging, and dogs with significant concurrent disease. (See Suggested Readings for detailed information on surgical techniques.)

PERIOPERATIVE MANAGEMENT OF DOGS UNDERGOING SURGERY

The success of surgery depends in part on providing appropriate fluid therapy, dextrose, and supportive care during the perioperative period to avoid severe hypoglycemia and postoperative pancreatitis and to improve the likelihood of an uneventful recovery. This can usually be accomplished through frequent feeding of small meals and administration of glucocorticoids (Box 49.14). A continuous IV infusion of a balanced electrolyte solution containing 2.5% to 5% dextrose is important during the perioperative period. The goal of the dextrose infusion is to provide substrate for CNS function thereby minimizing signs of hypoglycemia while maintaining blood glucose concentrations greater than 40 mg/dL—not to reestablish a normal blood glucose concentration.

BOX 49.14

Long-Term Medical Therapy for Dogs With β-Cell Neoplasia

Standard Treatments

1. Dietary therapy
   a. Feed canned or dry food in three to six small meals daily.
   b. Dietary fat, complex carbohydrates, and fiber help prolong postprandial glucose absorption.
   c. Avoid foods containing monosaccharides, disaccharides, propylene glycol, and corn syrup.
2. Limit exercise to walks; avoid strenuous exercise.
3. Glucocorticoid therapy
   a. Prednisone, 0.5 mg/kg divided into two doses initially
   b. Gradually increase dose and frequency of administration, as needed.
   c. Goal is to control clinical signs, not to reestablish euglycemia.
   d. Consider alternative treatments if signs of iatrogenic hypercortisolism become severe or if glucocorticoids become ineffective.

Additional Treatments

1. Diazoxide therapy
   a. Continue standard treatment; reduce glucocorticoid dose if polyuria-polydipsia (PU-PD) is unacceptable.
   b. May initiate diazoxide early when glucocorticoid dose is low or later when glucocorticoids become ineffective or PU-PD becomes unacceptable
   c. Diazoxide, 5 mg/kg q12h initially
   d. Gradually increase dose as needed, not to exceed 60 mg/kg/day.
   e. Goal is to control clinical signs, not to reestablish euglycemia.
2. Somatostatin therapy
   a. Continue standard treatment; reduce glucocorticoid dose if PU-PD is unacceptable.
   b. Octreotide (Sandostatin), 10 to 40 µg/dog administered subcutaneously q12h to q8h

The IV dextrose infusion can be initiated the evening before surgery, at the time food and water are withheld and continued throughout the perioperative period. Initiating fluid therapy before surgery helps ensure adequate circulation to the pancreas thereby minimizing the risk of postoperative pancreatitis.

Concentrations of dextrose in excess of 5% should be avoided to prevent overstimulation of the pancreatic tumor and rebound hypoglycemia. If the dextrose infusion is ineffective in preventing severe hypoglycemia, a constant-rate infusion of glucagon should be considered. Glucagon is a potent stimulant of hepatic glycogenolysis and gluconeogenesis and is effective in maintaining normal blood glucose concentrations in dogs with β-cell neoplasia when administered by constant rate infusion (Fig. 49.20). Lyophilized glucagon USP (1 mg) is reconstituted with the diluent provided by the manufacturer (Eli Lilly), and the solution is added to 1 L of 0.9% saline, making a 1-μg/mL solution that can be administered by syringe pump. The initial dose is 5 to 10 ng/kg of body weight/min. The dose is adjusted, as needed, to maintain blood glucose concentration between 60 and 100 mg/dL. When glucagon is discontinued, the dose should be gradually decreased over 1 to 2 days and the blood glucose concentration monitored for recurrence of hypoglycemia.

POSTOPERATIVE COMPLICATIONS

The most common postoperative complications are pancreatitis, hyperglycemia, and hypoglycemia. The development of these complications is directly related to the expertise of the surgeon in handling pancreas and excising these tumors, the location of the tumor in the pancreas (i.e., peripheral limb versus body of the pancreas; Fig. 49.21), the presence or absence of functional metastatic lesions, and the adequacy of fluid therapy during the perioperative period. Severe pancreatitis occurs most commonly with attempts to remove tumors located in the body of the pancreas, where the blood supply and the pancreatic ducts are located. Tumors located in the body of the pancreas should be considered inoperable because of the high prevalence of postoperative life-threatening pancreatitis despite appropriate perioperative treatment aimed at preventing its development. The reader is referred to Chapter 37 for information on the treatment of pancreatitis.

The development of transient diabetes mellitus after surgical removal of a β-cell tumor is not an indication of cure. It is believed to result from inadequate insulin secretion by "atrophied" normal β cells. Removal of all, or most, of the neoplastic cells acutely deprives the dog of insulin. Until the atrophied normal cells regain their secretory abilities, the dog will be hypoinsulinemic and may require exogenous insulin injections to maintain euglycemia. Insulin therapy is initiated postoperatively only if hyperglycemia and glycosuria persist for longer than 1 to 2 days beyond the time that all dextrose-containing IV fluids have been discontinued. Initial insulin therapy should be conservative, that is, 0.25 U of lente or NPH insulin per kilogram of body weight should be given once daily. Subsequent adjustments in insulin dosage or frequency of administration should be made according to clinical response and blood glucose determinations. The need for insulin treatment is usually transient, lasting from a few days to a few months. Rarely will a dog remain diabetic for longer than 6 months. Client evaluation

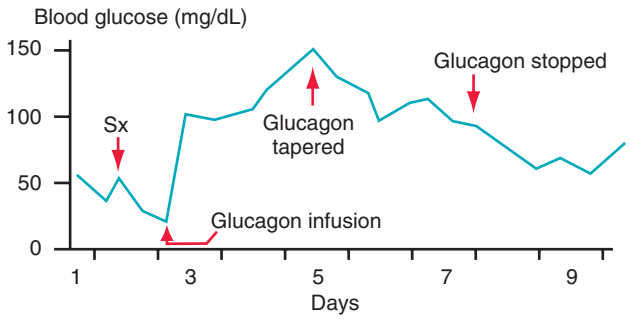


FIG 49.20
Blood glucose concentrations in a 13-year-old female spayed Pomeranian before and after surgical removal of an insulin-secreting β-cell tumor. Pancreatitis and severe hypoglycemia developed postoperatively. The hypoglycemia resolved and euglycemia was maintained after the initiation of a constant-rate intravenous (IV) infusion of glucagon. The dosage of glucagon was gradually tapered beginning on day 5, feeding of small amounts of food was begun on day 7, and the IV infusion of glucagon was stopped on day 8. Severe hypoglycemia did not recur. *Sx,* surgery (From Feldman EC et al: *Canine and feline endocrinology,* ed 4, St Louis, 2015, Elsevier Saunders.)

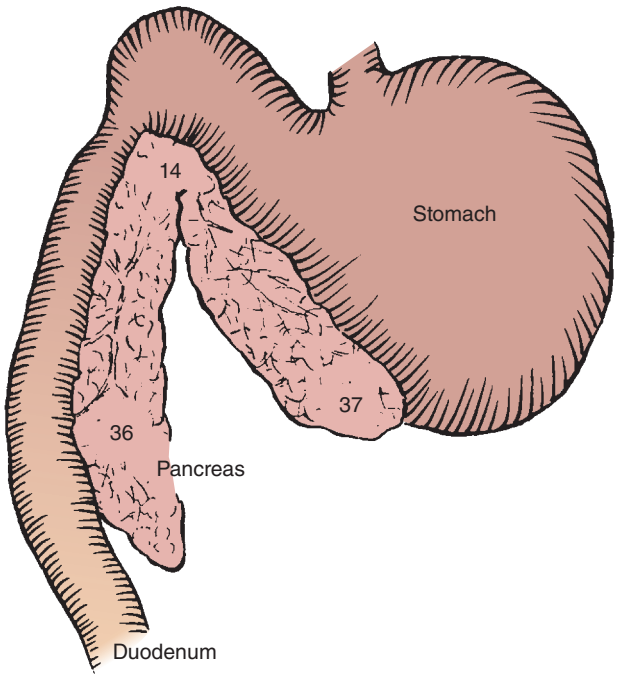


FIG 49.21
Tumor location in 87 dogs with islet β-cell tumors. (Adapted from Feldman EC et al: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

of the pet's urine glucose is helpful in identifying when insulin therapy is no longer needed. Failure to identify glucose in the urine in conjunction with the disappearance of polyuria and polydipsia is an indication that insulin therapy should be discontinued. If hyperglycemia and glycosuria recur, insulin therapy can be reinstituted but at a lower dose.

Dogs that remain hypoglycemic after surgical removal of a β-cell tumor have functional metastatic lesions. The dextrose and/or glucagon infusion should be continued postoperatively until pancreatitis has resolved (if present); the dog is stable, eating, and drinking; and medical treatment for chronic hypoglycemia can be initiated.

MEDICAL TREATMENT FOR CHRONIC HYPOGLYCEMIA

Medical treatment for chronic hypoglycemia should be initiated if surgery is not performed, or when metastatic or inoperable neoplasia results in the recurrence of hypoglycemia following surgery. The goals of medical treatment are to reduce the frequency and severity of clinical signs of hypoglycemia and to prevent an acute hypoglycemic crisis—not to establish euglycemia, per se. Medical treatment is palliative and minimizes hypoglycemia by providing a continuous source of glucose from the gastrointestinal tract (frequent feedings); increasing hepatic gluconeogenesis and glycogenolysis (glucocorticoids); or inhibiting the synthesis, secretion, or peripheral cellular actions of insulin (glucocorticoids, diazoxide, somatostatin; see Box 49.14). Surgical debulking of functional masses may enhance the effectiveness of medical therapy. The best results are obtained when surgical debulking is performed shortly after the diagnosis of an insulin-secreting tumor has been established.

Frequent Feedings

Frequent feedings provide a constant source of calories as a substrate for the excess insulin secreted by β-cell tumors. Diets that are high in fat, complex carbohydrates, and fiber will delay gastric emptying and slow intestinal glucose absorption, helping to minimize the postprandial increase in portal blood glucose concentration and the stimulation of insulin secretion by the tumor. Simple sugars are rapidly absorbed, have a potent stimulatory effect on insulin secretion by neoplastic β cells, and should be avoided. A combination of canned and dry dog food, fed in three to six small meals daily, is recommended. Daily caloric intake should be controlled because hyperinsulinemia promotes obesity. Exercise should be limited to short walks on a leash.

Glucocorticoid Therapy

Glucocorticoid therapy should be initiated when dietary manipulations are no longer effective in preventing clinical signs of hypoglycemia. Glucocorticoids antagonize the effects of insulin at the cellular level, stimulate hepatic glycogenolysis, and indirectly provide the necessary substrates for hepatic gluconeogenesis. Prednisone (dog) or prednisolone (cat) are most often used at an initial dose of 0.25 mg/kg every 12 hours. Adjustments in the dose are based on clinical response. The dose of prednisone required to control clinical signs increases with time in response to growth of the tumor and its metastatic sites. Eventually, the adverse effects of prednisone, specifically polyuria and polydipsia, become unacceptable to clients. When this occurs, the dose of prednisone should be reduced by 25% to 50% but not stopped and additional therapy considered.

Diazoxide Therapy

Diazoxide (Proglycem) is a benzothiadiazide diuretic that inhibits insulin secretion, stimulates hepatic gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose. The net effect is hyperglycemia. Diazoxide therapy can be initiated early in the medical treatment of a β-cell tumor when the glucocorticoid dose is low and polyuria and polydipsia are acceptable to the client, or it can be initiated later when glucocorticoids are no longer effective in controlling clinical signs of hypoglycemia or when the severity of polyuria and polydipsia has become unacceptable to the client. In the latter situation, glucocorticoids should be continued but at a lower dose. The initial dose of diazoxide is 5 mg/kg every 12 hours. The dose may be gradually increased as needed to control clinical signs but should not exceed 60 mg/kg/day. The most common adverse reactions to diazoxide are anorexia and vomiting. Administering the drug with a meal or decreasing the dose, at least temporarily, is usually effective in controlling adverse gastrointestinal signs. Other potential complications include diarrhea, bone marrow suppression, pancreatitis and diabetes mellitus.

Somatostatin Therapy

Octreotide (Sandostatin) is an analog of somatostatin that inhibits the synthesis and secretion of insulin by normal and neoplastic β cells. The responsiveness of β-cell tumors to the suppressive effects of octreotide is unpredictable and depends on the presence of somatostatin-binding membrane receptors on the tumor cells. Octreotide at a dose of 10 to 40 μg/dog, administered subcutaneously two to three times a day, has alleviated hypoglycemia in approximately 40% of treated dogs, but the suppressive effect on serum insulin concentration is short (<6 hours). Adverse reactions have not been seen at these doses. Octreotide is not a viable option for most clients because of cost.

Streptozotocin Therapy

Streptozotocin is a naturally occurring nitrosourea that selectively destroys pancreatic β cells and has been used to treat β-cell tumors in dogs. Unfortunately, the effectiveness of streptozotocin in improving hypoglycemia, controlling clinical signs, and prolonging survival time has been variable, and adverse reactions to streptozotocin (severe vomiting, acute pancreatitis, kidney failure) can be severe and life-threatening. In one study, diabetes mellitus developed in 8 of 19 dogs and, in 6 dogs, resulted in euthanasia or death (Northrup et al., 2013). (See Suggested Readings for more information on streptozotocin.)

Prognosis

The long-term prognosis for β-cell neoplasia is guarded to poor. Studies suggest that survival is longer in dogs that undergo surgical exploration and tumor debulking followed by medical therapy, compared with dogs that receive only medical treatment. Tobin et al. (1999) and Polton et al. (2007) reported median survival times after diagnosis of 74 and 196 days for dogs treated medically compared with 381 and 785 days for dogs that initially underwent surgery followed by medical therapy, respectively. The extent to which surgery can alter the prognosis depends on the clinical stage of the disease, most notably the extent of metastatic lesions. In our hospital, approximately 10% to 15% of dogs undergoing surgery for a β-cell tumor die or are euthanized at the time of or within 1 month of surgery because metastatic disease causes postoperative hypoglycemia that is refractory to medical management, or because complications related to pancreatitis develop. An additional 20% to 25% of dogs die or are euthanized within 6 months of surgery because of recurrence of clinical hypoglycemia that becomes refractory to medical management. The remaining 60% to 70% live beyond 6 months postoperatively, many beyond 1 year after surgery, before uncontrollable hypoglycemia develops, resulting in death or necessitating euthanasia. Additional surgery to debulk metastatic lesions may improve the dog's responsiveness to medical therapy and prolong survival time in some dogs that become nonresponsive to medical treatment after the initial surgery.

GASTRIN-SECRETING NEOPLASIA

Gastrin-secreting tumors (gastrinomas) are functional malignant tumors that are usually located in the pancreas of dogs and cats. Sites of metastasis include the liver, regional lymph nodes, spleen, and mesentery. Clinical signs result from the consequences of excess gastric hydrochloric acid secretion in response to excess secretion of gastrin by the tumor.

Clinical Features

The most consistent clinical signs are chronic vomiting, weight loss, anorexia, and diarrhea in an older animal (Box 49.15). Gastric and duodenal ulcers and esophagitis are common and may cause hematemesis, hematochezia, melena, and regurgitation. Acidification of intestinal contents may inactivate pancreatic digestive enzymes, precipitate bile salts, interfere with formation of chylomicrons, and damage intestinal mucosal cells. Diarrhea with malabsorption and steatorrhea may develop as a consequence. Findings on physical examination include lethargy, fever, dehydration, abdominal pain, and shock if blood loss is severe or ulcers have perforated. Potential abnormalities identified on a CBC include regenerative anemia, hypoproteinemia, and neutrophilic leukocytosis. Abnormalities in the serum biochemistry panel include hypoproteinemia, hypoalbuminemia, hypocalcemia, and mild increases in serum ALT and alkaline phosphatase activities. Hyponatremia, hypochloremia, hypokalemia, and metabolic alkalosis may develop in dogs and cats that vomit frequently. Hyperglycemia and hypoglycemia have been noted in a few cases. The urinalysis is usually unremarkable.

BOX 49.15

Clinical Signs of Gastrinoma in Dogs and Cats

Vomiting*
Anorexia*
Lethargy, depression*
Diarrhea*
Weight loss*
Melena
Hematemesis
Fever
Polydipsia
Abdominal pain
Hematochezia

*Common clinical signs.

Abdominal radiographs are usually normal. If an ulcer has perforated through the serosal surface, radiographic signs consistent with peritonitis may be present. Contrast-enhanced radiographic studies may show gastric or duodenal ulcers; thickening of the gastric rugal folds, pyloric antrum, or intestine; and the rapid intestinal transit of barium. In an animal with concurrent severe esophagitis, secondary megaesophagus or aberrant, nonperistaltic esophageal motility may be identified fluoroscopically. Ultrasonographic evaluation of the abdomen may identify a pancreatic mass or its metastasis. However, gastrinomas vary tremendously in size and may not be detected with ultrasound.

Gastroduodenoscopy may reveal severe esophagitis and ulceration, especially near the cardia. Gastric rugal folds may be thickened. Gastric and duodenal hyperemia, erosions, or ulcerations are often visible. Histologic evaluation of esophageal, gastric, and duodenal biopsy specimens may be normal or may reveal variable degrees of inflammation consisting of infiltrates of lymphocytes, plasma cells, and neutrophils; gastric mucosal hypertrophy; fibrosis; and loss of the mucosal barrier.

Diagnosis

Gastrinoma should be included among the differential diagnoses for any dog or cat with melena or hematemesis or in which severe gastric and duodenal ulceration is identified. Unless a pancreatic mass is identified by ultrasonography, most dogs and cats with gastrinoma will inadvertently be diagnosed with severe inflammatory bowel disease, gastroduodenal erosions, and ulcers, and they will be treated with inhibitors of gastric acid secretion, mucosal protectants, antibiotics, and changes in diet. The probability of a gastrinoma increases if ultrasonography reveals a pancreatic mass, the dog or cat does not respond to medical therapy directed at nonspecific inflammation and ulceration of the gastrointestinal tract, or clinical signs and gastrointestinal tract

ulceration recur after antiulcer therapy is discontinued. A definitive diagnosis of gastrinoma requires histologic and immunocytochemical evaluation of a pancreatic mass excised at surgery. A finding of increased baseline serum gastrin concentrations from blood obtained after an overnight fast increases the suspicion of gastrinoma. Additional differential diagnoses for increased serum gastrin concentrations include gastric outflow tract obstruction, kidney failure, short-bowel syndrome, chronic gastritis, hepatic disease, and animals receiving antacid therapy (e.g., H_2-receptor antagonists, proton pump inhibitors). Baseline serum gastrin concentrations may vary, with occasional values in the reference range in animals with gastrinoma. Provocative testing (e.g., secretin stimulation test, calcium challenge test) or exploratory laparotomy should be considered in dogs strongly suspected of having gastrinoma but with normal baseline serum gastrin concentrations. (See Suggested Readings for more information on provocative testing.)

Treatment

Treatment should be directed at surgical excision of the tumor and control of gastric acid hypersecretion. Gastrointestinal tract ulceration can usually be managed by reducing gastric hyperacidity through administration of H_2-receptor antagonists (e.g., ranitidine, famotidine), proton pump inhibitors (e.g., omeprazole), gastrointestinal tract protectants (e.g., sucralfate), or prostaglandin E_1 analogs (e.g., misoprostol). (See Chapter 28 for more information on these gastrointestinal tract drugs.) Surgical resection of an ulcer may be required, especially if the ulcer has perforated the bowel. Surgical resection of the tumor is necessary to obtain a cure, although metastasis to the liver, regional lymph nodes, and mesentery is common. Even if metastatic disease is present, tumor debulking may enhance the success of medical therapy.

Prognosis

The long-term prognosis for gastrinoma is guarded to poor. Evidence of metastasis was present in 76% of reported dogs and cats at the time a gastrinoma was diagnosed. Reported survival time in dogs and cats treated surgically, medically, or both ranged from 1 week to 18 months (mean, 4.8 months). However, the short-term prognosis has improved with the advent of drugs that can reduce gastric hyperacidity and protect and promote healing of the ulcers.

Suggested Readings

Feldman EC, et al. *Canine and feline endocrinology*. ed 4. St. Louis: Elsevier; 2015.

Johnston SA, Tobias KM. *Veterinary surgery: small animal*. St Louis: Elsevier Saunders; 2018.

Canine Diabetes Mellitus

Beam S, et al. A retrospective-cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases. *Vet Ophthalmol*. 1999;2:169.

Briggs C, et al. Reliability of history and physical examination findings for assessing control of glycemia in dogs with diabetes mellitus: 53 cases (1995-1998). *J Am Vet Med Assoc*. 2000;217:48.

Cohen TA, et al. Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs. *J Am Vet Med Assoc*. 2009;235:276.

Cohn LA, et al. Assessment of five portable blood glucose meters, a point-of-care analyzer, and color test strips for measuring blood glucose concentration in dogs. *J Am Vet Med Assoc*. 2000;216:198.

Davison LJ, et al. Study of 253 dogs in the United Kingdom with diabetes mellitus. *Vet Rec*. 2005;156:467.

Davison LJ, et al. Anti-insulin antibodies in diabetic dogs before and after treatment with different insulin preparations. *J Vet Intern Med*. 2008;22:1317.

Davison LJ, et al. Autoantibodies to GAD65 and IA-2 in canine diabetes mellitus. *Vet Immunol Immunopathol*. 2008;126:83.

Della Maggiore A, et al. Efficacy of protamine zinc recombinant human insulin for controlling hyperglycemia in dogs with diabetes mellitus. *J Vet Intern Med*. 2012;26:109.

Fall T, et al. Diabetes mellitus in a population of 180,000 insured dogs: incidence, survival, and breed distribution. *J Vet Intern Med*. 2007;21:1209.

Fall T, et al. Diabetes mellitus in Elkhounds is associated with diestrus and pregnancy. *J Vet Intern Med*. 2010;24:1322.

Ford SL, et al: Evaluation of detemir insulin in diabetic dogs managed with home blood glucose monitoring, Proceedings, ACVIM Forum, Anaheim, CA, 2010, p.442.

Fracassi F, et al. Breed distribution canine diabetes mellitus in Italy. *Vet Res Commun*. 2004;28:339.

Fracassi F, et al. Use of insulin glargine in dogs with diabetes mellitus. *Vet Rec*. 2012;170:52.

Guptill L, et al. Time trends and risk factors for diabetes mellitus in dogs: analysisi of veterinary medical data base records (1970-1999). *Vet J*. 2003;165:240.

Hofer-Inteeworn N, et al. Effect of hypothyroidism on insulin sensitivity and glucose tolerance in dogs. *Am J Vet Res*. 2012;735:529.

Lorenzen FH. The use of isophane inulin for the control of diabetes mellitus in dogs. *Acta Vet Scand*. 1992;33:219.

Mazzi A, et al. Ratio of urinary protein to creatinine and albumin to creatinine in dogs with diabetes mellitus and hyperadrenocorticism. *Vet Res Commun*. 2008;32:S299.

Monroe WE, et al. Efficacy and safety of a purified porcine insulin zinc suspension for managing diabetes mellitus in dogs. *J Vet Intern Med*. 2005;19:675.

Mori A, et al. Comparison of glucose fluctuations between day- and night-time measured using a continuous glucose monitoring system in diabetic dogs. *J Vet Med Sci*. 2013;75:113.

Mori A, et al. Comparison of time-action profiles of insulin glargine and NPH insulin in normal and diabetic dogs. *Vet Res Commun*. 2008;32:563.

Niessen SJM, et al. Evaluation of a quality-of-life tool for dogs with diabetes mellitus. *J Vet Intern Med*. 2012;26:953.

Palm CA, et al. An investigation of the action of neutral protamine Hagedorn human analogue insulin in dogs with naturally occurring diabetes mellitus. *J Vet Intern Med*. 2009;23:50.

Paul AEH, et al. Effect of hematocrit on accuracy of two point-of-care glucometers for use in dogs. *Am J Vet Res*. 2011;72:1204.

Struble AL, et al. Systemic hypertension and proteinuria in dogs with naturally occurring diabetes mellitus. *J Am Vet Med Assoc*. 1998;213:822.

Verkest KR, et al. Spontaneously obese dogs exhibit greater postprandial glucose, triglyceride, and insulin concentrations than lean dogs. *Domest Anim Endocrinol*. 2012;42:103.

Wess G, Reusch C. Evaluation of five portable blood glucose meters for use in dogs. *J Am Vet Med Assoc*. 2000;216:203.

Wiedmeyer CE, et al. Continuous glucose monitoring in dogs and cats. *J Vet Intern Med*. 2008;22:2.

Zeugswetter FK, et al. Metabolic and hormonal responses to subcutaneous glucagon in healthy beagles. *J Vet Emerg Crit Care*. 2012;22:211.

Feline Diabetes Mellitus

Alt N, et al. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc*. 2007;230:1011.

Bennett N, et al. Comparison of a low carbohydrate-low fiber diet and a moderate carbohydrate-high fiber diet in the management of feline diabetes mellitus. *J Feline Med Surg*. 2006;8:73.

Callegari C, et al. Survival time and prognostic factors in cats with newly diagnosed diabetes mellitus: 114 cases (2000-2009). *J Am Vet Med Assoc*. 2013;243:91.

Casella M, et al. Home-monitoring of blood glucose in cats with diabetes mellitus: evaluation over a 4-month period. *J Feline Med Surg*. 2004;7:163.

Costes S, et al. β-cell failure in type 2 diabetes: a case of asking too much of too few? *Diabetes*. 2013;62:327.

Dietiker-Moretti S, et al. Comparison of a continuous glucose monitoring system with a portable blood glucose meter to determine insulin dose in cats with diabetes mellitus. *J Vet Intern Med*. 2011;25:1084.

Gilor C, et al. Pharmacodynamics of insulin detemir and insulin glargine assessed by an isoglycemic clamp method in healthy cats. *J Vet Intern Med*. 2010;24:870.

Gottlieb S, et al. Glycemic status and predictors of relapse for diabetic cats in remission. *J Vet Intern Med*. 2015;29:184.

Henson MS, et al. Evaluation of plasma islet amyloid polypeptide and serum glucose and insulin concentrations in nondiabetic cats classified by body condition score and in cats with naturally occurring diabetes mellitus. *Am J Vet Res*. 2011;72:1052.

Hoenig M. The cat as a model for human obesity and diabetes. *J Diabetes Sci Technol*. 2012;6:52.

Hoenig M, et al. Activity and tissue-specific expression of lipases and tumor-necrosis factor in lean and obese cats. *Domest Anim Endocrinol*. 2006;30:333.

Michiels L, et al. Treatment of 46 cats with porcine lente insulin—a prospective, multicentre study. *J Feline Med Surg*. 2008;10:439.

Moretti S, et al. Evaluation of a novel real-time continuous glucose-monitoring system for use in cats. *J Vet Intern Med*. 2010;24:120.

Nelson RW, et al. Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. *J Vet Intern Med*. 2009;23:787.

Nelson RW, et al. Transient clinical diabetes mellitus in cats: 10 cases (1989-1991). *J Vet Intern Med*. 1999;13:28.

Niessen SJM, et al. Evaluation of a quality-of-life tool for cats with diabetes mellitus. *J Vet Intern Med*. 2010;24:1098.

Öhlund M, et al. Incidence of diabetes mellitus in insured Swedish cats in relation to age, breed and sex. *J Vet Intern Med*. 2015;29:1342.

Öhlund M, et al. Environmental risk factors for diabetes mellitus in cats. *J Vet Intern Med*. 2017;31:129.

O'Neill DG, et al. Epidemiology of diabetes mellitus among 193,435 cats attending primary care veterinary practices in England. *J Vet Intern Med*. 2016;30:964.

Riederer A, et al. Effect of the glucagon-like peptide-1 analogue exenatide extended release in cats with newly diagnosed diabetes mellitus. *J Vet Intern Med*. 2016;30:92.

Roomp K, et al. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. *J Feline Med Surg*. 2009;11:668.

Smith JR, et al. A survey of southeastern United States veterinarians' preferences for managing cats with diabetes mellitus. *J Feline Med Surg*. 2012;14:716.

Zini E, et al. Hyperglycemia but not hyperlipidemia causes beta cell dysfunction and beta cell loss in the domestic cat. *Diabetologia*. 2009;52:336.

Zini E, et al. Longitudinal evaluation of serum pancreatic enzymes and ultrasonographic findings in diabetic cats without clinically relevant pancreatitis at diagnosis. *J Vet Intern Med*. 2015;29:529.

Zini E, et al. Predictors of clinical remission in cats with diabetes mellitus. *J Vet Intern Med*. 2010;24:1314.

Diabetic Ketoacidosis

Bolton TA, et al. Pancreatic lipase immunoreactivity in serum of dogs with diabetic ketoacidosis. *J Vet Intern Med*. 2016;630:958.

Brady MA, et al. Evaluating the use of plasma hematocrit samples to detect ketones utilizing urine dipstick colorimetric methodology in diabetic dogs and cats. *J Vet Emerg Crit Care*. 2003;13:1.

Claus MA, et al. Comparison of regular insulin infusion doses in critically ill diabetic cats: 29 cases (1999-2007). *J Vet Emerg Crit Care*. 2010;20:509.

Di Tommaso M, et al. Evaluation of a portable meter to measure ketonemia and comparison of ketonuria for the diagnosis of canine diabetic ketoacidosis. *J Vet Intern Med*. 2009;23:466.

Duarte R, et al. Accuracy of serum β-hydroxybutyrate measurements for the diagnosis of diabetic ketoacidosis in 116 dogs. *J Vet Intern Med*. 2002;16:411.

Hume DZ, et al. Outcome of dogs with diabetic ketoacidosis: 127 cases (1993-2003). *J Vet Intern Med*. 2006;20:547.

Marshall RD, et al. Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis. *J Vet Emerg Crit Care*. 2013;23:286.

Sears KW, et al. Use of Lispro insulin for treatment of diabetic ketoacidosis in dogs. *J Vet Emerg Crit Care*. 2012;22:211.

Sieber-Ruckstuhl S, et al. Remission of diabetes mellitus in cats with diabetic ketoacidosis. *J Vet Intern Med*. 2008;22:1326.

Insulin-Secreting Islet Cell Neoplasia

Fischer JR, et al. Glucagon constant-rate infusion: a novel strategy for the management of hyperinsulinemic-hypoglycemic crisis in the dog. *J Am Anim Hosp Assoc*. 2000;36:27.

Iseri T, et al. Dynamic computed tomography of the pancreas in normal dogs and in a dog with pancreatic insulinoma. *Vet Radiol Ultrasound*. 2007;48:328.

Mai W, et al. Dual-phase computed tomographic angiography in three dogs with pancreatic insulinoma. *Vet Radiol Ultrasound*. 2008;49:141.

Moore AS, et al. A diuresis protocol for administration of streptozotocin to dogs with pancreatic islet cell tumors. *J Am Vet Med Assoc*. 2002;221:811.

Northrup NC, et al. Prospective evaluation of biweekly streptozotocin in 19 dogs with insulinoma. *J Vet Intern Med*. 2013;27:483.

Polton GA, et al. Improved survival in a retrospective cohort of 28 dogs with insulinoma. *J Small Anim Pract*. 2007;48:151.

Tobin RL, et al. Outcome of surgical versus medical treatment of dogs with beta-cell neoplasia: 39 cases (1990-1997). *J Am Vet Med Assoc*. 1999;215:226.

Gastrinoma

Diroff JS, et al. Gastrin-secreting neoplasia in a cat. *J Vet Intern Med*. 2006;20:1245.

Simpson KW. Gastrinoma in dogs. In: Bonagura JD, eds. *Kirk's current veterinary therapy XIII*. Philadelphia: WB Saunders; 2002.

CHAPTER 50

Disorders of the Adrenal Gland



HYPERADRENOCORTICISM IN DOGS

Etiology

Hyperadrenocorticism (Cushing's disease) is classified as pituitary dependent, adrenocortical dependent, or iatrogenic (i.e., resulting from excessive administration of glucocorticoids by the veterinarian or client).

PITUITARY-DEPENDENT HYPERADRENOCORTICISM

Pituitary-dependent hyperadrenocorticism (PDH) is the most common cause of spontaneous hyperadrenocorticism, accounting for approximately 80% to 85% of cases. A functional adrenocorticotropic hormone (ACTH)–secreting pituitary tumor is found at necropsy in approximately 85% of dogs with PDH. Adenoma of the pars distalis is the most common histologic finding, with a smaller percentage of dogs diagnosed with adenoma of the pars intermedia and a few dogs diagnosed with functional pituitary carcinoma. Approximately 50% of dogs with PDH have pituitary tumors measuring less than 3 mm in diameter, and most of the remaining dogs, specifically those without central nervous system (CNS) signs, have tumors 3 to 10 mm in diameter at the time PDH is diagnosed. Approximately 10% to 20% of dogs have pituitary tumors (i.e., macrotumors) exceeding 10 mm in diameter at the time PDH is diagnosed. These tumors have the potential to compress or invade adjacent structures and cause neurologic signs as they expand dorsally into the hypothalamus and thalamus (i.e., pituitary macrotumor syndrome) (Fig. 50.1).

Excessive secretion of ACTH causes bilateral adrenocortical hyperplasia and excess cortisol secretion from the zona fasciculata of the adrenal cortex (Fig. 50.2). Because normal feedback inhibition of ACTH secretion by cortisol is missing, excessive ACTH secretion persists despite increased adrenocortical secretion of cortisol. Episodic secretion of ACTH and cortisol is common and results in fluctuating plasma concentrations that, at times, may be within the reference range.

ADRENOCORTICAL TUMORS

Adrenocortical tumors causing hyperadrenocorticism (adrenal-dependent hyperadrenocorticism [ADH]) account for the remaining 15% to 20% of dogs with spontaneous hyperadrenocorticism. Adrenocortical adenoma and carcinoma occur with approximately equal frequency. No consistent clinical or biochemical features can help distinguish dogs with functional adrenal adenomas from those with adrenal carcinomas, although large adrenocortical masses (maximum width >4 cm) are more likely to be carcinomas. Adrenocortical carcinomas may invade adjacent structures (e.g., phrenicoabdominal vein, caudal vena cava, kidney, body wall) or may metastasize to the liver and lung—findings that are not consistent with adrenocortical adenomas.

Bilateral adrenocortical tumors can occur in dogs, but this is uncommon. A nonfunctional adrenocortical tumor or ADH with a pheochromocytoma in the contralateral gland is a more common cause of bilateral adrenal masses in dogs. Macronodular hyperplasia of the adrenals has also been identified in dogs. The adrenals in such animals are usually grossly enlarged, with multiple nodules of varying sizes within the adrenal cortex. The exact pathogenesis of this latter syndrome is unclear, although most cases in dogs are presumed to represent an anatomic variant of PDH. Adrenocortical tumors can also secrete one of the precursor hormones involved in adrenal steroid synthesis (e.g., progesterone and 17-OH-progesterone; see the section on occult [atypical] hyperadrenocorticism, p. 878).

Adrenal tumors causing ADH are autonomous and functional, and randomly secrete excessive amounts of cortisol independent of pituitary control. The cortisol produced by these tumors suppresses circulating plasma ACTH concentrations, causing cortical atrophy of the uninvolved adrenal and atrophy of all normal cells in the involved adrenal (see Fig. 50.2). This atrophy creates asymmetry in the size of the adrenal glands, which can be identified on abdominal ultrasonography. Most, if not all, of these tumors appear to retain ACTH receptors and respond to administration of exogenous ACTH. Adrenocortical tumors causing ADH are

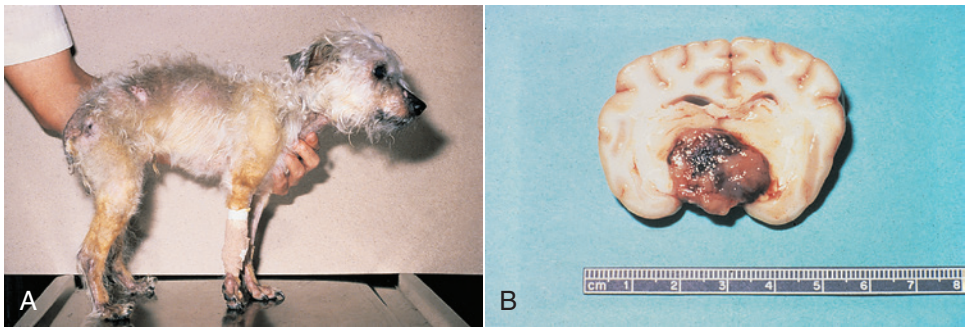


FIG 50.1
(A) A 10-year-old male castrated mixed-breed dog with pituitary-dependent hyperadrenocorticism. Initial clinical signs of polyuria, polydipsia, and endocrine alopecia progressed to severe stupor, anorexia, adipsia, weight loss, and loss of body temperature regulation. **(B)** Cross-section of the brain from the dog in **A,** showing a pituitary macroadenoma severely compressing surrounding brain structures.

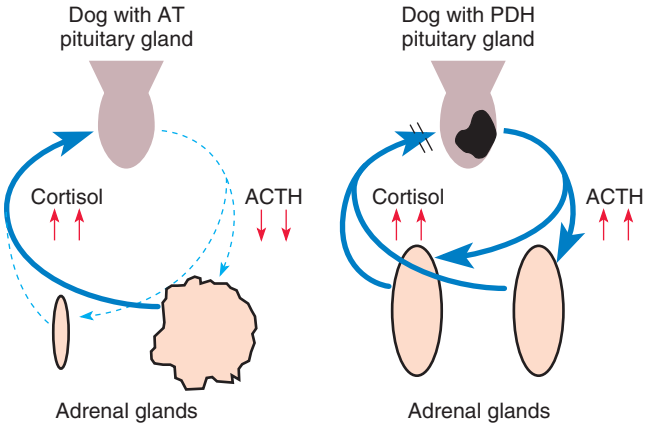


FIG 50.2
The pituitary-adrenocortical axis in dogs with a functioning adrenocortical tumor *(AT; left)* and in dogs with pituitary-dependent hyperadrenocorticism *(PDH; right)*. Excessive cortisol secretion from an AT causes pituitary suppression, decreased plasma adrenocorticotropic hormone *(ACTH)* concentration, and atrophy of the contralateral adrenal gland. Dogs with PDH have excessive ACTH secretion, usually from a functional pituitary adenoma, which causes bilateral adrenomegaly and excessive plasma cortisol concentrations.

typically unresponsive to manipulation of the hypothalamic-pituitary axis with glucocorticoids such as dexamethasone.

IATROGENIC HYPERADRENOCORTICISM

Iatrogenic hyperadrenocorticism typically results from excessive administration of glucocorticoids to control allergic or immune-mediated disorders. It can also develop as a result of the administration of eye, ear, or skin medications containing glucocorticoids, especially in small dogs receiving them long term. Because the hypothalamic-pituitary-adrenocortical axis is normal, the prolonged excessive administration of glucocorticoids suppresses circulating plasma ACTH concentrations, causing bilateral adrenocortical atrophy. In these dogs ACTH stimulation test results are consistent with spontaneous hypoadrenocorticism despite clinical signs of hyperadrenocorticism.

Clinical Features

SIGNALMENT

Hyperadrenocorticism typically develops in dogs 6 years of age and older (median age, 10 years) but has been documented in dogs younger than 5 years of age. There is no apparent sex-related predisposition, although ADH appears to be diagnosed more commonly in female dogs. PDH and ATH have been diagnosed in numerous breeds. All Poodle breeds, Dachshunds, various Terrier breeds, German Shepherd dogs, Beagles, Labrador Retrievers, and Australian Shepherds are commonly represented, and Boxers and Boston Terriers appear to be at increased risk for PDH. PDH tends to occur more frequently in smaller dogs; 75% of dogs with PDH weigh less than 20 kg. Approximately 50% of dogs with ADH weigh more than 20 kg.

CLINICAL SIGNS

The most common clinical signs are polyuria, polydipsia, polyphagia, panting, abdominal enlargement, endocrine alopecia, and mild muscle weakness (Fig. 50.3 and Table 50.1). Most dogs exhibit several, but not all, of these clinical signs. Cutaneous changes such as nonpruritic truncal alopecia, thin skin, and failure to regrow shaved hair may be the only clinical signs. A history that includes a greater number of signs leads to a greater index of suspicion for hyperadrenocorticism. Additional findings on physical examination (see Table 50.1) provide further support for hyperadrenocorticism and strengthen the indication to pursue diagnostic testing.

Additional uncommon clinical manifestations of hyperadrenocorticism may develop as a consequence of chronic hypercortisolism. Suppression of pituitary function can result in persistent anestrus, testicular atrophy, and secondary hypothyroidism. Laxity of ligaments may lead to tearing of a ligament and lameness. Severe polyuria may



FIG 50.3
(A) A 1-year-old male Miniature Poodle with pituitary-dependent hyperadrenocorticism (PDH). Note the truncal distribution of the endocrine alopecia with the pot-bellied appearance. **(B)** A 9-year-old male castrated mixed-breed dog with PDH. Note the severe laxity of the ligaments, resulting in hyperextension of the carpal ligaments and ambulation on the hocks. A "rat tail" has also developed and is a finding associated with hypothyroidism. **(C)** An 8-year-old male castrated Chihuahua with PDH. Note the pot-bellied appearance and the severe calcinosis cutis. **(D)** A 7-year-old Standard Poodle with PDH. Complaints of the primary owner at presentation included polyuria, polydipsia, and progressively worsening symmetric endocrine alopecia. **(E)** An adult mixed-breed dog with PDH. Complaints of the primary owner included polyuria, polydipsia, excessive panting, and severe weakness of the rear limbs. Note the absence of hair growth on the ventral abdomen, which had been shaved for an abdominal ultrasound 2 months before presentation.

lead to dribbling of urine, especially when the dog is asleep, and owner-perceived urinary incontinence in the home. Hypercoagulability may result in formation of spontaneous thrombi, typically involving pulmonary vessels and resulting in acute onset of respiratory distress. Cortisol-induced insulin resistance may play a role in the development of diabetes mellitus in dogs and definitely interferes with the effectiveness of insulin treatment. Hyperadrenocorticism is a differential for persistent systemic hypertension. Cholestatic disease and gall bladder mucocele formation may develop possibly as a consequence of hypercholesterolemia. Clinical manifestations of hyperadrenocorticism may also develop as a consequence of growth of the pituitary or adrenal tumor independent of cortisol secretion. For all of these less common clinical presentations of hyperadrenocorticism, a thorough review of the history, findings on physical examination, and results of routine blood and urine tests usually provide evidence of the disease and the need for additional tests.

PITUITARY MACROTUMOR SYNDROME

Neurologic signs may develop in dogs with PDH as a result of expansion of the pituitary tumor into the hypothalamus and thalamus (see Fig. 50.1; Video 50.1). Neurologic signs may be present at the time PDH is diagnosed but more commonly develop 12 months or longer after PDH is identified. The most common neurologic sign is a dull, listless attitude (i.e., stupor). Additional signs of pituitary macroadenoma include inappetence, aimless wandering, pacing, ataxia, head pressing, circling, and behavioral alterations. In the

TABLE 50.1

Clinical Signs and Physical Examination Findings in Dogs With Hyperadrenocorticism

CLINICAL SIGNS	PHYSICAL EXAMINATION FINDINGS
Polyuria, polydipsia*	Endocrine alopecia*
Polyphagia*	Epidermal atrophy (thin skin)*
Panting*	Failure of hair regrowth*
Abdominal distention*	Abdominal distention*
Endocrine alopecia*	Hepatomegaly*
Weakness*	Muscle wasting*
Lethargy	Cutaneous hyperpigmentation
Calcinosis cutis	Comedones
Cutaneous hyperpigmentation	Calcinosis cutis
Urine dribbling	Bruising
Persistent anestrus (female)	Testicular atrophy
Decreased libido (male)	Neurologic signs (PMA)
Neurologic signs (PMA)	Facial nerve paralysis
Stupor	Respiratory distress—tachypnea (PTE)
Ataxia	Myotonia
Circling	Lameness (ligament laxity, torn)
Aimless wandering	
Pacing	
Behavioral alterations	
Respiratory distress—tachypnea (PTE)	
Lameness (ligament problems)	
Stiff gait (myotonia)	

PMA, Pituitary macroadenoma; *PTE,* pulmonary thromboemboli.
*Common findings.

event of severe compression of the hypothalamus, abnormalities related to dysfunction of the autonomic nervous system, including adipsia, loss of temperature regulation, erratic heart rate, and inability to be roused from a sleep-like state, may develop. Identification of a pituitary macrotumor requires computed tomography (CT) or magnetic resonance imaging (MRI; Fig. 50.4). No biochemical or endocrine test results reliably correlate with the size of the pituitary tumor.

MEDICAL COMPLICATIONS: THROMBOEMBOLISM

Several medical complications can develop secondary to prolonged cortisol excess (Box 50.1). The most worrisome is

BOX 50.1

Medical Complications Associated With Hyperadrenocorticism in Dogs

Systemic hypertension
Pyelonephritis
Cystic calculi (calcium phosphate, oxalate)
Glomerulonephropathy, proteinuria
Congestive heart failure
Pancreatitis
Insulin resistant diabetes mellitus
Steroid hepatopathy
Pulmonary thromboembolism
Persistent anestrus
Pituitary macrotumor syndrome
Degenerative myopathy
Pseudomyotonia

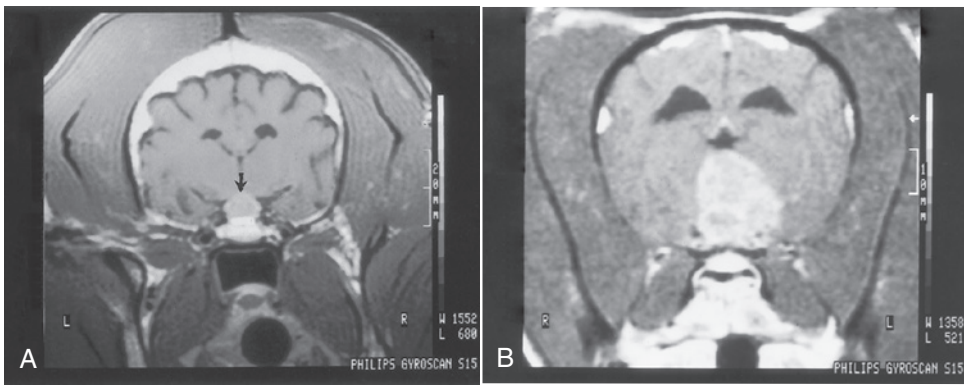


FIG 50.4
(A) Postgadolinium administration magnetic resonance imaging (MRI) scan of a 9-year-old male castrated German Shepherd dog with pituitary-dependent hyperadrenocorticism (PDH) and a pituitary mass *(arrow)*. No neurologic signs were present at the time the MRI scan was performed. **(B)** Postgadolinium administration MRI scan of an 8-year-old Boston Terrier with PDH, a large pituitary mass invading the brainstem, and signs of disorientation, ataxia, and circling. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 3, St Louis, 2004, WB Saunders.)

hypercoagulability, which is a common finding at the time hyperadrenocorticism is diagnosed, may persist despite treatment of PDH with trilostane, and may result in spontaneous thromboembolism, typically involving pulmonary vessels and causing acute respiratory distress. Pulmonary thromboembolism (PTE) occurs most often in dogs undergoing adrenalectomy for ADH. Thromboemboli may also affect the kidney, gastrointestinal tract, heart, and CNS. There is no apparent correlation between control of hyperadrenocorticism and development of thromboemboli. Factors predisposing to the development of PTE in dogs with hyperadrenocorticism include inhibition of fibrinolysis, systemic hypertension, protein-losing glomerulonephropathy, decreased serum antithrombin III concentrations, increased concentrations of several coagulation factors, and an increased hematocrit value.

Thoracic radiographs may reveal no abnormalities, or they may show hypoperfusion, alveolar pulmonary infiltrates, or a pleural effusion. Increased diameter and blunting of the pulmonary arteries may be noted, along with absence of perfusion of the obstructed pulmonary vasculature and overperfusion of the unobstructed pulmonary vasculature. Normal thoracic radiographic findings in a dyspneic dog that does not have a large airway obstruction suggest a diagnosis of PTE. Arterial blood gas analysis typically reveals a decrease in the partial pressures of arterial oxygen and carbon dioxide, as well as mild metabolic acidosis. Thrombosis may be confirmed by angiography of the lungs or by radionuclear lung scanning. Therapy consists of general supportive care, oxygen, anticoagulants, and time (see Chapter 12). The prognosis for dogs with PTE is guarded to grave. If dogs do recover, it typically takes 5 to 7 days before they can be safely removed from oxygen support.

Initial Diagnostic Evaluation

A thorough evaluation should be done in any dog suspected of having hyperadrenocorticism and should include a complete blood count (CBC); a serum biochemistry panel; urinalysis with bacterial culture; and, if available, abdominal ultrasonography and systemic blood pressure readings. Results of these tests will increase or decrease the index of suspicion for hyperadrenocorticism; will reveal common concurrent problems (e.g., urinary tract infection, systemic hypertension); and, in the case of ultrasonography, will provide valuable information for localizing the cause of the disorder (i.e., PDH versus ADH). Endocrine studies required to confirm the diagnosis and localize the cause of the disorder can then be performed.

CLINICAL PATHOLOGY

Common clinicopathologic alterations caused by hyperadrenocorticism are listed in Box 50.2. Laboratory test results must be interpreted within the context of the history and physical examination findings. None of the findings listed in Box 50.2 is diagnostic for hyperadrenocorticism; all can be seen with many other diseases. An absence of common abnormalities noted in Box 50.2 should strongly decrease the suspicion of hyperadrenocorticism. Increases in serum alkaline phosphatase (ALP) activity and cholesterol concentration are the most common abnormalities identified on the serum biochemistry panel. The major contributor to increased serum ALP is the corticosteroid-induced isoenzyme of ALP derived from the bile canalicular membrane of hepatocytes. Approximately 85% of dogs with hyperadrenocorticism have increased serum ALP activities, and values in excess of 1000 IU/L are common. No correlation has been noted between the magnitude of increase in serum ALP activity and the severity of hyperadrenocorticism, response to therapy, or prognosis, and no correlation has been observed between the magnitude of increase in serum ALP activity and hepatocellular death or hepatic failure. ALP activity can be normal in some dogs with hyperadrenocorticism, and an increase in ALP activity by itself is not diagnostic for hyperadrenocorticism. Similarly, an increase in activity of the corticosteroid-induced isoenzyme of alkaline phosphatase (SIAP) is not a finding specific to hyperadrenocorticism or exogenous glucocorticoid administration; an increase in SIAP activity occurs commonly with many disorders, including diabetes mellitus, primary hepatopathies, pancreatitis, congestive heart failure, and neoplasia, as well as in dogs receiving certain drugs (e.g., anticonvulsants). However, a finding of no SIAP in the serum may be of diagnostic value in ruling out hyperadrenocorticism.

Urine specific gravity typically is less than 1.020 and often is less than 1.006 in dogs with hyperadrenocorticism that have free access to water. Water-deprived hyperadrenal dogs maintain the ability to concentrate urine, although usually their concentrating ability remains less than normal. As

BOX 50.2

Clinicopathologic Abnormalities Commonly Identified in Dogs With Hyperadrenocorticism

Complete Blood Count

Neutrophilic leukocytosis
Lymphopenia
Eosinopenia
Thrombocytosis
Mild erythrocytosis

Serum Biochemistry Panel

Increased alkaline phosphatase activity
Increased alanine aminotransferase activity
Hypercholesterolemia
Hypertriglyceridemia
Lipemia
Hyperglycemia

Urinalysis

Urine specific gravity < 1.020
Indicators of urinary tract infection
Proteinuria
Mild increase in preprandial and postprandial bile acids

such, urine specific gravities of 1.020 to 1.025 may be identified if urine is obtained after water has been withheld from the dog.

Proteinuria is a common finding in dogs with untreated hyperadrenocorticism. Proteinuria may be caused by glucocorticoid-induced systemic and glomerular hypertension, glomerulonephritis, or glomerulosclerosis. Urine protein/creatinine ratios are usually less than 4, although values in excess of 8 have been identified. Proteinuria decreases and often resolves in response to treatment of hyperadrenocorticism.

Urinary tract infection is a common sequela of hyperadrenocorticism. Hyposthenuria and the antiinflammatory effects of glucocorticoids commonly interfere with the identification of bacteria or inflammatory cells in the urine. Whenever hyperadrenocorticism is suspected, antepubic cystocentesis with bacterial culture of the urine and antibiotic sensitivity testing is strongly recommended, regardless of urinalysis findings.

DIAGNOSTIC IMAGING

Abnormalities identified by thoracic and abdominal radiography and by abdominal ultrasonography are listed in Box 50.3. The most consistent radiographic findings in dogs with hyperadrenocorticism are enhanced abdominal contrast secondary to increased fat distribution in the abdomen; hepatomegaly caused by steroid hepatopathy; an enlarged urinary bladder secondary to the polyuric state; and calcification of soft tissues, most notably the trachea, the bronchi, and occasionally the skin and abdominal blood vessels. The most important but least common radiographic finding is a soft tissue mass or calcification in the area of an adrenal gland (Fig. 50.5); a finding suggestive of an adrenal tumor. The frequency of calcification is equally distributed between adenoma and carcinoma. Metastasis of an adrenocortical carcinoma to the pulmonary parenchyma is occasionally evident on thoracic radiographs.

Abdominal ultrasonography is used to evaluate the size and shape of the adrenals and to search for additional abnormalities in the abdomen (e.g., cystic calculi, vascular invasion, tumor thrombus; Fig. 50.6). Adrenal gland width is the most informative parameter. In healthy dogs, the maximum width of the adrenal gland ranges from approximately 0.4 to 0.75 cm. The finding of bilaterally symmetric normal-size or large adrenals (defined as having a maximum width > 0.8 cm) in a dog with hyperadrenocorticism serves as evidence of adrenal hyperplasia caused by PDH. A study by Choi et al. (2011) found that smaller dogs (<10 kg body weight) had smaller adrenal glands and recommended a cut-off of 0.6 cm as the criterion for differentiating a normal adrenal gland from adrenal hyperplasia. A subsequent study by Bento et al. (2016) involving a large population of dogs with nonadrenal gland illness concluded that, regardless of age, dogs that weighed 12 kg or less should have a maximum adrenal gland width no greater than 0.62 cm, whereas dogs that weighed greater than 12 kg should have an adrenal gland width no greater than 0.72 cm. The adrenal glands in dogs with PDH are similar but not exactly the same in size and shape; should have smooth, not irregular borders; can exceed 2 cm in maximum width; may have a bulbous cranial or caudal pole; and do not invade surrounding blood vessels or organs (see Fig. 50.6). An adrenal tumor is typically identified as an adrenal mass (Fig. 50.7). Size is variable, ranging from 1.0 to greater than 8 cm in maximum width. Small adrenal masses (i.e., <2 cm in maximum width) often maintain a smooth contour and may distort only a portion of the adrenal gland; one or both poles of the adrenal gland may still appear normal. With large adrenal masses (typically > 4 cm in maximum width), the adrenal gland usually becomes distorted and unrecognizable, the contour of the gland becomes irregular, and compression and/or invasion into adjacent blood vessels and organs, most notably the kidney, may occur (Fig. 50.8). These changes suggest adrenocortical carcinoma. Identification of calcification within

BOX 50.3

Abnormalities Identified by Abdominal and Thoracic Radiography and Abdominal Ultrasonography in Dogs With Hyperadrenocorticism

Abdominal Radiographs

Excellent abdominal detail
Hepatomegaly*
Distention of urinary bladder*
Cystic calculi
Adrenal mass
Calcified adrenal gland
Dystrophic calcification of soft tissues, calcinosis cutis
Osteoporosis of vertebrae

Thoracic Radiographs

Calcification of trachea and bronchi*
Osteoporosis of vertebrae
Pulmonary metastases from adrenocortical carcinoma
Pulmonary thromboembolism
- Hypovascular lung fields
- Alveolar infiltrates
- Enlarged right pulmonary artery
- Right-sided cardiomegaly
- Pleural effusion

Abdominal Ultrasonography

Bilateral adrenomegaly (PDH)*
Adrenal mass (ATH)*
Tumor thrombus (ATH)
Hepatomegaly*
Hyperechogenic liver*
Distention of urinary bladder*
Cystic calculi
Calcification of adrenal gland (ATH)
Dystrophic calcification of soft tissues

*Common findings.
ATH, Adrenocortical tumor causing hyperadrenocorticism; *PDH,* pituitary-dependent hyperadrenocorticism.

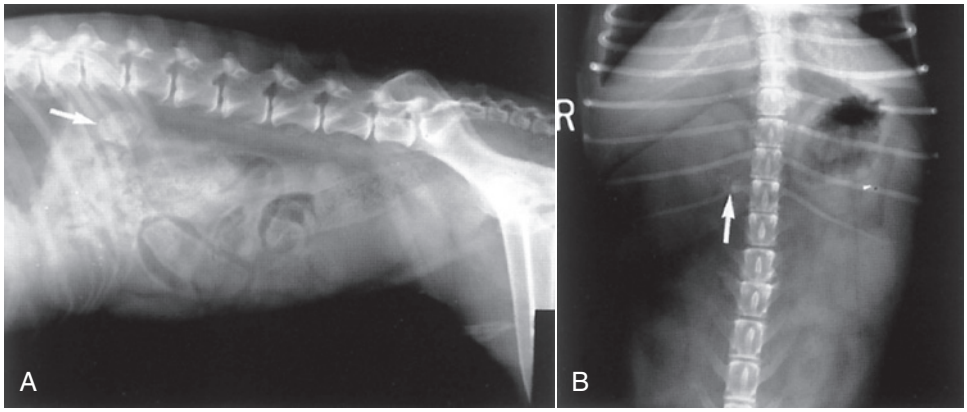


FIG 50.5
(A) Lateral radiograph from a dog with adrenal-dependent hyperadrenocorticism showing a calcified adrenal mass cranial to the kidney *(arrow)*. **(B)** Ventrodorsal radiograph from a dog with adrenal-dependent hyperadrenocorticism showing a calcified adrenal mass craniomedial to the kidney and lateral to the spine *(arrow)*. Compression of the abdomen in the region of the adrenal gland with a paddle has enhanced radiographic contrast, allowing better visualization of the adrenal mass.

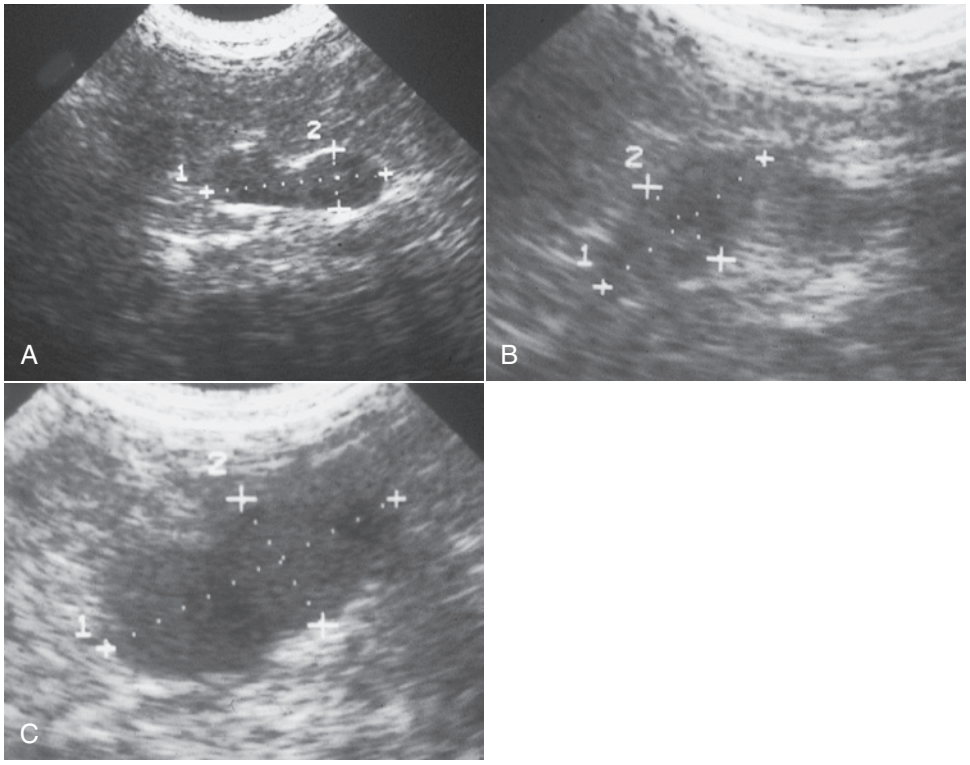


FIG 50.6
Ultrasound images of the adrenal gland in three dogs with pituitary-dependent hyperadrenocorticism (PDH), illustrating the differences in size and shape of the adrenal gland that can occur with PDH. **(A)** The adrenal gland in this dog has maintained the typical kidney-bean shape often identified in normal dogs. However, the maximum diameter of the gland was enlarged at 0.85 cm. The contralateral adrenal gland was similar in size and shape. **(B)** The adrenal gland in this dog is uniformly thickened and appears plump rather than kidney-bean shaped. The maximum diameter of the gland was 1.2 cm. The contralateral adrenal gland was similar in size and shape. **(C)** Although the adrenal gland has maintained some semblance of a kidney-bean shape in this dog, the gland has undergone marked enlargement, with a maximum diameter of 2.4 cm. The contralateral adrenal gland was similar in size and shape.

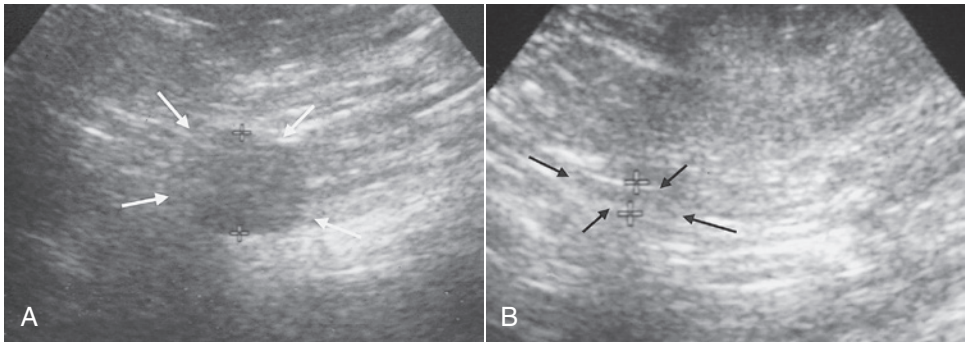


FIG 50.7
Ultrasound images of the adrenal glands in an 11-year-old male castrated Golden Retriever with adrenal-dependent hyperadrenocorticism. **(A)** Cortisol-secreting tumor affecting the right adrenal gland *(arrows)*. The maximum diameter of the adrenal mass was 1.6 cm. **(B)** The left adrenal gland has undergone marked atrophy *(arrows* and *crosses)* as a result of suppression of pituitary adrenocorticotropic hormone secretion after negative feedback inhibition caused by the adrenocortical tumor. The maximum diameter of the left adrenal gland was less than 0.2 cm.

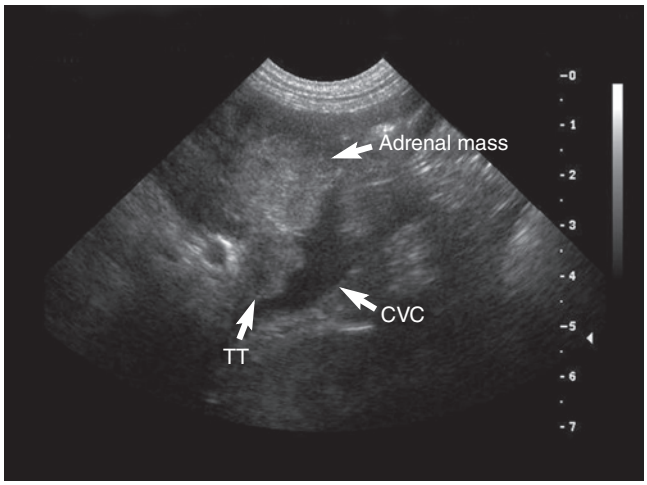


FIG 50.8
Ultrasound image of a mass affecting the left adrenal gland (adrenal mass) and extending into the lumen of the caudal vena cava *(CVC),* creating a tumor thrombus *(TT)* in a 9-year-old male Standard Poodle. The maximum width of the adrenal mass was 3.8 cm. The histopathologic diagnosis was pheochromocytoma.

the mass does not differentiate adenoma from carcinoma. Generally, the larger the mass, the more likely it is carcinoma. Asymmetry in the size of the adrenal glands is evident (see Fig. 50.2). Ideally, the contralateral unaffected adrenal should be small or undetectable (maximum width typically < 0.4-0.5 cm) as a result of ADH-induced adrenocortical atrophy (see Fig. 50.7), although a normal-size contralateral adrenal gland does not rule out ADH. Identification of an adrenal mass and a normal to large contralateral adrenal gland in a dog with clinical signs supportive of hyperadrenocorticism suggests the possibility of PDH with a concurrent adrenal mass that may be a pheochromocytoma, a functional adrenocortical tumor, or a nonfunctional adrenal tumor (Fig. 50.9). The finding of normal-size adrenal glands in a dog with confirmed hyperadrenocorticism is most consistent with a diagnosis of PDH. The finding of bilateral adrenomegaly with the appearance of multiple nodules of varying size is suggestive of macronodular hyperplasia (Fig. 50.10). Bilateral adrenal macronodular hyperplasia is believed to represent an anatomic variant of PDH. Failure to identify either adrenal is considered an inconclusive finding, and ultrasonography should be repeated at a later time.

CT and MRI can be used to evaluate the pituitary gland for a macroadenoma, to assess the size and symmetry of the adrenal glands, and to detect the presence of an adrenal tumor thrombus in the adjacent vasculature. Contrast enhancement using an iodinated contrast agent (CT) or gadolinium (MRI) given by continuous intravenous (IV) infusion during the imaging procedure aids in identification of a pituitary macroadenoma and the adrenal glands during CT and MRI examination, respectively (see Fig. 50.4). The primary indications for CT or MRI are (1) to confirm the presence of a visible pituitary tumor in a dog with clinical signs suggestive of macrotumor (see the section on pituitary macrotumor syndrome) or in a dog diagnosed with PDH for which the client is willing to consider pituitary irradiation or hypophysectomy should a pituitary mass be identified (see the sections on pituitary irradiation and hypophysectomy) and (2) to assess the size of an adrenal mass and the extent of infiltration of the mass into surrounding blood vessels, organs, and body wall before adrenalectomy. MRI is superior to CT for detecting small pituitary tumors; for revealing associated tumor features such as edema, cysts, hemorrhage, and necrosis; and for imaging the adrenal glands.

TESTS OF THE PITUITARY-ADRENOCORTICAL AXIS

Clinical signs, physical examination findings, and clinicopathologic alterations should provide strong support for

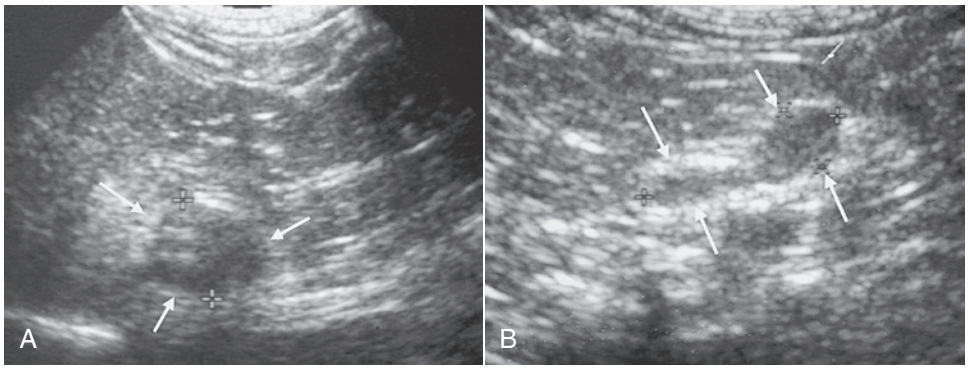


FIG 50.9
Ultrasound images of the adrenal glands in a 10-year-old female spayed Bichon Frise presented for acute onset of vomiting. **(A)** An unexpected mass involving the right adrenal gland, measuring 1.4 cm in maximum diameter, was identified *(arrows)*. **(B)** The left adrenal gland was normal in size and shape *(arrows);* the maximum diameter was 0.6 cm. The normal-size left adrenal gland suggests that the right adrenal mass is a pheochromocytoma or is nonfunctional. Results of routine blood work and of tests for hyperadrenocorticism were normal.

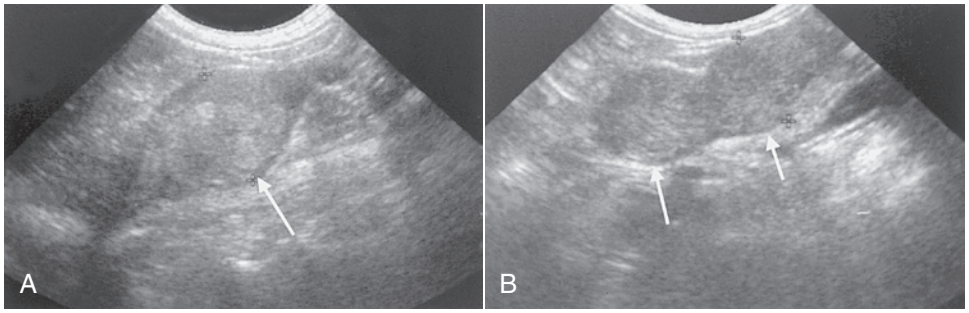


FIG 50.10
Ultrasound images of the adrenal glands *(arrows)* in an 11-year-old female spayed Shih Tzu. The right adrenal gland **(A)** measured 1.8 cm in maximum diameter and had a nodular echogenic pattern. In contrast, the left adrenal gland **(B)** had a large nodule located in each pole of the gland; each measured approximately 1.4 cm in maximum diameter. Tests of the pituitary-adrenocortical axis were diagnostic for pituitary-dependent hyperadrenocorticism; this finding, in conjunction with the findings on ultrasound, suggests macronodular hyperplasia of the adrenal glands.

diagnostic testing for hyperadrenocorticism, and results of an abdominal ultrasound may include valuable information regarding probable location of the lesion. Tests to establish the diagnosis of hyperadrenocorticism include the urine cortisol/creatinine ratio (UCCR), the ACTH stimulation test, the low-dose dexamethasone suppression (LDDS) test, and the oral dexamethasone suppression test (Table 50.2). Discriminatory tests are used to identify the cause (i.e., PDH versus ATH) in dogs with confirmed hyperadrenocorticism and include the LDDS test, the high-dose dexamethasone suppression (HDDS) test, and baseline endogenous ACTH concentration. Tests that we commonly use to establish the diagnosis of hyperadrenocorticism are UCCR in conjunction with the LDDS test, and tests that we commonly use to identify the cause (i.e., PDH versus ATH) include the LDDS test and abdominal ultrasound. The HDDS test can be used if abdominal ultrasound is not available. An endogenous ACTH concentration is evaluated when abdominal ultrasound suggests an adrenal mass but results of the LDDS test are inconclusive or suggest PDH, and when an adrenal mass is identified with contralateral adrenomegaly.

Baseline serum cortisol measurement, by itself, provides no diagnostic value in diagnosing hyperadrenocorticism. We use the ACTH stimulation test to establish the diagnosis of hypoadrenocorticism, to identify iatrogenic hyperadrenocorticism, and to monitor trilostane and mitotane treatment. We do not routinely use the ACTH stimulation test to diagnose hyperadrenocorticism because of problems with sensitivity and specificity. We never establish the diagnosis of hyperadrenocorticism solely on the basis of results of an ACTH stimulation test.

Indicators for performing diagnostic tests for hyperadrenocorticism recommended by the 2012 *American College of Veterinary Internal Medicine* (*ACVIM*) consensus statement

TABLE 50.2

Diagnostic Tests to Assess the Pituitary-Adrenocortical Axis in Dogs With Suspected Hyperadrenocorticism

TEST	PURPOSE	PROTOCOL	RESULTS		INTERPRETATION
Urine cortisol/creatinine ratio	Rule out HAC	Urine collected at home	Normal Increased		Not supportive of HAC Additional tests for HAC indicated
			4 hours post-dexamethasone:	*8 hours post-dexamethasone:*	
Low-dose dexamethasone suppression test	Diagnose HAC and differentiate PDH from ATH	0.01 mg dexamethasone/kg IV; serum pre- and 4- and 8-hour post-dexamethasone	— — <50% of pre-value — >50% of pre-value	<1.0 µg/dL 1.0-1.4 µg/dL >1.4 µg/dL >1.4 µg/dL and <50% of pre-value >1.4 µg/dL and >50% of pre-value	Normal Inconclusive PDH PDH PDH or ATH
ACTH stimulation	Diagnose HAC	5 µg of synthetic ACTH*/kg IV; serum pre- and 1-hour post-ACTH	*Post-ACTH cortisol concentration:* >24 µg/dL 19-24 µg/dL 6-18 µg/dL <6 µg/dL		 Suggestive† Inconclusive‡ Normal Iatrogenic HAC
High-dose dexamethasone suppression test	Differentiate PDH from ATH	0.1 mg of dexamethasone/kg IV; serum pre- and 4- and 8-hour post-dexamethasone	*Post-dexamethasone cortisol concentration:* 4- or 8-hour <50% of pre-value 4- or 8-hour <1.4 µg/dL 4- and 8-hour >50% of pre-value		 PDH PDH PDH or ATH
Oral dexamethasone suppression test	Differentiate PDH from ATH	Urine sample for UCCR on 2 consecutive mornings, then 0.1 mg of dexamethasone/kg per os q8h for 3 treatments, then urine sample for UCCR the following morning	*Post-dexamethasone UCCR value:* <50% of baseline value§ ≥50% of baseline value		 PDH PDH or ATH
Endogenous ACTH	Differentiate PDH from ATH	Specific sample handling required	Below reference range Upper half of reference range or greater than reference range Lower half of reference range		ATH PDH Nondiagnostic

ACTH, Adrenocorticotropic hormone; *ATH,* adrenocortical tumor-dependent hyperadrenocorticism; *HAC,* hyperadrenocorticism; *IM,* intramuscular; *IV,* intravenous; *PDH,* pituitary-dependent hyperadrenocorticism; *UCCR,* urine cortisol/creatinine ratio.

*Synthetic ACTH: Cortrosyn, Cosyntropin, Synacthen.

†Suggestive of hyperadrenocorticism.

‡Inconclusive for hyperadrenocorticism.

§Baseline value is the mean of two UCCR values obtained on two consecutive mornings before dexamethasone administration.

on diagnosis of spontaneous canine hyperadrenocortisim are given in Box 50.4 (Behrend et al., 2013). Ideally, testing for hyperadrenocorticism should be avoided if serious illness exists. Many illnesses affect results of screening tests for hyperadrenocorticism. Testing for hyperadrenocorticism is not mandatory at the time suspicion arises. Postponing testing until concurrent illness is resolved or controlled is recommended, but the current illness must be considered when interpreting test results (Behrend et al., 2013).

Urine Corticoid/Creatinine Ratio

The UCCR is an excellent initial screening test for hyperadrenocorticism in dogs. The UCCR should be determined from free-catch urine samples collected on two consecutive mornings by the client in the nonstressful home environment. The stress associated with driving the dog to the veterinary hospital and having the dog undergo a physical examination before urine is collected can influence test results (Fig. 50.11). There is considerable variation in results between different urinary cortisol assays so it is important that an assay specific reference range is established by the laboratory used to determine UCCRs. A normal UCCR in one or both urine samples serves as evidence against hyperadrenocorticism. Normal UCCR test results can occur in dogs with hyperadrenocorticism but are very uncommon. Increased UCCR in both urine samples is supportive of but not definitively diagnostic for hyperadrenocorticism. The reported sensitivity and specificity of the UCCR measured on a single urine sample ranges from 75% to 100% and 20% to 25%, respectively in dogs. The UCCR is often increased in dogs with nonadrenal illness and in dogs with clinical signs consistent with hyperadrenocorticism but with a normal pituitary-adrenocortical axis (Fig. 50.12). Additional tests are indicated when the UCCR is increased or when the UCCR is normal but the clinical picture strongly suggests hyperadrenocorticism.

BOX 50.4

Indicators for Performing Diagnostic Tests for Hyperadrenocorticism in Dogs*

- Compatible history and physical examination findings; the greater the number of findings, the stronger the suspicion
- A pituitary macrotumor
- A diabetic dog with persistently poor response to high dosages of insulin not attributed to another cause including owner issues
- An adrenal mass
- Biochemical, complete blood count, urinalysis, and urine protein:creatinine ratio and blood pressure measurements, by themselves, are not indicators to test

*From: Behrend EN et al.: Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (Small Animal), *J Vet Intern Med* 27:1292, 2013.

Low-Dose Dexamethasone Suppression Test

The LDDS test is considered the screening test of choice for hyperadrenocorticism unless iatrogenic hyperadrenocorticism is suspected (Behrend et al., 2013). In the normal dog relatively small doses of dexamethasone given intravenously can inhibit pituitary secretion of ACTH, causing a prolonged decline in the serum cortisol concentration (Fig. 50.13). Dexamethasone is used because it does not interfere with the assays used to measure cortisol. The abnormal pituitary in dogs with PDH is somewhat resistant to the negative

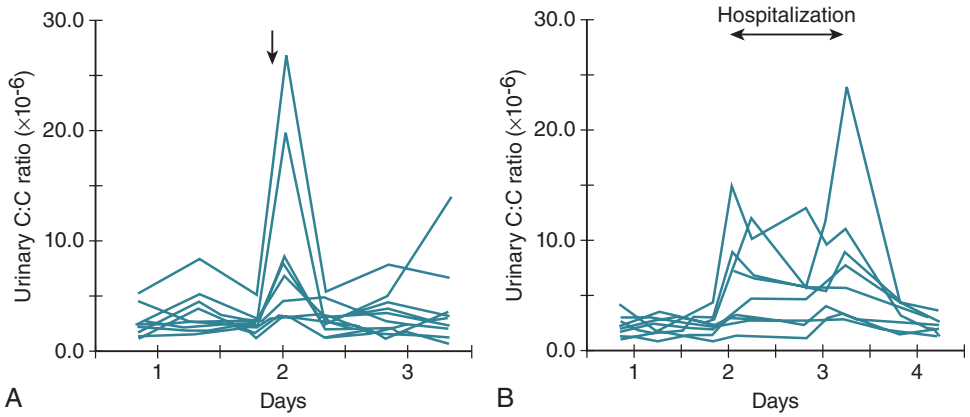


FIG 50.11
Urinary corticoid/creatinine (C:C) ratio measured in 12 pet dogs before and after a visit to a referral clinic for orthopedic examination **(A)** and in 9 healthy pet dogs before, during, and after a 1.5-day hospitalization at a referral clinic **(B).** The *arrows* indicate time of visit to the referral clinic. Note the increase in the urinary C:C ratio in a few dogs, affiliated with a visit to a veterinary practice. (From van Vonderen IK et al.: Influence of veterinary care on the urinary corticoid:creatinine ratio in dogs, *J Vet Intern Med* 12:431, 1998.)

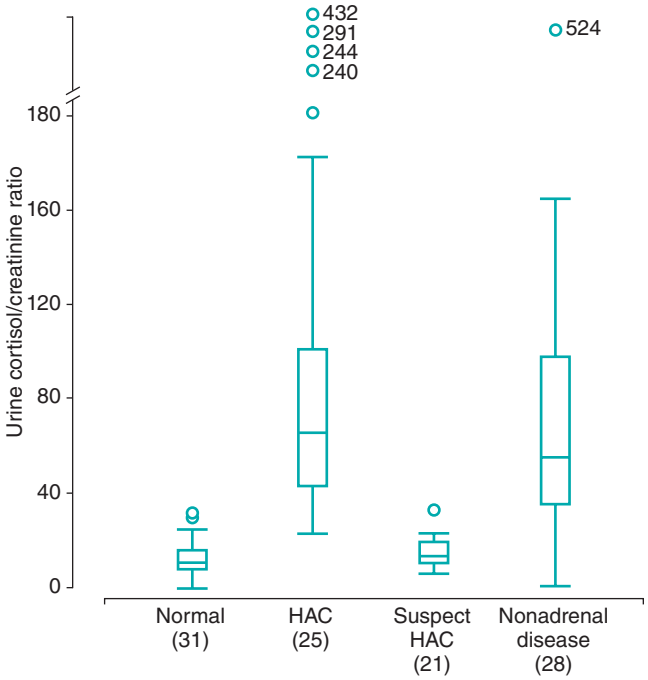


FIG 50.12
Box plots of the urine cortisol/creatinine ratios found in normal dogs, dogs with hyperadrenocorticism *(HAC)*, dogs in which hyperadrenocorticism was initially suspected but that did not have the disease (suspect HAC), and dogs with a variety of severe, nonadrenal diseases. For each box plot, T-bars represent the main body of data, which in most instances are equal to the range. Each box represents an interquartile range (twenty-fifth to seventy-fifth percentile). The horizontal bar in each box is the median. *Open circles* represent outlying data points. Numbers in parentheses indicate the numbers of dogs in each group. (From Smiley LE et al.: Evaluation of a urine cortisol/creatinine ratio as a screening test for hyperadrenocorticism in dogs, *J Vet Intern Med* 7:163, 1993.)

feedback action of dexamethasone, and the metabolic clearance of dexamethasone may be abnormally accelerated as well. Administration of a small dose of dexamethasone to a dog with PDH causes the serum cortisol concentration to be variably suppressed; however, it is no longer suppressed by 8 hours after dexamethasone administration, compared with the response seen in normal dogs. Tumors causing ADH function independently of ACTH control, and dexamethasone does not affect the serum cortisol concentration, regardless of the dose or time of blood sampling, because pituitary corticotrophs are already suppressed and blood ACTH concentration is undetectable.

The LDDS test is a reliable diagnostic test for differentiating normal dogs from those with hyperadrenocorticism and may identify PDH. Sensitivity and specificity are approximately 90% and 75%, respectively. The LDDS does not identify iatrogenic hyperadrenocorticism, nor is it used to assess a dog's response to trilostane or mitotane (lysodren) therapy. A normal or inconclusive LDDS test result does not by itself rule out hyperadrenocorticism. If hyperadrenocorticism is suspected, additional tests of the pituitary-adrenocortical axis should be performed. Similarly, an abnormal LDDS test result does not by itself confirm hyperadrenocorticism. Results of the LDDS test may be affected by concurrently administered anticonvulsant drugs, stress, excitement, exogenous glucocorticoids, and nonadrenal disease; the more severe the nonadrenal disease, the more likely it is that the LDDS test result will be falsely positive. When performing the LDDS test, the clinician must ensure that all stressors are kept to a minimum; other procedures should not be performed until the test is completed, and the effect of concurrent clinical problems should be considered when results are interpreted.

The protocol for the LDDS test and interpretation of results are described in Table 50.2. The clinician may use dexamethasone sodium phosphate or dexamethasone in polyethylene glycol. The dexamethasone sodium phosphate dosage should be calculated based on the active compound (i.e., 1.3 mg dexamethasone sodium phosphate is equivalent to 1 mg dexamethasone). The 8-hour postdexamethasone serum cortisol concentration is used to confirm hyperadrenocorticism. Normal dogs typically have serum cortisol values less than 1.0 µg/dL (28 nmol/L)—usually less than 0.5 µg/dL (14 nmol/L). Dogs with PDH and ADH typically have serum cortisol concentrations greater than 1.4 µg/dL (40 nmol/L) 8 hours after dexamethasone administration. In general, the higher the 8-hour postdexamethasone serum cortisol concentration is above 1.4 µg/dL, the more supportive the test result is for hyperadrenocorticism. Cortisol concentrations between 1.0 and 1.4 µg/dL are inconclusive. Cortisol results in this range are supportive of hyperadrenocorticism if the clinical manifestations, the results of routine blood and urine tests, and UCCRs support the disease but should not be considered diagnostic for hyperadrenocorticism if the clinical picture is questionable.

If the 8-hour postdexamethasone serum cortisol value supports a diagnosis of hyperadrenocorticism, the 4-hour serum cortisol value may be of value in identifying PDH. Low doses of dexamethasone suppress pituitary ACTH secretion and serum cortisol concentrations in approximately 60% of dogs with PDH. Suppression does not occur in dogs with ADH, nor does it occur in approximately 40% of dogs with PDH. *Suppression* is defined as a 4-hour postdexamethasone serum cortisol concentration less than 1.4 µg/dL (40 nmol/L), a 4-hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration, or an 8-hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration. Any dog with hyperadrenocorticism that meets one or more of these criteria most likely has PDH. If none of these criteria is met, then results of the LDDS test are consistent with lack of suppression but not informative in terms of whether it is pituitary or adrenal in origin. Differentiation between PDH and ADH must rely on results of abdominal ultrasound, the HDDS test, or plasma endogenous ACTH concentration.

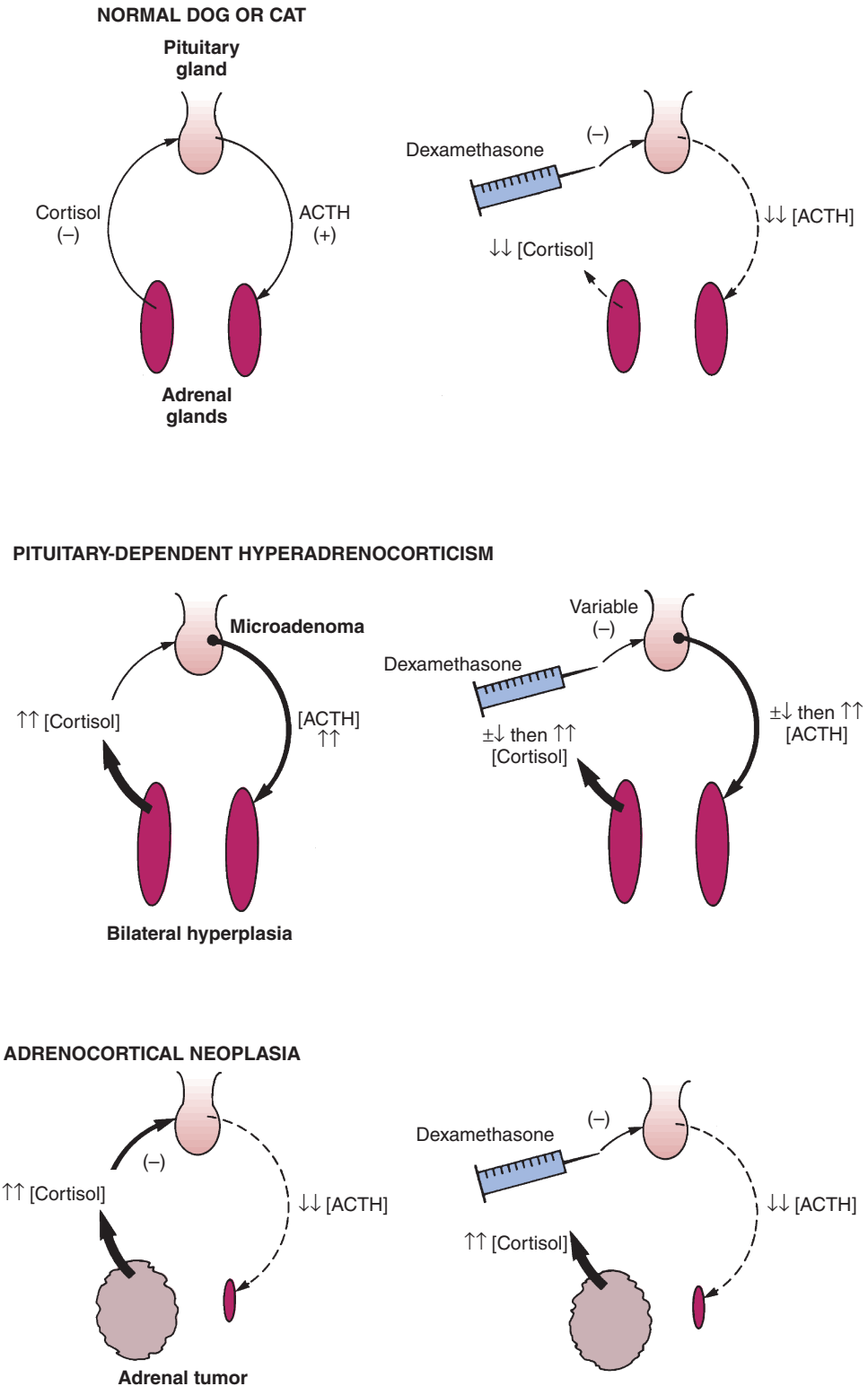


FIG 50.13
Effects of dexamethasone administration on the pituitary-adrenocortical axis in healthy dogs or cats and in dogs or cats with pituitary-dependent hyperadrenocorticism (PDH) or adrenocortical neoplasia. In PDH, dexamethasone may initially suppress pituitary adrenocorticotropic hormone *(ACTH)* secretion, but suppression is short-lived. The plasma cortisol concentrations initially decline but increase to above normal within 2 to 6 hours of dexamethasone administration. In adrenocortical neoplasia pituitary ACTH secretion is already suppressed; thus dexamethasone has no effect.

Oral Dexamethasone Suppression Test

An alternative at-home oral dexamethasone suppression test has been used for years at the University of Utrecht, The Netherlands. This test relies entirely on results of UCCRs to establish the diagnosis of hyperadrenocorticism and to identify PDH. The client is instructed to collect two urine samples from the dog on two consecutive mornings and to store them in the refrigerator. After collection of the second urine sample, the client should administer three doses of dexamethasone (0.1 mg/kg/dose) to the dog orally at 8-hour intervals. Urine is collected on the morning of the third day, and all three samples are delivered to the veterinarian for measurement of UCCRs. The first two urine samples are used as the screening test to diagnose hyperadrenocorticism. Abnormal values support hyperadrenocorticism; normal values rule out the disease. If both values are abnormal, the average of the two values is used as the baseline value and compared with the third value obtained after dexamethasone administration. The dog is described as having responded to dexamethasone (suppressed) if the UCCR result from the third urine sample is less than 50% of the baseline value. Dogs meeting this criterion have results consistent with PDH, whereas those that fail to demonstrate suppression could have either ADH or PDH.

Adrenocorticotropic Hormone Stimulation Test

The ACTH stimulation test is the gold standard for diagnosis of hypoadrenocorticism, for identification of iatrogenic hyperadrenocorticism, and for monitoring of trilostane and mitotane treatment. Because of problems with sensitivity (PDH, 80%-83%; ADH, 57%-63%) and specificity (59%-93%) and the cost of synthetic ACTH, the diagnostic usefulness of the ACTH stimulation test as a screening test for spontaneous hyperadrenocorticism is inferior to the LDDS test. We do not use the ACTH stimulation test when evaluating dogs for hyperadrenocorticism. Test results of ACTH stimulation are commonly inconclusive, and clearly abnormal test results (>30 µg/dL [800 nmol/L]) occur in dogs that do not have hyperadrenocorticism. ACTH stimulation test results do not distinguish between PDH and ADH.

The protocol for the ACTH stimulation test is given in Table 50.2. Only synthetic ACTH should be used; the lyophilized and liquid solution synthetic ACTH products can be used interchangeably. We typically administer 5 µg of synthetic ACTH/kg IV and obtain blood for serum cortisol concentration immediately before and 1 hour after ACTH administration. The unused reconstituted ACTH can be stored frozen at –20° C in plastic syringes for 6 months with no adverse effects on bioactivity of the ACTH. We use four ranges of values for interpretation of the ACTH stimulation test (Fig. 50.14). Post-ACTH serum cortisol values between 6 and 18 µg/dL (150 and 500 nmol/L) are within the normal reference range, values of 5 µg/dL (150 nmol/L) and below are suggestive of iatrogenic hyperadrenocorticism, values between 18 and 24 µg/dL (500 and 650 nmol/L) are inconclusive, and values greater than 24 µg/dL (650 nmol/L) are supportive of hyperadrenocorticism, as long as the clinical findings and clinicopathologic data are strongly consistent with the disease. An increased post-ACTH serum cortisol value does not by itself confirm a diagnosis of hyperadrenocorticism, especially if clinical features and clinicopathologic data are not consistent with the diagnosis.

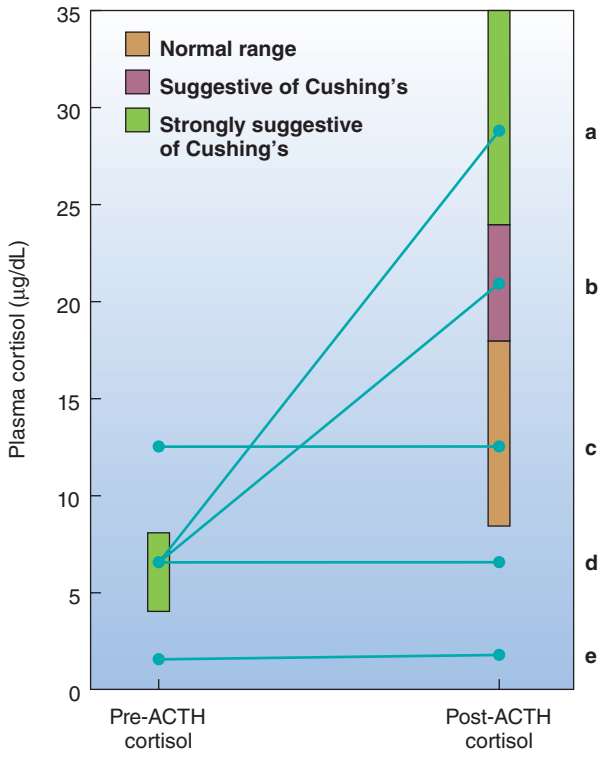


FIG 50.14
Interpretation of the adrenocorticotropic hormone *(ACTH)* stimulation test in dogs. Ideally, dogs with Cushing's syndrome have an increased post-ACTH administration cortisol concentration *(line a)*. Post-ACTH cortisol values that fall into the "gray zone" *(line b)* could be consistent with Cushing's syndrome or may result from the effects of concurrent illness or chronic stress. Post-ACTH cortisol values may also fall into the normal range in dogs with Cushing's syndrome. The absence of a response to ACTH stimulation is suggestive of adrenocortical neoplasia *(lines c* and *d)* or iatrogenic hyperadrenocorticism *(lines d* and *e)*. History and physical examination findings should differentiate between these possibilities.

Post-ACTH serum cortisol concentrations that do not increase to above the preadministration value suggest iatrogenic hyperadrenocorticism or spontaneous hypoadrenocorticism, especially if the cortisol values are below the normal baseline reference range (see Fig. 50.14). A history of recent glucocorticoid administration and the clinical presentation of the dog can help differentiate iatrogenic hyperadrenocorticism from spontaneous hypoadrenocorticism. In rare instances a dog with ADH will have a minimal cortisol response to ACTH; however, its pre-ACTH and post-ACTH administration serum cortisol concentrations should be within or above the reference range.

High-Dose Dexamethasone Suppression Test

Adrenocortical tumors causing ADH function independently of pituitary ACTH; therefore regardless of the dose, dexamethasone should never suppress the serum cortisol concentration if the source of the cortisol is an adrenocortical tumor. In contrast, dexamethasone-induced suppression of ACTH secretion from a pituitary tumor is variable and may depend on the dexamethasone dose. Administration of increased amounts of dexamethasone should eventually suppress pituitary ACTH secretion in most dogs with PDH. The protocol for the HDDS test is similar to that for the LDDS test, except that a higher dose (i.e., 0.1 mg/kg of body weight) of dexamethasone is used in an attempt to suppress pituitary ACTH secretion (see Table 50.2). Suppression is defined as a 4-hour or 8-hour postdexamethasone serum cortisol concentration less than 1.4 μg/dL (40 nmol/L) or a 4-hour or 8-hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration. Any dog with hyperadrenocorticism that meets one or more of these criteria most likely has PDH. If a dog does not meet any of these criteria, this is consistent with lack of suppression. Approximately 25% of dogs with PDH and essentially 100% of dogs with ADH do not show suppression with the HDDS test.

Endogenous Adrenocorticotropic Hormone Concentration

We do not routinely measure plasma ACTH concentrations because the LDDS test and abdominal ultrasound are very effective in differentiating between PDH and ADH. We use plasma ACTH concentrations to provide clarity in confusing cases in which test results for hyperadrenocorticism and findings on abdominal ultrasound conflict (e.g., a dog with an adrenal mass but suppression on the LDDS test, or a dog with an adrenal mass, enlargement of the contralateral adrenal gland, and lack of suppression on the LDDS test). Determination of a baseline plasma ACTH concentration is not used to diagnose hyperadrenocorticism because many of the concentrations in dogs with hyperadrenocorticism are within the reference range. However, determination of a single baseline plasma ACTH concentration may aid in distinguishing dogs with ADH from those with PDH once the diagnosis of hyperadrenocorticism has been established. Adrenocortical tumors and iatrogenic hyperadrenocorticism should suppress ACTH secretion, and PDH is the result of excessive ACTH secretion (see Fig. 50.2). Dogs with ADH should have plasma endogenous ACTH concentrations below the reference range, ideally undetectable, whereas dogs with PDH should have plasma ACTH concentrations in the upper half of the reference range or greater than the upper limit of the reference range. Plasma ACTH concentrations near the lower end of the reference range can be identified in dogs with ADH and PDH and are nondiagnostic. Timing of blood sample collection does not appear to affect results. Appropriate sample handling and appropriate analytic sensitivity and the working range of the ACTH assay are critical for ensuring accurate and interpretable results. The most common problem with the ACTH assay is poor sensitivity. The laboratory should be consulted for information on sample collection and handling; results should be interpreted on the basis of the reference range established for the laboratory being used.

Discordant Test Results

False-positive and false-negative test results occur with all of the diagnostic tests for hyperadrenocorticism. When the results are unexpected or questionable, another diagnostic test can be performed or the same diagnostic test repeated, preferably after waiting several weeks. Occasionally, results of different diagnostic tests performed in the same dog are contradictory. The decision to perform discriminatory tests or to initiate therapy should depend on the clinician's index of suspicion for the disease formulated from a review of the history, findings on physical examination, and results of diagnostic tests. If there is doubt or uncertainty about the diagnosis, therapy for hyperadrenocorticism should be withheld and the dog reevaluated several months later.

Treatment is indicated when clinical signs, findings on physical examination, and results of routine blood and urine tests and tests of the pituitary adrenocortical axis are all supportive of the diagnosis of hyperadrenocorticism. The decision to treat becomes more problematic when there is conflicting information, when the common clinical manifestations of hyperadrenocorticism are absent, when hyperadrenocorticism was not considered a differential for the tests performed (e.g., increased ALP identified during a geriatric dog evaluation), when the adrenal glands are normal in size on abdominal ultrasound, when LDDS test results are inconclusive, or when concurrent especially severe illness is present. The most important pieces of information that we rely on when deciding whether to initiate treatment are the history, findings on physical examination, and our index of suspicion for the disease after a review of all blood and urine test results. We do not initiate treatment until we are certain of the diagnosis. When in doubt, we prefer to wait and reevaluate if and when clinical manifestations of hyperadrenocorticism become more apparent. When we are contemplating a wait-and-see approach, we always try to rule out an adrenal mass with abdominal ultrasound—a finding that may warrant adrenalectomy regardless of the index of suspicion for hyperadrenocorticism.

Medical Treatment

The most viable medical treatment options for hyperadrenocorticism in dogs are trilostane and mitotane.

TRILOSTANE

Trilostane (Vetoryl, Dechra) is a competitive inhibitor of 3-β-hydroxysteroid dehydrogenase, which mediates the conversion of pregnenolone to progesterone and 17-hydroxy-pregnenolone to 17-hydroxy-progesterone in the adrenal cortex. The net effect is inhibition of cortisol, aldosterone, and progesterone production (Fig. 50.15). Trilostane is currently the preferred enzyme blocker for treating

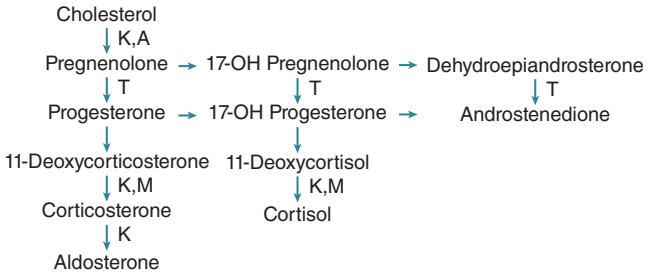


FIG 50.15
Steroid biosynthetic pathways in the adrenal cortex. The branching pathways for glucocorticoids, mineralocorticoids, and adrenal androgens are shown. The site of blockade in the steroid biosynthetic pathways by the enzyme inhibitors trilostane *(T),* ketoconazole *(K),* metyrapone *(M),* and aminoglutethimide *(A)* are also shown.

hyperadrenocorticism. Trilostane is effective in dogs with PDH and ADH, the clinical efficacy of trilostane is excellent (~90%), and trilostane can control clinical signs of hyperadrenocorticism in dogs for prolonged periods (longer than 1 year). Trilostane is used as the primary treatment modality for PDH in dogs, as an alternative in dogs in which mitotane is ineffective or not usable because of problems with drug sensitivity, as a means of reversing the metabolic derangements of hyperadrenocorticism before adrenalectomy in dogs with ADH, and as a medical option to control clinical signs in dogs with metastatic adrenocortical tumors causing ADH.

Trilostane is currently available as 5-, 10-, 30-, 60-, and 120-mg capsules. Compounded trilostane products are not recommended because of documented variation in actual trilostane content in some compounded capsules versus the prescribed strength of the compounded capsule (Cook et al., 2012)—a variation that could influence the dog's response to treatment. Some dogs have problems with short duration of cortisol suppression (<10 hours) that may result in persistence of clinical signs, subsequent administration of large doses of trilostane, and greater likelihood of adverse reactions to the drug. In our experience, twice-daily dosing using a lower dose provides better control than once-daily dosing, and the occurrence and severity of adverse reactions are less frequent. We routinely use an initial dosage of approximately 1 mg/kg twice a day administered with food to increase gastrointestinal absorption.

Dosage adjustments are based on the history, findings on physical examination, and results of serum electrolytes, ACTH stimulation test, and UCCR. Baseline serum cortisol concentrations should not be used to monitor trilostane treatment. A history and physical examination should be performed 2 weeks after trilostane treatment is initiated to ensure that problems related to hypocortisolism (e.g., lethargy, loss of appetite, vomiting) have not developed and that the dog is healthy. An ACTH stimulation test and serum electrolytes should be performed if problems have developed at 2 weeks; otherwise an ACTH stimulation test and serum electrolytes should be performed 4 weeks after initiation of treatment and approximately 4 hours after trilostane administration. Results of ACTH stimulation tests started at different times may yield significantly different results so subsequent ACTH stimulation tests should be started at or about the same time (Bonadio et al., 2014). In addition, the client should bring in a urine sample collected at home the morning of the ACTH stimulation test for a UCCR. The goals of therapy include clinical improvement without development of illness, a suppressed adrenocortical response to ACTH, and a normal UCCR. Results of the ACTH stimulation test are used to adjust the dosage of trilostane, and serum electrolytes are monitored for changes consistent with the onset of hypoaldosteronism. The goal of the ACTH stimulation test is a post-ACTH cortisol concentration between 2 and 5 μg/dL (60 and 145 nmol/L). However, it may take several weeks before maximum suppression of adrenocortical function is attained, and some dogs may need TID treatment to attain control of hyperadrenocorticism. Frequent adjustments in the trilostane dose should be avoided, especially if post-ACTH cortisol concentrations are between 5 and 8 μg/dL (145 and 225 nmol/L), the owner is reporting improvement in clinical signs, and the dog appears to be doing well. Similarly, dogs that attain a post-ACTH cortisol concentration between 2 and 5 μg/dL shortly after trilostane treatment is initiated should be watched closely for development of clinical signs of hypoadrenocorticism. Once control of the hyperadrenal state is attained, an ACTH stimulation test, serum electrolytes, and UCCR should be evaluated every 3 to 4 months—sooner if clinical signs of hypercortisolism or hypocortisolism develop.

Adverse effects of trilostane include lethargy, vomiting, and electrolyte shifts compatible with hypoadrenocorticism. Trilostane should be discontinued until adverse effects dissipate and then trilolstane should be reinitiated at a lower dose, frequency of administration, or both. Permanent hypoadrenocorticism has been reported in a small number of dogs, presumably caused by trilostane-induced adrenocortical necrosis. Acute death has been reported in a small number of dogs shortly after initiation of trilostane treatment. The reason for this is not known, but it may be affiliated with concurrent disease such as a hepatopathy.

MITOTANE

Chemotherapy using mitotane (o,p′DDD; Lysodren) is an effective treatment for PDH and should be considered in dogs that have a poor response to trilostane. Mitotane has also been used to treat ADH (i.e., cortisol secreting adrenal tumor) although our preference is to use trilostane (see section on adrenalectomy). Two treatment protocols have been used: the traditional approach, the goal of which is to control the hyperadrenal state without causing clinical signs of hypoadrenocorticism; and medical adrenalectomy, the goal of which is to destroy the adrenal cortex using mitotane to create permanent hypoadrenocorticism. We prefer the traditional approach, which involves two phases of mitotane

therapy: an initial induction phase designed to gain control of the disorder, and a lifelong maintenance phase designed to prevent recurrence of signs of the disease.

Induction Therapy

The mitotane dosage during induction therapy is approximately 50 mg/kg/day, divided into two doses. The daily dosage is reduced to 25 to 35 mg/kg in dogs without polydipsia or with concurrent diabetes mellitus. Gastrointestinal absorption of mitotane is enhanced in the presence of fat. Mitotane is more effective when each dose is ground up, mixed with a small amount of vegetable oil, and administered with food. Concurrent prednisone administration (0.25 mg/kg q24h) during induction therapy is a matter of personal preference. If prednisone is not used during induction therapy, it should always be dispensed before induction therapy is begun so that the client has prednisone on hand should adverse reactions to mitotane develop.

The induction phase of mitotane treatment is typically done with the dog in the home environment. Client awareness of the dog's activity, mental awareness, appetite, water consumption, and overall well-being is imperative for success. Clients are instructed to stop mitotane treatment and contact the veterinarian if they observe lethargy, inappetence, vomiting, weakness, decreased water intake, or any other change in the dog that does not seem right. The induction phase of therapy is usually complete once any reduction in appetite is noted or once daily water consumption decreases into the normal range (i.e., ≤80 mL/kg). Control is confirmed with the ACTH stimulation test. The first ACTH stimulation test should be performed 5 to 7 days after the start of induction therapy, even if clinical signs of hyperadrenocorticism persist.

The goal of therapy is to achieve a post-ACTH serum cortisol concentration of 2 to 5 μg/dL (60-145 nmol/L). Daily mitotane therapy and weekly ACTH stimulation tests should be continued until a post-ACTH serum cortisol concentration falls within the desired range or until clinical signs of hypocortisolism (i.e., lethargy, inappetence, vomiting) develop. In most dogs clinical signs resolve and a post-ACTH serum cortisol concentration of less than 5 μg/dL is achieved within 5 to 10 days of initiating treatment. A small number of dogs respond within 5 days, and an equally small number of dogs show minimal improvement after 20 or more consecutive days of therapy.

Reasons for a prolonged or poor response to mitotane treatment include inadequate dose, inadequate absorption from the gastrointestinal tract, concurrent administration of drugs (e.g., phenobarbital) that could accelerate the metabolism of mitotane and decrease its serum concentration, client compliance issues, and existence of ADH rather than PDH. If tests to differentiate PDH from ADH were not performed, dogs that are shown to be resistant to therapy, defined as showing little or no reduction in the post-ACTH plasma cortisol concentration after 20 or more days of therapy, should undergo further evaluation (i.e., abdominal ultrasound) to rule out ADH.

Maintenance Therapy

Mitotane must be administered periodically to prevent recurrence of clinical signs. The maintenance phase of mitotane therapy should be initiated once the post-ACTH serum cortisol concentration is less than 5 μg/dL and the dog appears healthy. The maintenance dose is defined as the weekly amount of mitotane administered, regardless of whether the weekly dose is given once per week or is divided into multiple doses and given on several days. Adverse reactions caused by sensitivity to the drug are less likely to occur when the weekly dose is divided and given on several days of the week. The typical initial weekly maintenance dosage of mitotane is 50 mg/kg administered orally, divided into two or three doses, and administered on 2 or 3 days of each week. The maintenance dose of mitotane is decreased from 50 mg/kg/wk to 25 mg/kg/wk if the post-ACTH serum cortisol concentration is less than 2 μg/dL (60 nmol/L) and the dog appears healthy. Mitotane treatment is discontinued and prednisone treatment initiated if the post-ACTH serum cortisol concentration is less than 2 μg/dL and the dog is exhibiting clinical signs of hypoadrenocorticism.

The initial dose of mitotane during maintenance therapy is arbitrary, and subsequent adjustments are made on the basis of results of ACTH stimulation tests; the first test is performed 3 to 4 weeks after the start of maintenance therapy. The goal of maintenance therapy is to maintain the post-ACTH serum cortisol concentration at between 2 and 5 μg/dL in an otherwise healthy dog. The dose and frequency of administration of mitotane are adjusted, as needed, to maintain a hypoadrenal response to ACTH administration. If the post-ACTH serum cortisol is between 2 and 5 μg/dL, a change in treatment is not indicated and the ACTH stimulation test should be repeated in 6 to 8 weeks. If the post-ACTH serum cortisol concentration is greater than 5 μg/dL, the amount of mitotane administered per week is increased. If the post-ACTH serum cortisol concentration is less than 2 μg/dL, the amount of mitotane administered per week is decreased; mitotane therapy is temporarily discontinued if clinical signs of hypoadrenocorticism are present. An ACTH stimulation test is performed 3 to 4 weeks after a change is made to the dose or frequency of administration of mitotane. Once the post-ACTH serum cortisol concentration is stable and in the range of 2 to 5 μg/dL, the frequency of performing the ACTH stimulation test can be decreased.

In most dogs an initially effective maintenance dose of mitotane becomes inadequate as the compensatory sustained increase in plasma ACTH concentration counters the adrenocorticolytic effects of mitotane. With time the dose and frequency of administration of mitotane usually increases to compensate for this effect. Periodic ACTH stimulation testing will identify when the post-ACTH serum cortisol concentration increases above 5 μg/dL, allowing the clinician to adjust the mitotane treatment protocol to maintain control of the disease. In some dogs, this can ultimately necessitate daily mitotane administration. Alternative therapy (i.e., trilostane) should be considered for dogs that become insensitive to mitotane.

Adverse Reactions to Mitotane Treatment

Adverse reactions to mitotane treatment result from sensitivity to the drug or from excessive administration and subsequent development of glucocorticoid and, if severe, mineralocorticoid deficiency (Box 50.5). The most common reactions to mitotane are gastric irritation and vomiting occurring shortly after its administration. If the gastric upset is the result of drug sensitivity and not of hypoadrenocorticism, dividing the dose further, increasing the interval between administrations, or both can help minimize vomiting.

Excessive administration of mitotane results in clinical signs of hypocortisolism, including weakness, lethargy, anorexia, vomiting, and diarrhea. Clinical improvement is usually seen within hours of administration of prednisone (0.25-0.5 mg/kg). If the dog responds, the initial dosage of glucocorticoids should be continued for 3 to 5 days and then gradually decreased and stopped over the ensuing couple of weeks. An ACTH stimulation test be performed once the dog is healthy and not receiving glucocorticoids can help determine when mitotane treatment should be started; usually when the post-ACTH serum cortisol concentration is 2 µg/dL or greater. The weekly dose of mitotane should be reduced when therapy is reinitiated.

BOX 50.5

Adverse Effects of Mitotane in Dogs

Direct Effect*

Lethargy
Inappetence
Vomiting
Neurologic signs
- Ataxia
- Circling
- Stupor
- Apparent blindness

Secondary to Overdosage*

Hypocortisolism
- Lethargy
- Anorexia
- Vomiting
- Diarrhea
- Weakness

Hypoaldosteronism (hyperkalemia, hyponatremia)
- Lethargy
- Weakness
- Cardiac conduction disturbances
- Hypovolemia
- Hypotension

PMA, Pituitary macroadenoma.
*Adrenocorticotropic hormone stimulation test, serum electrolytes, response to discontinuation of mitotane, and response to glucocorticoid therapy are used to differentiate these categories of adverse reactions.

Excessive administration of mitotane ultimately causes hypoaldosteronism. Mineralocorticoid deficiency should be considered in any dog with signs of hypocortisolism that does not respond to glucocorticoid therapy. A finding of hyponatremia and hyperkalemia supports a diagnosis of hypoaldosteronism, and mineralocorticoid therapy is indicated in such dogs (see p. 883). Hypoaldosteronism can develop within days of the start of mitotane therapy in some dogs. Hypoaldosteronism can resolve with hyperadrenocorticism recurring spontaneously, but this is unpredictable. Some dogs remain mineralocorticoid deficient for the remainder of their lives.

Medical Adrenalectomy Using Mitotane

An alternative to the traditional mitotane treatment protocol is to intentionally cause complete destruction of the adrenal cortices by administering an excessive amount of mitotane. In theory, therapy for the ensuing adrenocortical insufficiency would then be necessary for the life of the dog. The protocol consists of administering mitotane at a dosage of 75 to 100 mg/kg daily for 25 consecutive days, in three or four doses per day, with food, to minimize neurologic complications and ensure good intestinal absorption of the drug. Lifelong prednisone (0.1-0.5 mg/kg q12h initially) and mineralocorticoid therapy (see p. 888) is begun at the start of mitotane administration. The prednisone dose is tapered after completion of the 25-day protocol. Unfortunately, relapse with signs of hyperadrenocorticism occurs within the first year alone in approximately 33% of dogs so treated, indicating the need for periodic ACTH stimulation testing similar to that done in dogs treated with the traditional mode of therapy. This treatment can be considerably more expensive than long-term treatment with mitotane because of the expense of treating addisonian dogs.

Management of Concurrent Diabetes Mellitus

Hyperadrenocorticism and diabetes mellitus are common concurrent diseases in dogs. Presumably, hyperadrenocorticism develops initially and subclinical diabetes mellitus becomes clinically apparent as a result of the insulin resistance caused by the hyperadrenal state. For most of these dogs, glycemic control remains poor despite insulin therapy, and good glycemic control generally is not possible until the hyperadrenocorticism is controlled. Occasionally, diabetic dogs presumably in the early stages of hyperadrenocorticism (often identified while the cause of an increased ALP is being pursued) will be responsive to insulin and have good control of glycemia. Because the diabetes is well controlled, the decision to treat or not treat hyperadrenocorticism in these dogs should be based on other factors, such as the presence of additional clinical signs or physical examination findings and the clinician's index of suspicion for the disease. The clinician should adopt a wait-and-see approach in the absence of strong evidence for hyperadrenocorticism in these dogs. Poor control of the diabetic state will eventually occur if hyperadrenocorticism is present.

The initial focus should be on treating the hyperadrenal state in a poorly controlled diabetic dog diagnosed with hyperadrenocorticism. Concurrent insulin therapy is indicated; however, aggressive efforts to control the blood glucose concentration should not be attempted. Rather, a conservative dose (0.5-1 U/kg) of intermediate-acting insulin (i.e., lente) is administered twice a day to prevent ketoacidosis and severe hyperglycemia (blood glucose concentration > 500 mg/dL). Monitoring water consumption as a response to trilostane or mitotane treatment is not reliable when concurrent diabetes mellitus is present because both diseases cause polyuria and polydipsia, and because polyuria and polydipsia may persist if poor control of glycemia persists despite the fact that the hyperadrenocorticism is under control. As control of the hyperadrenocorticism is achieved, insulin antagonism caused by the hyperadrenocorticism resolves and tissue sensitivity to insulin improves. To help prevent hypoglycemic reactions, clients are asked to test urine for the presence of glucose, preferably two or three times each day. Any urine sample found to be negative for glucose should be followed by a 20% to 25% reduction in the insulin dose and performance of an ACTH stimulation test. Critical assessment of glycemic control and adjustments in insulin therapy, if indicated, should be initiated once hyperadrenocorticism is controlled.

KETOCONAZOLE

Ketoconazole reversibly inhibits adrenal steroidogenesis (see Fig. 50.15). The initial dosage of ketoconazole is 5 mg/kg q12h, and subsequent increases in the dosage are based on results of an ACTH stimulation test performed 10 to 14 days later, while the dog is still receiving ketoconazole. The goals of therapy are similar to those discussed for trilostane. Approximately 20% to 25% of dogs do not respond to the drug as a result of poor intestinal absorption. Adverse reactions are primarily a result of hypocortisolism and include lethargy, inappetence, vomiting, and diarrhea. Unfortunately, it is difficult to control the clinical signs of hyperadrenocorticism without creating problems with hypocortisolism. We do not recommend ketoconazole for the treatment of hyperadrenocorticism.

ADRENALECTOMY

Adrenalectomy is the treatment of choice for an adrenocortical tumor causing ADH unless metastatic lesions or invasion of surrounding organs or blood vessels is identified during the preoperative evaluation, or the dog is considered a poor anesthetic risk because it has a significant concurrent disease.

Dogs with large tumors (maximum width greater than 5 cm), dogs with extensive invasion of the caudal vena cava (especially thrombi that have extended beyond the hepatic hilus), dogs with metastatic lesions (typically in the liver and lungs) or tumors that have infiltrated the kidney or body wall, dogs with low antithrombin III concentrations, and debilitated dogs with advanced clinical manifestations of hyperadrenocorticism have a high probability of serious postoperative complications and a poor outcome. For these dogs, treatment with trilostane offers a viable alternative to adrenalectomy. Trilostane does not have antineoplastic properties but is effective in decreasing cortisol secretion by the tumor and is used to control clinical signs of hyperadrenocorticism. For dogs undergoing adrenalectomy, trilostane treatment for 3 to 4 weeks before surgery using the treatment protocol previously discussed can reverse the metabolic derangements of hyperadrenocorticism and minimize many of the complications associated with adrenalectomy.

The goals of trilostane therapy are improvement in clinical signs and a post-ACTH serum cortisol concentration between 2 and 6 µg/dL. Serum electrolytes are monitored for changes consistent with the onset of hypoaldosteronism. The dosage of trilostane is adjusted, as needed, until these goals are attained, which usually occurs within 30 days of initiating treatment. Adrenalectomy is performed once control of the hyperadrenal state is attained but generally no later than 30 days after initiating trilostane treatment, regardless of the state of control of the disease.

The reader is referred to Johnston and Tobias (2018) for more detailed information on the surgical techniques for adrenalectomy. Our current preference is laparoscopic adrenalectomy in dogs with noninvasive adrenal masses. Advantages of minimally invasive laparoscopic adrenalectomy include better visualization of abdominal organs and the adrenal mass (Videos 50.2 and 50.3), limited manipulation of other abdominal organs, decreased surgical wound complications, improved postoperative comfort, faster recovery period, and a shorter hospital stay. In our experience, recovery from the surgery is quicker, postoperative discomfort is noticeably less, most dogs are ambulatory a few hours postanesthesia, and many are discharged the next day. Problems with postoperative pancreatitis and PTE are uncommon, especially if dogs are treated with trilostane for 3 to 4 weeks before surgery.

Cortisol-secreting adrenal tumors are challenging to manage after adrenalectomy, in part because of concurrent immunosuppression, impaired wound healing, systemic hypertension and hypercoagulation, frequent infiltration of the tumor into surrounding blood vessels and soft tissues, potential development of pancreatitis postoperatively (especially with right-sided adrenal masses), and development of hypoadrenocorticism after removal of the mass. The most worrisome complication is thromboembolism, which typically develops during or within 24 hours of surgery and carries a high mortality rate (see p. 860). Prior treatment with trilostane and frequent short walks within hours of surgery to promote blood flow help minimize clot formation. Anesthetic drugs and pain medications should be administered at dosages that allow the dog to be ambulatory within 4 hours of the surgery. Glucocorticoid therapy is not indicated before adrenalectomy. Acute hypocortisolism uniformly occurs after adrenalectomy. When the surgeon begins to remove the adrenal tumor, dexamethasone (0.05-0.1 mg/kg) should be placed in the IV infusion bottle. This dose should be given over a 6-hour period. A tapering dose (e.g., decreasing the dose by 0.02 mg/kg/24 h) of dexamethasone

should continue to be administered intravenously at 12-hour intervals until the dog can safely be given oral medication without danger of vomiting (typically 24-48 hours postoperatively). At that point, the glucocorticoid supplement should be switched to oral prednisone (0.25-0.5 mg/kg q12h), and the dosage and frequency of prednisone administration should be gradually reduced during the ensuing 3 to 4 months. If a unilateral adrenalectomy has been performed, prednisone supplementation can eventually be discontinued once the contralateral normal adrenocortical tissue becomes functional. Lifelong prednisone therapy is required for dogs that undergo bilateral adrenalectomy.

Serum electrolyte concentrations should be closely monitored postoperatively. Mild hyponatremia and hyperkalemia commonly develop within 48 hours of surgery and usually resolve in a day or two as exogenous glucocorticoid doses are reduced and the dog begins to eat. Mineralocorticoid treatment is recommended if the serum sodium concentration decreases to less than 135 mEq/L or if serum potassium concentration increases to greater than 6.5 mEq/L. An injection of desoxycorticosterone pivalate (DOCP; Percorten-V) is recommended, with measurement of serum electrolytes performed 25 days after the injection (see p. 888). If the dog is healthy and serum electrolytes are normal on day 25, additional DOCP treatment usually is not needed for dogs undergoing unilateral adrenalectomy but will be needed in dogs undergoing bilateral adrenalectomy.

Reported median survival times for dogs that survived the postoperative period and were discharged from the hospital include 690 days, 492 days, 953 days, and 48 months (Schwartz et al., 2008; Lang et al., 2011; Massari et al., 2011; Helm et al., 2011). Long-term survival time was significantly shorter in dogs with adrenal carcinomas, adrenal tumors with a maximum width ≥ 5 cm, presence of metastasis, and presence of vena cava thrombosis (Massari et al., 2011).

PITUITARY IRRADIATION

Approximately 50% of dogs have a pituitary mass identified on CT or MRI at the time PDH is diagnosed. In approximately 50% of these dogs, the pituitary mass grows over the ensuing 1 to 2 years, eventually causing pituitary macrotumor syndrome (see p. 859). Pituitary macroadenoma is tentatively diagnosed by ruling out other causes of the neurologic disturbances and is confirmed by CT or MRI findings (see Fig. 50.4). Development of neurologic signs from a pituitary macrotumor is a common reason for clients to request euthanasia of dogs with PDH. Irradiation has successfully reduced the tumor size and lessened or eliminated neurologic signs in dogs with pituitary macrotumor syndrome (Fig. 50.16). Several universities and a few large referral practices in the United States offer pituitary irradiation treatment for pituitary macrotumors in dogs with PDH and cats with acromegaly. The type of irradiation (e.g., Cobalt 60, 4, 5, and 6 MV photon teletherapy using a linear accelerator, and stereotactic radiotherapy that uses a high dose of radiation delivered in a single or a few fractions) and the treatment protocol (e.g., total radiation dose, number of fractions, delivered per week, total treatment period) vary between radiation oncologists.

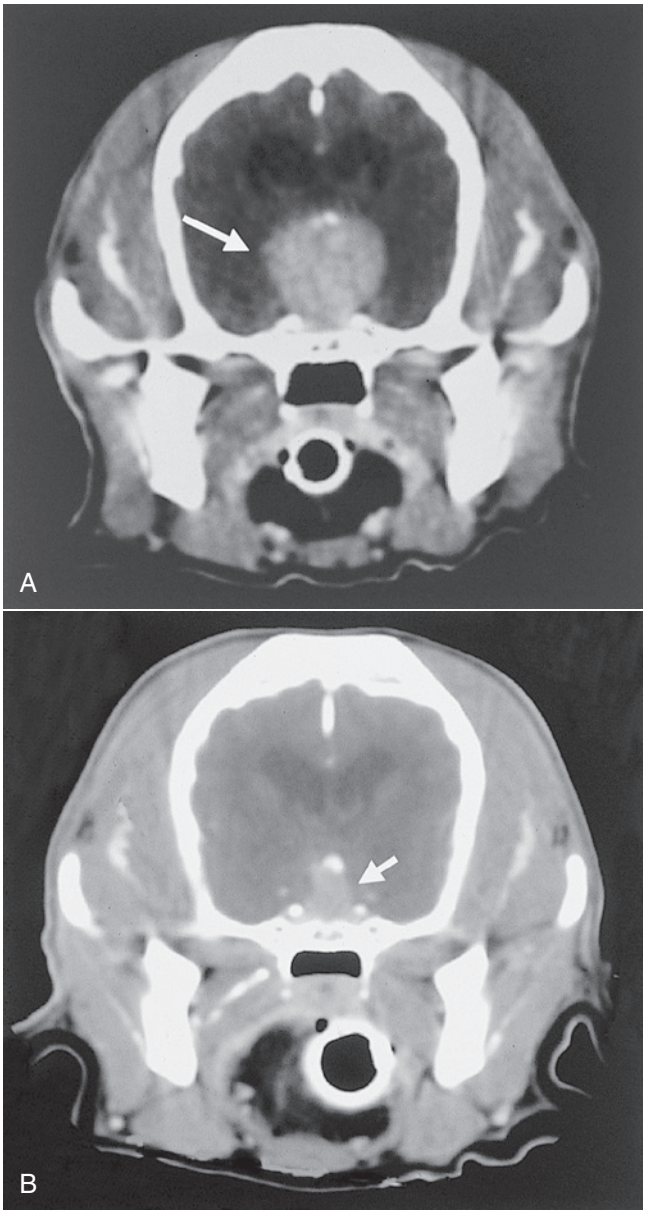


FIG 50.16
(A) Computed tomography (CT) image of the pituitary region of a 9-year-old, female, spayed Cocker Spaniel with pituitary-dependent hyperadrenocorticism (PDH). The PDH had been treated with mitotane for 2 years, at which time the dog developed lethargy, inappetence, and weight loss. A large mass measuring approximately 2.0 cm in diameter is evident in the hypothalamic-pituitary region *(arrow)*. **(B)** CT image of the pituitary region 18 months after completion of radiation therapy. The volume of the mass decreased by approximately 75%, compared with the volume before treatment. Clinical signs related to the pituitary macrotumor resolved, and mitotane treatment was discontinued after radiation treatment.

The goals of radiation therapy include shrinkage of the macrotumor, improvement or resolution of neurologic signs, improvement or resolution of clinical manifestations of

hyperadrenocorticism, and prolonged survival with a good quality of life. All studies evaluating the effect of irradiation on pituitary tumor size, to date, have documented a significant decrease in tumor size in almost all dogs treated.

Prognostic factors that affect survival time after radiation therapy include the severity of neurologic signs and the relative size of the tumor. Generally, dogs with subtle or mild neurologic clinical signs and the smallest tumors show the best response to treatment. Theon et al. (1998) found a mean survival time after radiation of 25 months in dogs with mild neurologic signs, 17 months in dogs with severe neurologic signs, and only 5 months in untreated dogs with neurologic signs. In a study by Kent et al. (2007), mean survival time in 19 dogs with pituitary masses treated with radiation therapy was 1405 days, and 1-, 2-, and 3-year estimated survival was 93%, 87%, and 55%, respectively. In contrast, mean survival time in 27 untreated dogs with pituitary masses was 551 days, and 1-, 2-, and 3-year estimated survival was 45%, 32%, and 25%, respectively.

Because of the high prevalence of a pituitary mass at the time PDH is diagnosed and the potential for future growth and development of neurologic signs, we routinely discuss CT imaging of the pituitary gland as part of the evaluation of a dog with newly diagnosed PDH even if there is no clinical evidence of a large pituitary mass, especially if the client is willing to consider irradiation therapy if a large pituitary mass is identified. Our preference is to perform CT imaging once clinical signs of hyperadrenocorticism are controlled with medical treatment. We understand that CT imaging is expensive but many of our clients are interested and want to know the status of the pituitary mass. No further evaluation of the pituitary is indicated if a pituitary mass is not identified on the initial CT scan. If a pituitary mass is identified and measures 3 to 7 mm in greatest vertical height, a repeat pituitary scan is recommended 12 months later. If a pituitary mass is identified equal to or greater than 8 mm in greatest vertical height, pituitary irradiation is recommended. The goal of pituitary irradiation is to shrink the mass and prevent development of macrotumor syndrome; trilostane or mitotane therapy may still be needed to control clinical signs of hyperadrenocorticism.

HYPOPHYSECTOMY

For several decades, selective pituitary microsurgery using the transsphenoidal approach has been considered the treatment of choice for pituitary tumors causing hyperadrenocorticism in humans. Initial studies in veterinary medicine developing the microsurgical technique, identifying postoperative complications and assessing postoperative pituitary function, or lack thereof, were done in healthy dogs approximately 25 years ago. Since then, Meij and co-investigators at Utrecht University, the Netherlands, have published several articles detailing their experiences with transsphenoidal hypophysectomy in dogs with PDH. In 2005, the Utrecht group reported on the long-term results of transsphenoidal hypophysectomy in 150 dogs with PDH (Hanson et al., 2005). Postoperative complications included transient and, less commonly, permanent central diabetes insipidus (CDI), hypernatremia, keratoconjunctivitis sicca (KCS), and secondary hypothyroidism (Hanson et al., 2005). Postoperative hormonal replacement therapy included synthetic vasopressin (DDAVP), glucocorticoids, and levothyroxine. CDI was present until death or until latest follow-up in 22% of the dogs. In another study, the incidence of postoperative permanent CDI in dogs undergoing transsphenoidal surgery for PDH was strongly influenced by the size of the pituitary tumor; the larger the tumor, the more likely for postoperative CDI to be permanent (Teshima et al., 2011). Twelve of the 150 dogs died within 4 weeks of surgery. One-hundred twenty-seven (92%) of 138 dogs that were alive after 4 weeks experienced remission within 8 weeks of surgery; remission was defined as resolution of clinical signs of hyperadrenocorticism and UCCR values in the reference range. Hyperadrenocorticism remained in remission in 95 of 127 dogs (75%). In 32 of 127 dogs (25%), signs of hyperadrenocorticism and increased UCCR values recurred at 6 weeks to 56 months (median, 18 months) after surgery. The 1-year, 2-year, 3-year, and 4-year estimated survival rate was approximately 84%, 76%, 72%, and 68%, respectively. The 1-year, 2-year, 3-year, and 4-year estimated relapse-free fraction was approximately 88%, 75%, 66%, and 59%, respectively. Survival and disease-free fractions of dogs with enlarged pituitaries were significantly lower than in dogs with nonenlarged pituitaries.

Based on the experiences at Utrecht University, microsurgical transsphenoidal hypophysectomy is an effective long-term treatment of PDH in dogs. Early diagnosis of a corticotroph adenoma is important. Transsphenoidal hypophysectomy is most effective in dogs with nonenlarged or moderately enlarged pituitaries. Size of the pituitary tumor has a direct impact on survival, disease-free fractions, and incidence of permanent CDI in dogs. Unfortunately, the number of sites currently offering hypophysectomy as a treatment option for PDH is limited in the United States.

Prognosis

Reported median survival times for dogs with ADH that survive the initial postadrenalectomy month range from 492 to 953 days, with some dogs living 4 to 5 years after surgery (Schwartz et al., 2008; Lang et al., 2011; Massari et al., 2011). In one study by Helm et al. (2011), median survival times for dogs with ADH treated with trilostane and mitotane were 353 days (95% confidence interval [CI], 95-528 days) and 102 days (95% CI, 43-277 days), respectively. Dogs with adrenocortical adenoma or adrenocortical carcinoma that has not metastasized (uncommon) have a good prognosis, whereas dogs with metastatic adrenocortical carcinoma or carcinoma with vein invasion (common) have a poorer prognosis, and these dogs typically succumb to the disease within 1 to 2 years of diagnosis. Although clinical signs can be controlled with trilostane and mitotane, death ultimately results from the debilitating effects of the tumor, complications of vein thrombosis (e.g., ascites) or metastatic growth, or other geriatric disorders (e.g., chronic kidney disease, congestive heart failure).

The prognosis for dogs with PDH depends in part on the age and overall health of the dog and on the client's commitment to therapy. The mean life span of affected dogs after diagnosis of PDH is approximately 30 months. Younger dogs may live considerably longer (i.e., 5 years or longer). Many dogs ultimately die or are euthanized because of complications related to hyperadrenocorticism (e.g., pituitary macrotumor syndrome) or other geriatric disorders.

OCCULT (ATYPICAL) HYPERADRENOCORTICISM IN DOGS

Occult hyperadrenocorticism is defined as a syndrome in which a dog appears to have hyperadrenocorticism based on history, physical examination and clinicopathologic findings, but results of the ACTH stimulation test, LDDS test, and UCCR are within reference ranges. Possible explanations for occult hyperadrenocorticism include dogs early in the course of hyperadrenocorticism, dogs that have a disease that mimics some of the clinical manifestations of hyperadrenocorticism (e.g., Alopecia X), and dogs that have increased of adrenocortical precursor hormones such as progesterone and 17-hydroxyprogesterone (see Fig. 50.15). Adrenal tumors that secrete progesterone may cause a clinical syndrome that mimics hyperadrenocorticism in dogs and cats. Clinical signs presumably result from intrinsic glucocorticoid activity of progestins, progestin-induced displacement of cortisol from cortisol-binding protein in the circulation, or both. Cortisol concentrations are inappropriately low on hyperadrenocorticism screening tests in dogs and cats with progesterone secreting tumors.

Abnormal secretion of adrenocortical precursor hormones has been proposed as a cause of occult hyperadrenocorticism but this proposal is controversial, in part, because adrenocortical precursor hormones have not been proven to cause occult hyperadrenocorticism. Results of studies aimed at documenting a relationship between adrenocortical precursor hormones and generation of the clinical abnormalities affiliated with this syndrome are conflicting and improvement of clinical signs after mitotane and trilostane treatment unpredictable.

Alterations in concentrations of adrenocortical precursor hormones before and after ACTH stimulation has been used to establish the diagnosis. Because these precursor hormones precede cortisol in the production pathway, dogs with hyperadrenocorticism also have increased concentrations of precursor hormones, as can dogs with nonadrenal illness, and healthy female dogs during estrus, diestrus, and pregnancy. A recent study by Frank et al. (2015) documented higher serum cortisol concentrations during a 9-hour blood sampling period in dogs with occult hyperadrenocorticism compared with control dogs but lower cortisol concentrations compared with dogs with pituitary-dependent hyperadrenocorticism. In addition, average transverse adrenal gland diameter determined by abdominal ultrasound was less in control dogs compared with dogs with PDH and occult hyperadrenocorticism, but transverse diameter did not differ between PDH and occult hyperadrenocorticism dogs. The authors speculated that occult hyperadrenocorticism not caused by an adrenal tumor may be due to increased 24-hour cortisol secretion, an increase that may not be detected using routine screening tests.

Currently, an ACTH stimulation test with measurement of serum and plasma adrenocortical steroid precursor hormones is used to identify occult hyperadrenocorticism in dogs. The most common finding is an increase in pre- and post ACTH stimulation serum 17-hydroxyprogesterone concentrations. Currently, the only laboratory with established reference ranges for precursor and sex steroids is the Endocrinology Laboratory at the University of Tennessee, College of Veterinary Medicine, in Knoxville, Tennessee. Treatment recommendations have included low dosages of mitotane and trilostane, although Sieber-Ruckstuhl et al. (2006) failed to document a decrease in 17-hydroxyprogesterone concentration in dogs with PDH treated with trilostane.

We do not routinely measure serum adrenocortical precursor hormones when evaluating dogs for hyperadrenocorticism. If results of the LDDS test and UCCR are normal or equivocal, we look for another cause for the clinical signs. If another cause is not identified and clinical signs are mild, we recommend waiting and testing for hyperadrenocorticism if progression is noted. Readers are referred to Behrend et al. (2013) in the suggested reading section for more information on occult hyperadrenocorticism.

HYPERADRENOCORTICISM IN CATS

Hyperadrenocorticism is uncommon in cats. Although many of the clinical characteristics of feline hyperadrenocorticism are similar to those seen in dogs, some important differences should be emphasized. Most notable is the very strong association with diabetes mellitus; the progressive, relentless weight loss leading to cachexia; and dermal and epidermal atrophy leading to extremely fragile, thin, and easily torn and ulcerated skin (i.e., feline fragile skin syndrome) in cats with hyperadrenocorticism. Establishing the diagnosis can be difficult, abnormalities on routine blood and urine tests that are suggestive of hyperadrenocorticism in dogs are usually absent in cats, and medical treatment for hyperadrenocorticism in cats is not consistently effective.

Etiology

Hyperadrenocorticism in cats may be classified as pituitary dependent (PDH) or adrenocortical tumor dependent (ADH). Approximately 80% of cats with hyperadrenocorticism have PDH and 20% have ADH, with 50% of adrenal tumors being adenomas and 50% carcinomas. Cats with PDH have a pituitary microadenoma, macroadenoma, or carcinoma identified at necropsy. Iatrogenic hyperadrenocorticism is uncommon in cats; typically prednisone or prednisolone administration for months is required before clinical signs occur.

Clinical Features

CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Hyperadrenocorticism is a disease of older (average age, 11 years; range, 5-7 years) mixed-breed cats. A strong correlation has been noted between hyperadrenocorticism and diabetes mellitus and almost all cats are diabetic or prediabetic at the time hyperadrenocorticism is diagnosed. The most common initial clinical signs of feline hyperadrenocorticism (i.e., polyuria, polydipsia, polyphagia) are more likely caused by diabetes than by hyperadrenocorticism. Other clinical signs and physical examination findings are not as frequently observed in cats as in dogs and tend to be very subtle in the early stages of the disease (Box 50.6 and Fig. 50.17).

A frequent clue to the existence of hyperadrenocorticism in cats is the presence of diabetes mellitus that is difficult to control and ultimately progresses to severe insulin resistance. Initially, clinical signs of hyperadrenocorticism are mild, and tests of the pituitary-adrenocortical axis are often inconclusive and difficult to interpret in the

BOX 50.6

Clinical Features of Hyperadrenocorticism in Cats

Clinical Signs

Polyuria, polydipsia*
Polyphagia*
Patchy alopecia*
Unkempt haircoat*
Symmetric alopecia
Lethargy
Thin, easily torn skin (feline fragile skin syndrome)*
Weight loss*
Drooping of pinna

Additional Physical Findings

"Pot-bellied" appearance*
Hepatomegaly*
Muscle wasting*
Skin infection

*Common.

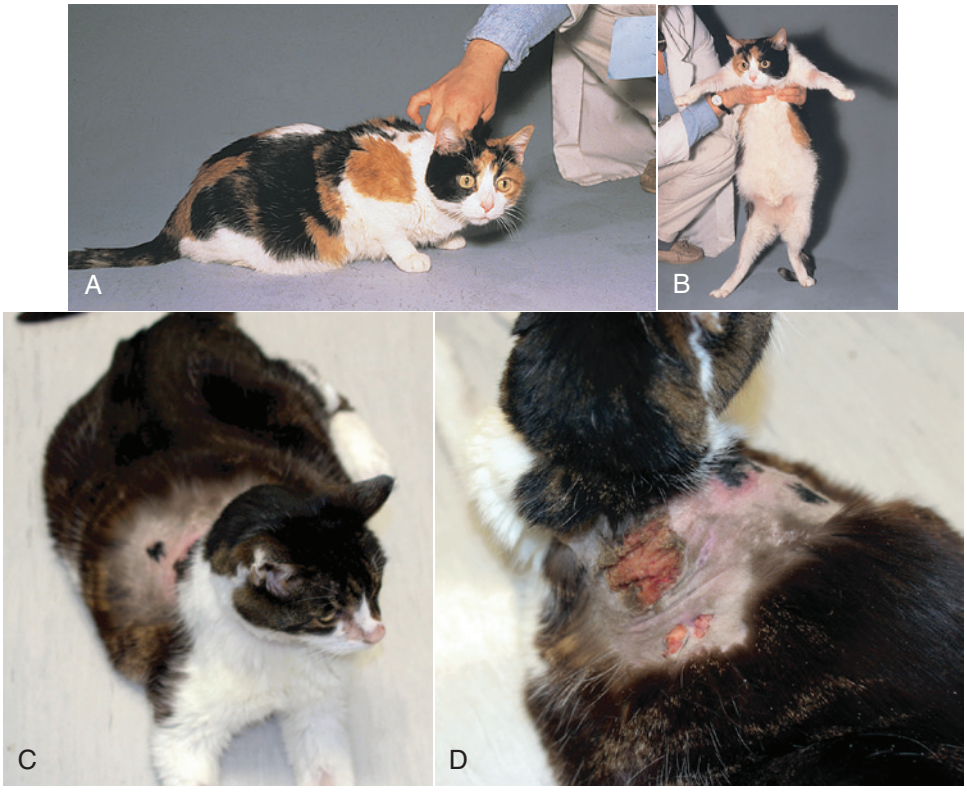


FIG 50.17
(A) and **(B)** A 9-year-old cat with pituitary-dependent hyperadrenocorticism (PDH) and insulin-resistant diabetes mellitus. Note the relatively normal physical appearance of the cat in its normal posture **(A).** Abdominal enlargement and inguinal alopecia are evident on physical examination **(B). (C)** and **(D)** A 16-year-old cat with PDH and insulin-resistant diabetes mellitus. Note the relatively normal appearance of the cat and the alopecia and ulceration in the dorsal cervical and anterior thoracic regions in the area of a collar worn by the cat. Alopecia was also present in the ventral region of the neck.

presence of poorly controlled diabetes. With time, hyperadrenocorticism becomes more apparent as affected cats become progressively more debilitated despite aggressive insulin therapy; weight loss leads to cachexia; and dermal and epidermal atrophy results in extremely fragile, thin, and easily torn and ulcerated skin (Fig. 50.18). Dermal and epidermal lesions often occur when the cat is groomed or when the cat is handled during the physical examination. Insulin resistance is usually severe by the time cachexia and skin fragility develop. The primary differential diagnosis for insulin resistance, cachexia, and feline fragile skin syndrome is excess progestins, as occur with progesterone-secreting adrenal tumors (see p. 894 and Table 50.6).

CLINICAL PATHOLOGY

The classic clinicopathologic alterations seen in dogs with hyperadrenocorticism are infrequently found in cats. The most frequently observed abnormalities in cats are hyperglycemia, glycosuria, hypercholesterolemia, and a mild increase in alanine aminotransferase activity. These alterations can be explained by concurrent, poorly regulated diabetes mellitus. A stress leukogram, an increase in ALP activity, and isosthenuric-hyposthenuric urine are not common findings in hyperadrenal cats. An inability to document histologic changes in the liver consistent with steroid-induced hepatopathy, an absence of the steroid-induced ALP isoenzyme activity, and the relatively short half-life of ALP activity in cats may account for the absence of an observed increase in



FIG 50.18
(A) A 15-year-old cat with pituitary-dependent hyperadrenocorticism (PDH), insulin-resistant diabetes mellitus, and feline fragile skin syndrome. Note the torn skin over the back of the neck, which occurred while the cat was being restrained during a physical examination. **(A)** A 12-year-old cat with hyperadrenocorticism and severe insulin-resistant diabetes mellitus. This cat weighed 2.2 kg and was receiving 25 units of regular insulin three times a day with no glucose-lowering effect. Note the emaciated appearance, presumably resulting from protracted poor glycemic control, alopecia, severe dermal and epidermal atrophy, and lesions resulting from easily torn skin *(arrow)*. **(C)** A 17-year-old cat with PDH and insulin-resistant diabetes mellitus. Note the emaciated appearance of the cat, the enlarged abdomen (pot-bellied appearance), and absence of hair growth on the ventral abdomen, which had been shaved for an abdominal ultrasound 10 months before presentation.

ALP activity. Urine abnormalities frequently identified in dogs with hyperadrenocorticism are not common in cats.

DIAGNOSTIC IMAGING

Abdominal ultrasonography is used to identify adrenal masses and to clarify the clinician's index of suspicion for PDH. Interpretation of results of adrenal imaging in cats is similar to that in dogs (see p. 862). The maximum width of the adrenal gland in healthy cats is typically less than 0.5 cm. Adrenomegaly should be suspected when the maximum width is greater than 0.5 cm; a maximum width greater than 0.8 cm is strongly suggestive of adrenomegaly. The finding of easily visualized, bilaterally large adrenals in a cat with appropriate clinical signs and physical examination findings and abnormal test results of the pituitary-adrenocortical axis is strong evidence for PDH. CT and MRI can be used to look for pituitary macroadenoma and to determine the size of an adrenal mass and the extent of infiltration of the mass into surrounding blood vessels and organs before adrenalectomy.

TESTS OF THE PITUITARY-ADRENOCORTICAL AXIS

Although the tests used to diagnose hyperadrenocorticism in cats and dogs are similar (see p. 864), some important differences have been noted in the testing protocol and in interpretation of results (Table 50.3). We rely most heavily on the UCCR, the dexamethasone suppression test (sensitivity ≈90%), and abdominal ultrasonography to establish the diagnosis of hyperadrenocorticism in cats. The ACTH stimulation test lacks sensitivity (≈40%) in the cat and is not recommended. We also rely on abdominal ultrasound rather than endogenous plasma ACTH concentration to differentiate PDH from ADH.

Urine Cortisol/Creatinine Ratio

The theory behind and the specifics regarding the UCCR are similar for dogs and cats and are discussed on page 867. The UCCR test is a sensitive diagnostic test for identifying hyperadrenocorticism in cats, but similar to dogs, specificity of the test is low in cats. We use the UCCR as the initial screening test for hyperadrenocorticism in cats. Urine should be collected at home, preferably on two consecutive days. A normal UCCR in one or both urine samples is strong evidence against hyperadrenocorticism. An increase in UCCR in both urine samples does not establish the diagnosis by itself but supports performing the dexamethasone suppression test.

Dexamethasone Suppression Test

The duration of the suppressive effects of intravenously administered dexamethasone on serum cortisol concentrations is

TABLE 50.3

Diagnostic Tests to Assess the Pituitary-Adrenocortical Axis in Cats With Suspected Hyperadrenocorticism

TEST	PURPOSE	PROTOCOL	RESULTS	INTERPRETATION
Urine cortisol/creatinine ratio	Rule out HAC	Urine collected at home	Normal Increased	Not supportive of HAC Additional tests for HAC indicated
			8 hours post-dexamethasone:	
Dexamethasone suppression test	Diagnose HAC	0.1 mg dexamethasone/kg IV; serum pre- and 4 and 8 hours post-dexamethasone	<1.0 µg/dL 1.0-1.4 µg/dL >1.5 µg/dL and 4 hours <1.5 µg/dL >1.5 µg/dL and 4 hours >1.5 µg/dL	Normal Nondiagnostic Suggestive[†] Strongly suggestive[‡]
			Post-ACTH cortisol concentration:	
ACTH stimulation	Diagnose HAC	125 µg of synthetic ACTH*/cat IV; serum pre- and 30 and 60 minutes post-ACTH	>20 µg/dL 15-20 µg/dL 5-15 µg/dL <5 µg/dL	Strongly suggestive Suggestive Normal Iatrogenic HAC
Endogenous ACTH	Differentiate PDH from ATH	Specific sample handling required	Below reference range Upper half of reference range or increased Lower half of reference range	ATH PDH Nondiagnostic

ACTH, Adrenocorticotropic hormone; *ATH,* adrenal tumor causing hyperadrenocorticism; *HAC,* hyperadrenocorticism; *IV,* intravenous; *PDH,* pituitary-dependent hyperadrenocorticism.
*Synthetic ACTH: Cortrosyn, Cosyntropin, Synacthen.
[†]Suggestive of hyperadrenocorticism.
[‡]Strongly suggestive of hyperadrenocorticism.

more variable in cats than in dogs. Approximately 20% of healthy cats do not experience the suppressive effects of dexamethasone, and their serum cortisol concentrations are greater than 1.4 µg/dL (40 nmol/L) 8 hours after dexamethasone administration. This "escape phenomenon" is more likely to occur in cats receiving lower doses of dexamethasone. Because of potential misinterpretation caused by the escape phenomenon and the fragile state of many diabetic hyperadrenal cats, we typically use only one dexamethasone suppression test protocol (0.1 mg/kg dexamethasone administered intravenously; blood obtained before and 4 and 8 hours after dexamethasone administration) when evaluating the pituitary-adrenocortical axis in cats. An 8-hour postdexamethasone serum cortisol concentration less than 0.8 µg/dL (22 nmol/L) is suggestive of a normal pituitary-adrenocortical axis, values between 0.8 and 1.4 µg/dL are inconclusive, and values greater than 1.4 µg/dL are supportive of the diagnosis of hyperadrenocorticism. The higher the 8-hour postdexamethasone serum cortisol concentration is above 1.4 µg/dL, the more supportive the test is for the diagnosis of hyperadrenocorticism. A serum cortisol concentration greater than 1.4 µg/dL at the 4-hour postdexamethasone blood sampling time adds further support for the diagnosis of hyperadrenocorticism (Fig. 50.19). Whenever the 4-hour postdexamethasone cortisol value is less than 1.4 µg/dL (especially < 0.8 µg/dL) and the 8-hour postdexamethasone cortisol value is greater than 1.4 µg/dL, test results should be considered consistent with, but not definitively diagnostic of, hyperadrenocorticism, and the clinician must rely on clinical signs, physical examination findings, and results of other diagnostic tests to help establish the diagnosis. The 0.1 mg/kg dexamethasone suppression test is an excellent and extremely sensitive screening test for hyperadrenocorticism in cats, however, results of the dexamethasone suppression test should never constitute the sole evidence for hyperadrenocorticism in cats.

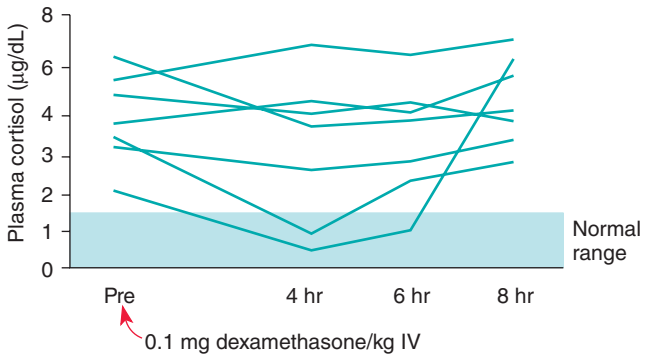


FIG 50.19
Dexamethasone suppression test results in seven cats with histologically confirmed hyperadrenocorticism. Blood for the cortisol determination was drawn before and 4, 6, and 8 hours after intravenous administration of 0.1 mg of dexamethasone/kg body weight. In most cats the plasma cortisol concentration remained greater than 1.4 µg/dL throughout the test—results that are very consistent with a diagnosis of hyperadrenocorticism.

Adrenocorticotropic Hormone Stimulation Test

The ACTH stimulation test is brief to perform and relatively easy to interpret. The peak increase in the post-ACTH serum cortisol concentration occurs earlier in cats than in dogs, and serum cortisol concentrations can approach baseline values by 1 hour after administration of synthetic ACTH. For this reason, blood samples should be obtained 30 minutes and 1 hour after administration of synthetic ACTH in cats. Unfortunately, the sensitivity of the ACTH stimulation test in identifying hyperadrenocorticism is low in cats. In one study, results of the dexamethasone suppression test were consistent with hyperadrenocorticism in 27 of 28 cats whereas ACTH stimulation testing was suggestive of hyperadrenocorticism in only 9 of 16 cats (Valentin et al., 2014). Because of low sensitivity, we do not rely on the ACTH stimulation test for diagnosing hyperadrenocorticism in cats.

Endogenous Plasma ACTH Concentration

The endogenous plasma ACTH concentration test is discussed on page 871. Plasma ACTH concentrations below the reference range, especially undetectable results, are consistent with ADH, and plasma ACTH concentrations in the upper half of the reference range or increased are consistent with PDH in cats. Plasma ACTH concentrations in the lower half of the reference range can occur with PDH and ADH and are nondiagnostic.

Diagnosis

Hyperadrenocorticism is diagnosed on the basis of history; findings on physical examination; results of routine blood and urine tests, abdominal ultrasonography, and tests of the pituitary-adrenocortical axis; and the clinician's index of suspicion for the disease. Ideally, all diagnostic tests performed in the assessment of a cat with suspected hyperadrenocorticism should be abnormal. Discordant test results raise doubt regarding the diagnosis. False-positive and false-negative results occur with all of the diagnostic tests used to assess the pituitary-adrenocortical axis. Although normal UCCR and dexamethasone suppression test results do not support the diagnosis of hyperadrenocorticism, abnormal results of these tests do not by themselves confirm the diagnosis. If there is doubt or uncertainty about the diagnosis, therapy for hyperadrenocorticism should be withheld and the cat reevaluated 1 to 2 months later.

Treatment

Trilostane is the current medical treatment of choice for PDH in cats. Trilostane is effective in controlling clinical signs of PDH, is generally well tolerated, and is effective in improving insulin resistance in those cats with concurrent diabetes. Trilostane treatment and monitoring protocols are similar for dogs and cats (see p. 871). Recommendations for the starting dose and frequency of administration vary among clinicians. Our initial starting dose is 30 mg/cat administered once a day. Adjustments in dose and frequency of administration are based on clinical response and on

results of the ACTH stimulation test, UCCR, and serum electrolyte concentrations, initially performed 4 weeks after initiation of trilostane treatment—earlier if clinical signs suggestive of hypoadrenocorticism or clinical signs suggestive of hypoglycemia in cats with insulin-resistant diabetes develop. The dosing schedule should be continued if improvement in clinical signs and test results are noted by 4 weeks, even if the goals of therapy have not yet been attained. The dosing schedule should be changed if no improvement or worsening of clinical signs and test results are observed at 4 weeks. In general, twice-daily dosing provides better control than once-daily dosing and should be the initial adjustment in cats that remain symptomatic at the starting dose given once daily. Subsequent adjustments in the dose of trilostane should be based on findings at the 4-week rechecks. A decrease in insulin requirements will usually occur as control of PDH is attained. Mellett et al. (2013) reported a median survival of 617 days in 15 cats treated with trilostane.

Adrenalectomy is the treatment of choice for ADH; bilateral adrenalectomy is also an effective treatment for PDH. Medical treatment with trilostane is usually necessary for 4 to 6 weeks before adrenalectomy to reverse the catabolic state of the cat, improve skin fragility and wound healing, and decrease the potential for perioperative complications. The surgical approach and medical management during and after surgery are similar to those used in dogs (see p. 875). Treatment for hypoadrenocorticism should begin immediately after bilateral adrenalectomy and should include injectable DOCP (2.2 mg/kg administered subcutaneously every 25 days initially; Percoten-V) or fludrocortisone acetate (0.05 mg/cat administered orally q12h initially; Florinef), as well as prednisolone (1-2.5 mg once daily). Subsequent adjustments in the dose of DOCP or fludrocortisone acetate should be based on periodic measurement of serum electrolyte concentrations (see p. 888). Insulin therapy can be discontinued in approximately 50% of cats once hyperadrenocorticism is eliminated, and diabetes is easier to control with the use of less insulin in the remaining cats.

Prognosis

The prognosis is guarded to poor. Untreated hyperadrenal cats die within months after the diagnosis has been established because of the deleterious effects of chronic hypercortisolism and insulin-resistant diabetes mellitus on skin integrity and immune function, and as a result of progressive weight loss leading to severe cachexia. The effectiveness of trilostane remains to be evaluated in a large group of hyperadrenal cats. Unilateral (ADH) or bilateral (PDH) adrenalectomy has the potential for excellent success; however, success depends, in part, on correction of the debilitated state and skin fragility with medical treatment before surgery, involvement of a surgeon with expertise in adrenal surgery, avoidance of perioperative complications, and the client's commitment to managing iatrogenic adrenal insufficiency after bilateral adrenalectomy. Periodic evaluation of serum electrolytes and review of the treatment protocol are important to avoid an addisonian crisis in cats undergoing bilateral adrenomegaly.

HYPOADRENOCORTICISM

Etiology

Hypoadrenocorticism is a deficiency of mineralocorticoids (i.e., aldosterone), glucocorticoids (i.e., cortisol), or both. Primary adrenocortical insufficiency (Addison's disease) with a deficiency of mineralocorticoid and glucocorticoid secretion is the most common. Primary hypoadrenocorticism is usually classified as idiopathic because the cause of the disease is not obvious, and necropsies are usually done years after the diagnosis is established, at which time idiopathic atrophy of all layers of the adrenal cortex is the most frequent histopathologic finding. Immune-mediated destruction of the adrenal cortices is believed to occur in most dogs with idiopathic adrenal insufficiency; lymphoplasmacytic inflammation and fibrosis are common findings in animals that undergo necropsy near the time of diagnosis. Bilateral destruction of the adrenal cortex by neoplasia (e.g., lymphoma), granulomatous disease, hemorrhagic infarction, arterial thrombosis, or drugs such as mitotane and trilostane can also cause primary adrenocortical insufficiency. For clinical signs to develop, it is believed that at least 90% of the adrenal cortices must be destroyed. The zones of the adrenal cortices are usually damaged at about the same rate, with aldosterone and cortisol deficiencies typically occurring in tandem. Destruction is progressive, ultimately leading to complete loss of adrenocortical function. Dogs and cats typically have complete loss of adrenocortical function at the time hypoadrenocorticism is diagnosed. A partial deficiency syndrome characterized by inadequate adrenal reserve may occur initially, with clinical signs manifested only during times of stress such as boarding, travel, and surgery. As destruction of the adrenal cortex progresses, hormone secretion becomes inadequate even under nonstressful conditions, and a true metabolic crisis occurs with no obvious inciting event.

Mineralocorticoids (i.e., aldosterone) control sodium, potassium, and water homeostasis. In the setting of primary adrenocortical insufficiency, loss of aldosterone secretion results in impaired renal conservation of sodium and chloride and excretion of potassium, leading to the development of hyponatremia, hypochloremia, and hyperkalemia. The inability to retain sodium and chloride reduces extracellular fluid volume, leading to progressive development of hypovolemia, hypotension, reduced cardiac output, and decreased perfusion of the kidneys and other tissues. Hyperkalemia has a deleterious effect on cardiac function, causing decreased myocardial excitability, an increased myocardial refractory period, and slowed conduction. A concurrent glucocorticoid deficiency typically results in gastrointestinal tract signs (e.g., anorexia, vomiting, diarrhea, weight loss) and changes in mental status (e.g., lethargy). One of the hallmark signs of hypocortisolism is impaired tolerance to stress, and

clinical signs often become more pronounced when the animal is placed in stressful situations.

Some dogs and cats with hypoadrenocorticism present to the veterinarian with clinical signs of glucocorticoid deficiency but serum electrolyte concentrations that are within the reference range at initial presentation. A deficiency in glucocorticoid but not mineralocorticoid secretion is referred to as *atypical hypoadrenocorticism* and is discussed on page 889. Glucocorticoid deficiency resulting from pituitary dysfunction causing a deficiency in ACTH is called *secondary hypoadrenocorticism*. Destructive lesions in the pituitary gland or hypothalamus, long-term administration of exogenous glucocorticoids, and idiopathic loss of function are the most common causes of secondary adrenal insufficiency. Naturally occurring, isolated hypoaldosteronism is rare in dogs and cats.

Clinical Features

SIGNALMENT

Hypoadrenocorticism is typically a disease of young to middle-aged female dogs with a median age of onset for all breeds of 4 years (range, 2 months to 14 years). Dogs with glucocorticoid-deficient hypoadrenocorticism tend to be older at the time of diagnosis than dogs with mineralocorticoid and glucocorticoid–deficient hypoadrenocorticism. Breeds reported to be at increased risk for hypoadrenocorticism are listed in Box 50.7. The disease is inherited as an autosomal recessive trait in Portuguese Water Spaniels, Nova Scotia Duck Tolling Retrievers, Standard Poodles, and Bearded Collies. Hypoadrenocorticism is rare in cats. There is no apparent sex-related predisposition in cats, although the disease tends to occur in young to middle-aged cats (average age, 6 years). Hypoadrenocorticism can, however, occur in aged dogs and cats as well.

CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Clinical signs and physical examination findings are listed in Box 50.8. The most common clinical manifestations are related to alterations in the gastrointestinal tract and mental status and include lethargy, anorexia, vomiting, and weight loss. Weakness is a common client complaint. Additional physical examination findings may include dehydration, bradycardia, weak femoral pulses, and abdominal pain. Hyperkalemia and hypoadrenocorticism should be suspected in an animal with bradycardia and signs consistent with hypovolemia. Bradycardia by itself, however, is not pathognomonic for hypoadrenocorticism, especially in an otherwise healthy dog. Similarly, dogs with hypoadrenocorticism can have normal heart rates. Polyuria and polydipsia are not common presenting signs, although they may surface during the taking of a complete history.

Clinical signs are often vague and easily ascribed to more common disorders involving the gastrointestinal and urinary tracts. Observant clients may occasionally describe an illness with a waxing-waning or episodic course; however, this bit of historic information is the exception rather than the rule. Most dogs with hypoadrenocorticism are first seen because of progressive problems that vary in severity, depending on the degree of stress and the adrenocortical reserve.

If hyponatremia and hyperkalemia become severe, the resultant hypovolemia, prerenal azotemia, and cardiac arrhythmias may result in an addisonian crisis. Clinical manifestations are the same as those previously described; the only difference is noted in the severity of signs. In severe cases the animal may be presented in shock and may be moribund. An addisonian crisis must be differentiated from other life-threatening disorders, such as diabetic ketoacidosis, necrotizing pancreatitis, acute hepatitis, septic peritonitis, and acute renal failure.

CLINICAL PATHOLOGY

Several abnormalities may be identified on CBC, serum biochemistry panel, and urinalysis (Box 50.9). Hyperkalemia, hyponatremia, and hypochloremia are the classic electrolyte alterations in animals with adrenal insufficiency and provide perhaps the most important evidence ultimately used to

BOX 50.7

Breeds at Increased Risk for Hypoadrenocorticism

Portuguese Water Dog*
Standard Poodle*
Nova Scotia Duck Tolling Retriever*
Bearded Collie†
Leonberger‡
Great Dane‡
Rottweiler‡
West Highland White Terrier‡
Soft Coated Wheaten Terrier‡

*Autosomal recessive mode of inheritance strongly suspected.
†Highly heritable but mode of inheritance undetermined.
‡Genetic predisposition suspected.

BOX 50.8

Clinical Signs Caused by Hypoadrenocorticism in Dogs and Cats

Dogs	Cats
Lethargy*	Lethargy*
Anorexia*	Anorexia*
Vomiting*	Weight loss*
Weakness*	Vomiting
Diarrhea	Polyuria, polydipsia
Weight loss	
Shivering/shaking	
Polyuria, polydipsia	
Abdominal pain	

*Common.

BOX 50.9

Clinicopathologic Abnormalities Associated With Primary Hypoadrenocorticism in Dogs and Cats

Hemogram

Nonregenerative anemia
Lack of a stress leukogram
±Neutrophilic leukocytosis
±Mild neutropenia
±Eosinophilia
±Lymphocytosis

Biochemistry Panel

Hyperkalemia
Hyponatremia
Hypochloremia
Prerenal azotemia
Hyperphosphatemia
±Hypercalcemia
±Hypoglycemia
±Hypoalbuminemia
±Hypocholesterolemia
Metabolic acidosis (low total CO_2, HCO_3^-)

Urinalysis

Urine specific gravity < 1.030

establish a diagnosis of hypoadrenocorticism. Serum sodium concentrations vary from normal to as low as 105 mEq/L (mean, 128 mEq/L), and serum potassium concentrations vary from normal to greater than 10 mEq/L (mean, 7.2 mEq/L). The sodium/potassium ratio reflects changes in these electrolyte concentrations in serum and frequently has been used as a diagnostic tool to identify adrenal insufficiency. The normal ratio varies between 27:1 and 40:1. Values are often less than 27 and may be less than 20 in animals with primary adrenal insufficiency.

Electrolyte alterations by themselves can be misleading. Normal serum electrolyte concentrations do not rule out adrenal insufficiency. Electrolyte abnormalities may not be evident in early stages of the disorder, when clinical signs result from glucocorticoid deficiency, and do not develop with secondary adrenal insufficiency caused by pituitary failure. Alternatively, other disorders can cause alterations in serum electrolyte concentrations that mimic adrenal insufficiency, most notably disorders involving the hepatic, gastrointestinal, and urinary systems (see Boxes 53.2 and 53.3). For most disorders, a thorough history and physical examination, together with a critical evaluation of results of the CBC, serum biochemistry panel, and urinalysis, allow the clinician to prioritize the potential differential diagnoses. Important clues for hypoadrenocorticism include lack of a stress leukogram in a sick dog or cat and identification of hypoalbuminemia, hypocholesterolemia, hypoglycemia, or a combination of these on the serum biochemistry panel.

The most challenging aspect of diagnosis is the differentiation between acute renal failure and primary adrenal insufficiency. The azotemia of adrenal insufficiency occurs secondary to reduced renal perfusion and an associated decrease in glomerular filtration rate after the onset of hypovolemia and hypotension. A compensatory increase in urine specific gravity to greater than 1.030 allows prerenal azotemia to be differentiated from primary renal azotemia and therefore adrenal insufficiency to be differentiated from acute renal failure, respectively.

Unfortunately, many hypoadrenal dogs and cats have an impaired ability to concentrate urine caused by chronic urinary sodium loss, depletion of the renal medullary sodium content, loss of the normal medullary concentration gradient, and impaired water resorption by the renal collecting tubules. As a result, some hypoadrenal dogs and cats with prerenal azotemia have urine specific gravities in the isosthenuric range (i.e., 1.007-1.015). Fortunately, the initial therapy for acute renal failure is similar to that used for adrenal insufficiency. Ultimately, the differentiation between these two disorders must rely on testing of the pituitary-adrenocortical axis and the animal's response to initial fluid and other supportive therapy.

ELECTROCARDIOGRAPHY

Hyperkalemia depresses cardiac conduction and causes characteristic alterations on an electrocardiogram (ECG; see Box 53.4). The severity of the ECG abnormalities correlates with the severity of hyperkalemia. The ECG can be used as a diagnostic tool to identify and estimate the severity of hyperkalemia and as a therapeutic tool to monitor changes in the blood potassium concentration during therapy.

DIAGNOSTIC IMAGING

Hypoadrenal dogs and cats with severe hypovolemia often have microcardia, a descending aortic arch that is flattened and has a decreased diameter, and a narrow caudal vena cava, as seen on lateral thoracic radiographs. These findings serve as a crude means of evaluating the degree of hypovolemia and hypotension. Concurrent generalized megaesophagus may be evident and may resolve in response to treatment for hypoadrenocorticism. Abdominal ultrasonography may reveal small adrenal glands (i.e., maximum width of 0.3 cm or less)—a finding strongly suggestive of adrenocortical atrophy. A finding of normal-size adrenal glands, especially glands with a maximum width less than 0.5 cm, does not rule out hypoadrenocorticism.

Diagnosis

Hypoadrenocorticism is often tentatively diagnosed on the basis of the history; physical examination findings; clinicopathologic findings; and, in the case of primary adrenal insufficiency, identification of appropriate electrolyte abnormalities. Results of an ACTH stimulation test confirm the diagnosis (see Table 50.2). The post-ACTH serum cortisol concentration is less than 2 µg/dL (55 nmol/L) (see Fig. 50.14). A baseline serum cortisol concentration can be used

as an initial screening test to rule out hypoadrenocorticism, as long as glucocorticoids (e.g., hydrocortisone, prednisone, prednisolone) that may be measured by the cortisol assay have not been recently administered to the dog or cat. Baseline serum cortisol concentrations greater than 2 µg/dL do not support the diagnosis of hypoadrenocorticism. Baseline serum cortisol concentrations of 2 µg/dL or less are suggestive of but not definitively diagnostic for hypoadrenocorticism. An ACTH stimulation test should be done on these dogs to confirm the diagnosis. UCCRs are not reliable for confirming the diagnosis. Post-ACTH serum cortisol values between 2 and 4 µg/dL (55 and 110 nmol/L) may occur with secondary hypoadrenocorticism and with critical illness-induced corticosteroid insufficiency (CIRCI; also called relative adrenal insufficiency)—a syndrome defined as inadequate production of cortisol in relation to increased demand during periods of critical illness such as sepsis. Prolonged or excessive inflammatory cytokine activity suppresses pituitary and adrenal function in humans and possibly in dogs as well. In a study by Burkitt et al. (2007), dogs with severe sepsis had suppressed response of the adrenal cortex to exogenously administered ACTH, an increase in serum cortisol concentration of less than 3 µg/dL (82 nmol/L) after ACTH administration, and resolution of the relative adrenal insufficiency after resolution of the illness. Fortunately, baseline cortisol concentrations are usually within the reference range in dogs with CIRCI.

Results of the ACTH stimulation test do not distinguish dogs and cats with naturally occurring primary adrenal insufficiency from those with secondary insufficiency resulting from pituitary failure, dogs and cats with secondary insufficiency resulting from prolonged iatrogenic glucocorticoid administration, or dogs with primary adrenocortical destruction caused by mitotane or trilostane overdosing. Concurrent abnormal serum electrolyte concentrations imply the existence of primary adrenal insufficiency and the need for mineralocorticoid and glucocorticoid replacement therapy. Normal serum electrolyte concentrations do not differentiate between primary hypoadrenocorticism that progresses and primary hypoadrenocorticism that does not progress to mineralocorticoid deficiency, or between primary hypoadrenocorticism and secondary hypoadrenocorticism (see the section on atypical hypoadrenocorticism). If secondary hypoadrenocorticism can be documented, only glucocorticoid replacement therapy is indicated. Primary and atypical or secondary hypoadrenocorticism can be differentiated prospectively by periodic measurement of serum electrolyte concentrations, by measurement of baseline endogenous ACTH concentration, or by measurement of plasma aldosterone concentrations during the ACTH stimulation test (Table 50.4). In theory, measurement of plasma aldosterone concentration should be helpful in distinguishing between the various forms of adrenal insufficiency. Unfortunately, there is no clear demarcation in plasma aldosterone concentrations between these groups of dogs.

Treatment

The aggressiveness of therapy depends on the clinical status of the animal and the nature of the insufficiency (i.e., glucocorticoid, mineralocorticoid, or both). Many dogs and cats with primary adrenal insufficiency are presented at varying stages of an acute addisonian crisis, requiring immediate, aggressive therapy. In contrast, dogs and cats with isolated glucocorticoid deficiency often have a chronic course that poses more of a diagnostic than a therapeutic challenge.

THERAPY FOR ACUTE ADDISONIAN CRISIS

An acute addisonian crisis involves both a mineralocorticoid and a glucocorticoid deficiency. Treatment of acute primary adrenal insufficiency is directed toward correcting hypotension, hypovolemia, electrolyte imbalances, and metabolic acidosis; improving vascular integrity; and providing an immediate source of glucocorticoids (Box 50.10). Because death resulting from hypoadrenocorticism is often attributed to vascular collapse and shock, correction of hypovolemia is the first and most important therapeutic priority. The type of fluid used depends somewhat on the severity of the hyponatremia (see Table 53.2). Ringer's or Ringer's lactate solution can be used for mild hyponatremia (serum sodium concentration > 130 mEq/L) and physiologic saline solution for more severe hyponatremia (serum sodium concentration

TABLE 50.4

Differentiation of Primary Versus Secondary Hypoadrenocorticism

	PRIMARY HYPOADRENOCORTICISM	PRIMARY ATYPICAL HYPOADRENOCORTICISM	SECONDARY HYPOADRENOCORTICISM
Serum electrolytes	Hyperkalemia Hyponatremia	Normal	Normal
ACTH stimulation test			
Post-ACTH cortisol	Decreased	Decreased	Decreased
Post-ACTH aldosterone	Decreased	Normal	Normal
Endogenous ACTH	Increased	Increased	Decreased

ACTH, Adrenocorticotropic hormone.

BOX 50.10

Initial Treatment for Acute Addisonian Crisis

Fluid Therapy

Type: 0.9% saline solution if serum sodium concentration less than 130 mEq/L; isotonic crystalloid solution (e.g., Ringer's, Ringer's lactate) if serum sodium is 130 mEq/L or higher
Rate: 40 to 80 mL/kg/24 h IV initially
Potassium supplementation: not indicated
Dextrose: 5% dextrose infusion (100 mL of 50% dextrose per liter of fluids) if hypoglycemic

Glucocorticoid Therapy

Dexamethasone or dexamethasone sodium phosphate, 0.5 to 1 mg/kg IV, repeat q12h at dosage of 0.05 to 0.1 mg/kg in IV fluids until oral prednisone can be administered*

Mineralocorticoid Therapy

Desoxycorticosterone pivalate (DOCP; Novartis), 2.2 mg/kg IM

Bicarbonate Therapy

Indicated if HCO_3 < 12 mEq/L or total venous CO_2 < 12 mmol/L or animal is severely ill
mEq HCO_3 = body weight (kg) × 0.5 × base deficit (mEq/L); if base deficit unknown, use 10 mEq/L. Add one quarter of calculated HCO_3 dose to IV fluids and administer over 6 hours. Repeat only if plasma HCO_3 remains < 12 mEq/L.

IM, Intramuscular; *IV,* intravenous.
*Higher doses of glucocorticoids may be required if the dog or the cat is in shock.

< 130 mEq/L). Hyperkalemia is reduced by simple dilution and by improved renal perfusion even when potassium-containing fluids are used. The more acute and severe the hyponatremia, the more slowly the serum sodium concentration should be corrected. A rapid increase in the serum sodium concentration should be avoided in animals with severe hyponatremia (serum sodium concentration < 120 mEq/L), especially if severe hyponatremia has been present for 24 hours or longer. For these animals, the serum sodium concentration should be gradually increased by 10 to 12 mEq/L per day. If hypoglycemia is present, 50% dextrose should be added to the IV fluids to produce a 5% dextrose solution (i.e., 100 mL of 50% dextrose per liter of fluids). Dextrose added to isotonic solutions produces a hypertonic solution that ideally should be administered through a central vein to minimize phlebitis.

Dogs and cats with acute adrenal insufficiency usually have a mild metabolic acidosis that does not require therapy. Fluid therapy alone corrects the mild acidosis as hypovolemia lessens and tissue perfusion and glomerular filtration rate improve. If the total venous carbon dioxide or serum bicarbonate concentration is less than 12 mmol/L or 12 mEq/L, respectively, conservative bicarbonate therapy is indicated. In a severely ill animal for which laboratory results are not yet known, a base deficit of 10 mEq/L can be assumed to be present. The milliequivalents of bicarbonate needed to correct the acidosis can be determined from the following equation:

$$\text{Bicarbonate deficit}\left(\frac{\text{mEq}}{\text{L}}\right) = \text{Bodyweight (kg)} \times 0.5 \times \text{Base deficit (mEq/L)}$$

One fourth of the calculated bicarbonate dose should be administered in IV fluids during the initial 6 to 8 hours of therapy. The acid-base status of the animal should be reassessed at the end of this time. Rarely, a dog or cat may require additional parenterally administered sodium bicarbonate.

Sodium bicarbonate therapy helps correct the metabolic acidosis and decreases the serum potassium concentration. Intracellular translocation of potassium ions after bicarbonate administration, in conjunction with the dilutional effects of fluid therapy and improved renal perfusion, is usually effective in lowering the serum potassium concentration and returning any ECG abnormalities toward normal. Additional therapy to rapidly correct life-threatening hyperkalemia is rarely needed (see Table 53.3).

Glucocorticoid and mineralocorticoid therapy is also indicated in the initial management of an acute addisonian crisis. Ideally, glucocorticoids should not be given until after completion of the ACTH stimulation test. IV fluids are usually sufficient therapy during the initial 1 or 2 hours while the ACTH stimulation test is being completed. Point-of-care cortisol assays (e.g., SNAP Cortisol, IDEXX Laboratories) may be useful for an initial confirmation of hypoadrenocorticism, but the diagnosis should always be confirmed using a reference laboratory. Dexamethasone does not interfere with the cortisol assay and can be used if glucocorticoid therapy cannot be delayed. The glucocorticoid of choice for treating an acute addisonian crisis is dexamethasone sodium phosphate, given intravenously at an initial dosage of 0.5 to 1 mg/kg and repeated q12h at a dose of 0.05 to 0.1 mg/kg in the IV solution until oral medication can be safely given. Rapid-acting, water-soluble glucocorticoids such as hydrocortisone sodium succinate, hydrocortisone hemisuccinate, hydrocortisone phosphate, and prednisolone sodium succinate may be measured by the cortisol assay, causing falsely increased cortisol results, and should not be administered until after the ACTH stimulation test is completed. We do not routinely use these glucocorticoids for treating acute adrenal insufficiency.

Currently available mineralocorticoid supplements include DOCP (Percorten-V) and fludrocortisone acetate (Florinef). Both are intended as long-term maintenance therapy for primary adrenal insufficiency. Injectable DOCP is the preferred mineralocorticoid for the treatment of a sick dog or cat suspected of having adrenal insufficiency. The drug is initially administered at a dose of 2.2 mg/kg intramuscularly or subcutaneously. IV administration of fluids

and intramuscular administration of DOCP correct electrolyte abnormalities in most hypoadrenal animals within 24 hours. No adverse reactions have been noted to a single injection of DOCP administered to dogs subsequently shown to have normal adrenocortical function. Atrial natriuretic peptide provides natural protection against hypernatremia. Fludrocortisone acetate is also an effective treatment. However, it is available only in tablet form, and most dogs and cats are too ill to receive oral therapy initially.

Most dogs and cats with acute adrenal insufficiency show dramatic clinical and biochemical improvement within 24 to 48 hours. Over the ensuing 2 to 4 days, the animal should be gradually switched from IV fluids to oral water and food. Maintenance mineralocorticoid and glucocorticoid therapy should be initiated. If the animal fails to make this transition smoothly, persistent electrolyte imbalance, insufficient glucocorticoid supplementation, concurrent endocrinopathy (e.g., hypothyroidism), or concurrent illness (most notably renal damage, pancreatitis, or hemorrhagic gastroenteritis resulting from poor perfusion and hypoxia caused by adrenal insufficiency) should be suspected.

MAINTENANCE THERAPY FOR PRIMARY ADRENAL INSUFFICIENCY

Mineralocorticoids and usually glucocorticoids are required for maintenance of the dog or cat with primary adrenal insufficiency. The preferred mineralocorticoid supplementation is injectable DOCP (Percorten-V), which slowly releases the hormone at a rate of 1 mg/day/25 mg suspension. The initial dosage is 2.2 mg/kg body weight, given intramuscularly or subcutaneously every 25 days. Subsequent adjustments are based on results of serum electrolyte concentrations, which are initially measured 12 and 25 days after each of the first two or three DOCP injections. If the dog or cat has hyponatremia or hyperkalemia (or both) on day 12, the next dose should be increased by approximately 10%. If the day 12 electrolyte profile is normal but the day 25 profile is abnormal, the interval between injections should be decreased by 48 hours. DOCP is very effective in normalizing serum electrolyte concentrations. The only adverse reaction is polyuria and polydipsia that improve after reduction of the DOCP dose or frequency of administration. Most dogs (and presumably cats) receiving DOCP also require a low dose of glucocorticoids (prednisone, 0.25 mg/kg q12h initially).

Drawbacks to DOCP include problems with availability and the inconvenience and expense associated with the need to make frequent visits to the veterinarian for the injection. To minimize inconvenience and expense, the client can be taught to give the injection subcutaneously at home. Every third or fourth treatment, the client should bring the dog or cat into the clinic for a complete physical examination, measurement of serum electrolyte concentrations, and administration of DOCP to ensure that problems with administration of DOCP have not developed. Many dogs require much lower doses than the recommended starting dose to achieve normal electrolyte concentrations. Once the dog or cat is healthy and serum electrolyte concentrations are stable, the amount of DOCP administered can be decreased by 10% increments initially, and the frequency of DOCP administration can be shortened to every 21 days to allow lower doses of DOCP to be administered (typically ≈1.5 mg/kg/injection), thereby decreasing the expense of treatment. The goal is to identify the lowest dosage of DOCP that maintains the health of the dog or cat and keeps serum electrolyte concentrations in the reference range.

Fludrocortisone acetate (Florinef) is another commonly used mineralocorticoid supplement. The initial dose is 0.02 mg/kg/day, divided into two doses and administered orally. Subsequent adjustments in the dose are based on serum electrolyte concentrations, which initially are assessed every 1 to 2 weeks. The goal is to reestablish normal serum sodium and potassium concentrations. The dose of fludrocortisone acetate typically must be increased during the first 6 to 18 months of therapy. This increasing need may reflect the continuing destruction of the adrenal cortices. After this time the dose usually plateaus and remains relatively stable.

Major drawbacks to oral therapy with fludrocortisone acetate include the wide range in the doses required to control serum electrolyte concentrations; the development of polyuria, polydipsia, and incontinence in some dogs (presumably caused by the glucocorticoid activity of this drug); resistance to the effects of the drug, which has been observed in some animals; and persistent mild hyperkalemia and hyponatremia in some animals. Ineffectiveness of fludrocortisone acetate should be suspected when clients report that their pet is "just not right" and hyponatremia and hyperkalemia persist despite high dosages of the mineralocorticoid supplement. The concurrent administration of oral salt may help alleviate the electrolyte derangements in dogs and cats in which fludrocortisone acetate by itself is not completely effective. Alternatively, switching to DOCP should be considered.

Glucocorticoid supplementation is initially indicated for all dogs and cats with primary adrenal insufficiency. Prednisone (dogs) and prednisolone (cats) is given at an initial dose of 0.25 mg/kg twice a day orally. Over the ensuing 1 to 2 months the dose and frequency of administration of prednisone or prednisolone should gradually be reduced to the lowest amount given once a day that still prevents signs of hypocortisolism. Approximately 50% and less than 10% of dogs receiving fludrocortisone and DOCP, respectively, ultimately do not require glucocorticoid medication, except during times of stress. All clients should have glucocorticoids available to administer to their dogs and cats in times of stress. Veterinarians should be aware of the increased glucocorticoid requirements of hypoadrenal dogs and cats undergoing surgery or during times of illness with a non–adrenal-related disease. The glucocorticoid dose being administered should be doubled on days when increased stress is anticipated.

The most common reason for persistence of clinical signs despite appropriate treatment is inadequate glucocorticoid supplementation. When healthy and in a nonstressed environment, dogs and cats with adrenal insufficiency typically

require small amounts of prednisone or prednisolone, if any. However, when stressed or ill, these same animals may require large amounts of prednisone or prednisolone (i.e., 0.25-0.5 mg/kg) given twice a day. Failure to provide adequate quantities of glucocorticoids can lead to persistent and worsening lethargy, inappetence, and vomiting. The amount of prednisone or prednisolone required to offset the deleterious effects of stress and illness is variable and unpredictable. Therefore it is always better to err on the high end of the dosage range and then gradually decrease the dosage over the ensuing weeks.

Prognosis

The prognosis in dogs and cats with adrenal insufficiency is usually excellent. The most important factors in determining an animal's long-term response to therapy are client education about the disease and client dedication to treatment. If client–veterinarian communication is good, if frequent rechecks are performed, and if clients are conscientious about carrying out therapy, dogs and cats with adrenal insufficiency can have a normal life expectancy.

ATYPICAL HYPOADRENOCORTICISM

Some dogs with hypoadrenocorticism present to the veterinarian with clinical signs of glucocorticoid deficiency but with serum electrolyte concentrations within the reference range at initial presentation. A deficiency in glucocorticoid but not mineralocorticoid secretion is referred to as *atypical hypoadrenocorticism,* a syndrome identified in up to 30% of dogs with hypothyroidism. Glucocorticoid deficiency may be adrenocortical in origin (primary atypical hypoadrenocorticism; most common) or may result from impaired secretion of ACTH by the pituitary gland (secondary hypoadrenocorticism). Baseline endogenous plasma ACTH concentrations are normal or increased when the primary problem is adrenal in origin and are decreased when the primary problem is pituitary in origin (see Table 50.6). Glucocorticoid but not mineralocorticoid deficiency of adrenal origin may be seen in a dog in the early stages of development of typical primary hypoadrenocorticism with destruction of the zona fasciculata more advanced than destruction of the zona glomerulosa. Mineralocorticoid deficiency and abnormal serum electrolyte concentrations develop weeks to months later. In some dogs and cats glucocorticoid deficiency does not progress to mineralocorticoid deficiency. The cause of this form of hypoadrenocorticism is not known, although drugs such as mitotane, trilostane, and megestrol acetate (cats) are known to play a part.

Glucocorticoid deficiency resulting from pituitary dysfunction is called *secondary hypoadrenocorticism.* Destructive lesions (e.g., neoplasia, inflammation) involving the pituitary gland or hypothalamus and long-term administration of exogenous glucocorticoids are the most common recognized causes of secondary adrenal insufficiency. Adrenocortical atrophy may develop after the injectable, oral, or topical administration of glucocorticoids. Adrenal function usually returns within 2 to 4 weeks after the medication is discontinued, unless long-acting depot forms of glucocorticoids are used.

Glucocorticoid-deficient hypoadrenocorticism is usually identified during the diagnostic evaluation of dogs and cats with chronic, vague gastrointestinal clinical signs such as lethargy, anorexia, vomiting, diarrhea, and weight loss. Results of routine blood and urine tests are typically normal. Diagnosis requires an ACTH stimulation test (see p. 870). Therapy involves the administration of glucocorticoids, as previously described for the treatment of primary hypoadrenocorticism. The exception is secondary adrenal insufficiency induced by the overzealous administration of glucocorticoids, in which case treatment revolves around a gradual reduction in the dose and frequency of administration, with eventual discontinuation of the medication. Dogs and cats with secondary adrenal insufficiency should not have mineralocorticoid deficiency. Periodic measurement of serum electrolytes is advisable because primary glucocorticoid-deficient adrenal insufficiency may progress to mineralocorticoid deficiency weeks to months after glucocorticoid-deficient hypoadrenocorticism is diagnosed.

PHEOCHROMOCYTOMA

Etiology

Pheochromocytoma is a catecholamine-producing tumor derived from the chromaffin cells of the adrenal medulla. Pheochromocytomas are uncommon in dogs and rare in cats. Pheochromocytomas are usually solitary tumors ranging in size from nodules of less than 0.5 cm in diameter to masses greater than 10 cm in diameter. Pheochromocytoma involving both adrenal glands, pheochromocytoma involving one adrenal gland with a functional adrenocortical tumor in the contralateral gland, and pheochromocytoma with concurrent PDH have also been identified in dogs. Pheochromocytomas have an unpredictable growth pattern, ranging from slow to rapid, and infiltration of the phrenicoabdominal vein, caudal vena cava, and surrounding soft tissue structures can occur when the tumor is relatively small (<2.5 cm in maximum width; see Fig. 50.8). In one report, 87% of pheochromocytomas in 38 dogs were greater than 2.5 cm in width, 45% were greater than 5 cm in width, and most (62%) involved the right adrenal gland. Pheochromocytoma should always be considered a malignant tumor in dogs and cats. Distant sites of metastasis include the liver, lung, regional lymph nodes, bone, and CNS. Paragangliomas are tumors arising from chromaffin cells located outside the adrenal medulla, most commonly near the sympathetic ganglia; they are rare in dogs and cats.

Clinical Features

Pheochromocytomas occur most commonly in older dogs and cats, with a median age of 11 years at the time of diagnosis in dogs. There is no apparent sex- or breed-related predisposition.

TABLE 50.5

Clinical Signs and Physical Examination Findings Associated With Pheochromocytoma in Dogs

CLINICAL SIGNS	PHYSICAL EXAMINATION FINDINGS
Intermittent weakness*	No identifiable abnormalities*
Intermittent collapsing episodes*	Panting, tachypnea*
Intermittent panting*	Weakness*
Intermittent tachypnea*	Tachycardia*
Intermittent anxious behavior*	Cardiac arrhythmias
Polyuria, polydipsia	Weak pulses
Lethargy	Pale mucous membranes
Inappetence	Muscle wasting*
Vomiting	Findings from systemic hypertension:
Diarrhea	Nasal hemorrhage
Weight loss	Oral hemorrhage
Abdominal distention	Retinal hemorrhage
Rear limb edema	Retinal detachment
	Lethargy
	Abdominal pain
	Palpable abdominal mass
	Ascites
	Rear limb edema

*Common signs and physical examination findings.

Clinical signs and physical examination findings develop as a result of the space-occupying nature of the tumor and its metastatic lesions, as a result of excessive secretion of catecholamines, or as a result of spontaneous hemorrhage from the tumor into the retroperitoneal cavity (Table 50.5). The most common clinical signs and physical examination abnormalities involve the respiratory, cardiovascular, and musculoskeletal systems and include generalized weakness, anorexia, weight loss, episodic collapse, agitation, nervous behavior, excessive panting, tachypnea, and tachycardia. Excess catecholamine secretion may also cause severe systemic hypertension, resulting in nasal and retinal hemorrhage, retinal detachment, acute blindness and epistaxis. Catecholamine secretion by a pheochromocytoma typically is episodic and random, not sustained. Therefore clinical signs tend to be paroxysmal and usually are not evident at the time the dog is examined; the physical examination often does not provide clues to the presence of a pheochromocytoma because a catecholamine surge usually is not happening at the time the dog is examined. Because clinical signs and physical examination findings are often vague, nonspecific, and easily associated with other disorders, pheochromocytoma often is not considered a possible differential diagnosis until an adrenal mass is identified on abdominal ultrasound.

Diagnosis

Pheochromocytoma should be on the list of differential diagnoses for dogs presenting with clinical signs suggestive of catecholamine excess, dogs with an unexpected adrenal mass identified by abdominal ultrasound, and dogs that develop unexpected problems with systemic hypertension, nasal or retinal hemorrhage, or cardiac arrhythmia during anesthesia. Pheochromocytoma may also be an unexpected or incidental finding at necropsy or may cause sudden collapse and death from a sudden, massive, and sustained release of catecholamines by the tumor.

No consistent abnormalities are identified in the CBC, serum biochemistry panel, or urinalysis that would raise suspicion for pheochromocytoma. Many abnormalities identified in results of routine blood and urine tests are caused by concurrent disorders that are commonly present in dogs with pheochromocytoma or are nonspecific findings affiliated with hypertension. A history of acute or episodic collapse, identification of appropriate respiratory and cardiac abnormalities during physical examination, documentation of systemic hypertension, and identification of an adrenal mass by abdominal ultrasonography are most helpful in establishing a tentative diagnosis of pheochromocytoma. Systemic hypertension may be sustained or episodic. Failure to document systemic hypertension in a dog with appropriate clinical signs does not rule out a diagnosis of pheochromocytoma.

Ultrasound identification of an adrenal mass with a normal-size contralateral adrenal gland is perhaps the most important clue for pheochromocytoma. Pheochromocytoma is one of several differentials for an adrenal mass (Table 50.6; see also the discussion of incidental adrenal mass). Pheochromocytomas cannot be distinguished from other tumors in the adrenal gland on the basis of sonographic appearance, although identification of hypoechoic foci within the tumor is suggestive of pheochromocytoma. Regardless, the primary differential diagnosis for an adrenal mass is ADH. Many of the clinical signs (e.g., panting, weakness) and blood pressure alterations seen in dogs with hyperadrenocorticism (common) are similar to those observed in dogs with pheochromocytoma (uncommon). In addition, both pheochromocytoma and adrenocortical carcinoma invade adjacent structures and cause tumor thrombi in the phrenicoabdominal vein and caudal vena cava. It is important to rule out ADH before focusing on pheochromocytoma in a dog with an adrenal mass.

Measurement of urinary catecholamine concentrations is being used with increased frequency to aid in the diagnosis of pheochromocytomas. Urine normetanephrine-to-creatinine ratios and plasma-free normetanephrine can strengthen the tentative diagnosis of pheochromocytoma, but do not provide a definitive diagnosis. Urine normetanephrine ratio or plasma free-normetanephrine concentrations greater than or equal to four times the upper limit of the reference range increase the probability of a pheochromocytoma to nearly 100%; with smaller increases a pheochromocytoma may or may not be present. Proper sample handling and species specific reference ranges are critical for accurate results and interpretation. The antemortem definitive diagnosis of a pheochromocytoma ultimately

TABLE 50.6

Adrenal Tumors Reported in Dogs and Cats

	HORMONE SECRETED	SPECIES	CLINICAL SYNDROME	TESTS TO ESTABLISH DIAGNOSIS
Nonfunctional adrenal tumor	None	Dog,* Cat	—	Diagnosis by exclusion histopathology
Functional adrenocortical tumor	Cortisol	Dog,* Cat	Hyperadrenocorticism Cushing's syndrome	Urine C:C ratio Low-dose dexamethasone suppression test
	Aldosterone	Cat,* Dog	Hyperaldosteronism Conn's syndrome	Serum K^+ and Na^+ Baseline plasma aldosterone
	Progesterone	Cat,* Dog	Mimics hyperadrenocorticism	Serum progesterone
	Steroid hormone precursors			
	17-OH-progesterone	Dog, Cat	Mimics hyperadrenocorticism	ACTH stimulation test—measures steroid hormone precursors
	Desoxycorticosterone	Dog	Mimics hyperaldosteronism	ACTH stimulation test—measures steroid hormone precursors
Functional adrenomedullary tumor	Norepinephrine Epinephrine	Dog,* Cat	Pheochromocytoma	Urine normetanephrine to creatinine ratio; Plasma free normetanephrine concentration

ACTH, Adrenocorticotropic hormone.
*Species most commonly affected.

relies on histologic evaluation of the surgically excised adrenal mass.

Treatment

A period of medical therapy intended to reverse the effects of excessive adrenergic stimulation, followed by surgical removal of the tumor, is the treatment of choice for pheochromocytoma. The success of chemotherapy and radiation therapy in humans with pheochromocytoma has been limited, and results of chemotherapy or radiation therapy for the treatment of pheochromocytoma in dogs or cats have not been reported. Mitotane and trilostane are ineffective for tumors arising from the adrenal medulla and are not recommended. Long-term medical therapy is primarily designed to control excessive catecholamine secretion.

Potentially life-threatening complications are common during the perioperative period, especially during induction of anesthesia and manipulation of the tumor during surgery. The most worrisome complications include episodes of acute, severe hypertension (systolic arterial blood pressure > 300 mm Hg), episodes of severe tachycardia (heart rate > 250 beats/min) and arrhythmias, and hemorrhage. Preoperative α-adrenergic blockade using phenoxybenzamine helps control potentially life-threatening fluctuations of blood pressure and heart rate during anesthesia and surgery. The dose and frequency of phenoxybenzamine administration and the duration of therapy required to adequately achieve desired effects have not been defined for dogs. Our current protocol for the management of hypertension in dogs with pheochromocytoma includes preoperative phenoxybenzamine and intraoperative phentolamine. The initial dosage of phenoxybenzamine is 0.5 mg/kg q12h. Unfortunately, many dogs with pheochromocytoma have episodic clinical signs and hypertension, making it difficult to adjust dosage on the basis of improvement in clinical signs and blood pressure. In addition, this dosage is often ineffective in preventing severe hypertension during surgery. Therefore we gradually increase the phenoxybenzamine dosage every 3 to 4 days until clinical signs of hypotension (e.g., lethargy, weakness, syncope), adverse drug reactions (e.g., vomiting), or a maximum dosage of 2 mg/kg q12h is attained. Surgery is recommended 1 to 2 weeks later either by laparotomy or laparoscopic adrenalectomy. The drug should be continued until the time of surgery. Complications may occur despite prior treatment with α-adrenergic blocking drugs; close monitoring of the dog during the perioperative period is critical for a successful outcome after adrenalectomy. (See Suggested Readings for more information on the perioperative and surgical management of dogs with a pheochromocytoma.) In a study by Herrera et al. (2008), the significant prognostic indicators for survival after adrenalectomy for pheochromocytoma included lack of intraoperative arrhythmias, decreased surgical time, younger age, and pretreatment with phenoxybenzamine.

Medical management with α-adrenergic blockade is recommended whenever pheochromocytoma is suspected and

adrenalectomy is not performed. Long-term medical management is designed to control excessive catecholamine secretion, not to lessen the risk of local invasion or metastasis of the tumor. Phenoxybenzamine at an initial dosage of 0.50 mg/kg q12h is recommended. The dose is gradually titrated upward until clinical signs are controlled or clinical signs suggestive of hypotension occur.

Prognosis

The prognosis depends in part on the size of the adrenal mass, the presence of metastasis or local invasion of the tumor into adjacent blood vessels or organs (e.g., kidney), avoidance of perioperative complications if adrenalectomy is performed (i.e., hypertension, cardiac arrhythmias, respiratory distress, and hemorrhage), and the presence and nature of concurrent disease. Surgically excisable tumors carry a guarded to good prognosis. Survival time in our dogs that underwent adrenalectomy and survived the immediate postoperative period ranged from 2 months to longer than 3 years. If metastatic disease is not present, perioperative complications are prevented, and serious concurrent disease is not present, the dog has the potential to live a significantly longer time (i.e., longer than a year). Treatment with an α-adrenergic blocking drug before surgery and the involvement of an experienced anesthesiologist and surgeon with expertise in adrenal surgery help to minimize potentially serious perioperative complications associated with anesthesia and digital manipulation of the tumor. Medically treated dogs can live longer than 1 year from the time of diagnosis if the tumor is relatively small (<3 cm maximum width), vascular invasion is not present, and treatment with an α-adrenergic blocking drug is effective in minimizing the deleterious effects of episodic excessive catecholamine secretion by the tumor. Most dogs die or are euthanized because of complications caused by excessive catecholamine secretion, complications caused by tumor-induced venous thrombosis, or complications caused by invasion of the tumor or its metastases into surrounding organs.

INCIDENTAL ADRENAL MASS

Ultrasonography has become a routine diagnostic tool for the evaluation of soft tissue structures in the abdominal cavity. One consequence of abdominal ultrasonography is the unexpected finding of a seemingly incidental adrenal mass. Recent retrospective studies identified an unexpected adrenal lesion in 4% of 3478 dogs undergoing abdominal ultrasound (Cook et al., 2014) and 9% of 270 dogs undergoing abdominal CT (Baum et al., 2016). Several factors determine the aggressiveness of the diagnostic and therapeutic approach to an adrenal mass, including the severity of concurrent problems, the original reason for performing abdominal ultrasound, the age of the dog or cat, the likelihood that the mass is hormonally active, the likelihood that the mass is a malignant tumor, the size and invasiveness of the mass, and the client's desires and willingness to pursue the problem. The first consideration is to verify an adrenal mass exists by repeating the abdominal ultrasound. An adrenal tumor should be suspected when there is loss of the typical shape of the gland (i.e., the gland looks like a mass) regardless of size, there is asymmetry in shape and size between the affected adrenal gland and the contralateral adrenal gland, or there is infiltration of the mass into the phrenicoabdominal vena, vena cava, or surrounding soft tissues.

A bulbous enlargement or "nodule" of the cranial or caudal pole of an otherwise recognizable adrenal gland is a common finding in older dogs and is often misinterpreted as an adrenal mass or tumor (Fig. 50.20). Bulbous enlargements are typically less than 1.5 cm in maximum width and the contralateral adrenal gland is usually normal in size and shape. A bulbous enlargement is usually not neoplastic or functional (i.e., autonomously secreting a hormone). Histologic examination usually reveals normal tissue, inflammation, granuloma or clinically irrelevant benign tumor (e.g., myelolipoma). Less commonly, cortical tumors and pheochromocytomas in the early stages of development have been identified. If there are no clinical signs or findings on physical examination and routine blood and urine tests do not support a functional adrenal tumor, a conservative approach centered around periodic monitoring with ultrasound, initially at monthly intervals, for changes in size of the nodule and appearance of the adrenal gland is recommended. If the adrenal mass has not changed in size after 3 months, the clinician can increase the time interval between ultrasound evaluations recommended. However, if the adrenal nodule is increasing in size, changing in appearance, compressing or infiltrating surrounding blood vessels or soft tissues, or clinical signs affiliated with an excess of cortisol, catecholamines, or aldosterone develop, adrenalectomy may be warranted.

Adrenalectomy is the treatment of choice if the mass is suspected to be malignant. Unfortunately, it is not easy to determine whether an adrenal mass is neoplastic and malignant or benign before surgical removal and histopathologic evaluation. Guidelines to suggest malignancy include size of the mass, infiltration of the mass into surrounding organs and blood vessels, and identification of additional mass lesions with abdominal ultrasound and thoracic radiographs. The bigger the mass, the more likely it is malignant and the more likely metastasis has occurred, regardless of findings on abdominal ultrasound and thoracic radiographs. Cytologic evaluation of specimens obtained by ultrasound-guided fine-needle aspiration of the adrenal mass may provide guidance regarding malignancy and origin of the mass (i.e., adrenal cortex versus medulla).

An adrenal tumor may secrete a hormone or be nonfunctional. Excessive secretion of cortisol, catecholamines, aldosterone, progesterone, and steroid hormone precursors has been documented in dogs and cats (see Table 50.6). The most common functional adrenal tumors secrete cortisol

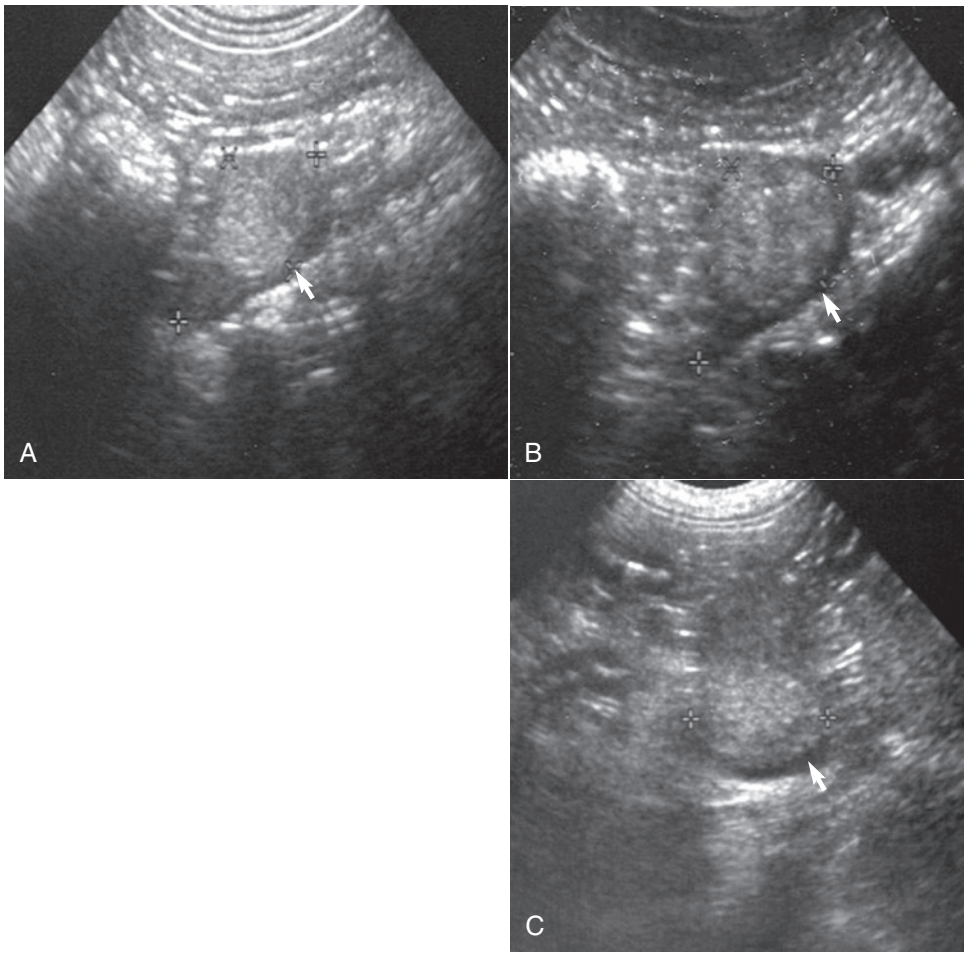


FIG 50.20
(A) An 11-year-old male castrated Doberman Pinscher mix presented for clinical signs consistent with acute gastroenteritis. Abdominal ultrasound identified a 1.4-cm-diameter adrenal mass *(arrow)* and a normal-size contralateral adrenal gland. The history, physical examination findings, and results of routine blood and urine tests were not supportive of adrenal disease, and the dog responded to symptomatic therapy for acute gastroenteritis. The adrenal mass was periodically evaluated with ultrasound. Over the ensuing 2 years, the dog remained healthy, and minimal growth or change was noted in the echogenicity of the adrenal mass. **(B)** The adrenal mass 1 year after presentation; maximum diameter was 1.8 cm. **(C)** The adrenal mass 2 years after presentation; maximum diameter was 2.0 cm.

or catecholamines. Aldosterone-secreting tumors causing primary hyperaldosternism (Conn's syndrome) are more common in cats than dogs. Excessive secretion of aldosterone causes sodium retention and potassium depletion which manifests as increased serum sodium (>155 mEq/L) and decreased serum potassium (<3.0 mEq/L) concentrations. Hypokalemia causes lethargy and weakness which are the most common clinical signs of primary hyperaldosteronism. Hypernatremia causes systemic hypertension. An adrenal mass should be identified on abdominal ultrasound, and the contralateral adrenal gland should be normal in size and shape. An increased baseline plasma aldosterone concentration is documented and used to establish the diagnosis.

Progesterone-secreting adrenal tumors are identified most commonly in cats. Excessive progesterone secretion in affected cats causes diabetes mellitus and feline fragile skin syndrome (Fig. 50.21). Clinical features mimic feline hyperadrenocorticism. Results of tests of the pituitary adrenocortical axis are normal to suppressed in cats with a progesterone-secreting adrenal tumor. Diagnosis requires documentation of an increased plasma progesterone concentration.

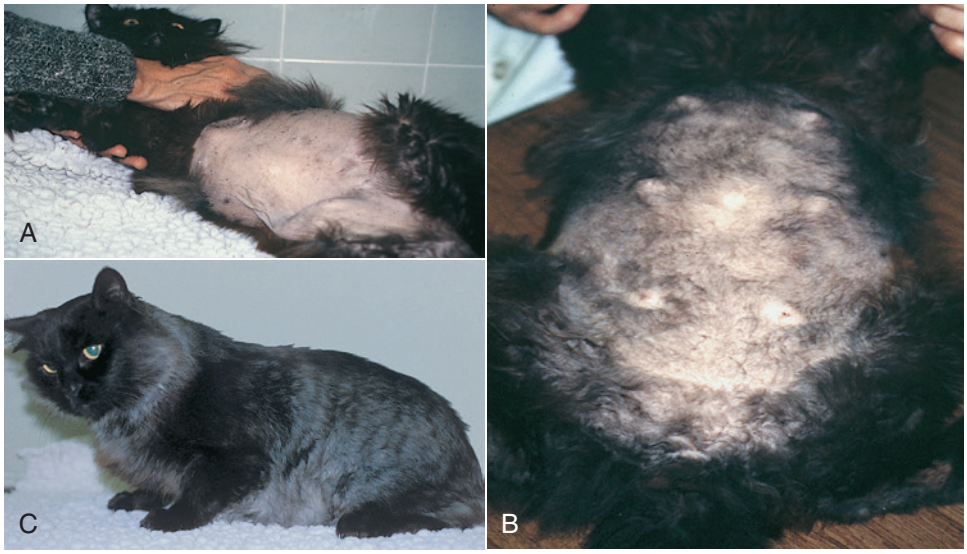


FIG 50.21
(A) A 9-year-old male castrated domestic long-haired cat with a 2-year history of poorly controlled diabetes mellitus, failure of hair to regrow after clipping 1 year before presentation, and recent development of feline fragile skin syndrome. Diagnostic evaluation revealed an adrenocortical tumor, increased serum progesterone concentration, and suppression of the pituitary-adrenocortical axis on adrenocorticotropic hormone stimulation and dexamethasone suppression testing. A progesterone-secreting adrenocortical tumor was suspected. **(B)** Five weeks after initiation of treatment with aminoglutethimide. Feline fragile skin syndrome was resolving, hair was growing, and gynecomastia had developed. The serum progesterone concentration had decreased from a pretreatment value of 4.7 ng/mL to less than 1 ng/mL. **(C)** Four months after adrenalectomy. Insulin-requiring diabetes mellitus had resolved.

Suggested Readings

Fossum TW. *Small animal surgery*. 4th ed. St Louis: Elsevier-Mosby; 2018.

Johnston SA, Tobias KM. *Veterinary surgery: small animal*. 2nd ed. St Louis: Elsevier-Saunders; 2018.

Hyperadrenocorticism in Dogs

Arenas C, et al. Evaluation of 2 trilostane protocols for the treatment of canine pituitary-dependent hyperadrenocorticism: twice daily versus once daily. *J Vet Intern Med*. 2013;27:1478.

Barker EN, et al. A comparison of the survival times of dogs treated with mitotane or trilostane for pituitary-dependent hyperadrenocorticism. *J Vet Intern Med*. 2005;19:810.

Behrend EN, et al. Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM Consensus statement (Small animal). *J Vet Intern Med*. 2013;27:1292.

Benchekroun G, et al. Ultrasonography criteria for differentiating ACTH dependency from ACTH independency in 47 dogs with hyperadrenocorticism and equivocal adrenal asymmetry. *J Vet Intern Med*. 2010;24:1077.

Bento PL, et al. Associations between sex, body weight, age, and ultrasonongraphically determined adrenal gland thickness in dogs with non-adrenal gland illness. *J Am Vet Med Assoc*. 2016;248:652.

Bonadio CM, et al. Comparison of adrenocorticotropic hormone stimulation test results started at 2 versus 4 hours after trilostane administration in dogs with naturally occurring hyperadrenocorticism. *J Vet Intern Med*. 2014;28:1239.

Choi J, et al. Ultrasonographic adrenal gland measurements in clinically normal small breed dogs and comparison with pituitary-dependent hyperadrenocorticism. *J Vet Med Sci*. 2011;73:985.

Cook AK, et al. Pharmaceutical evaluation of compounded trilostane products. *J Am Anim Hosp Assoc*. 2012;48:228.

Davis MK, et al. Ultrasonographic identification of vascular invasion by adrenal tumors in dogs. *Vet Radiol Ultrasound*. 2012;53:442.

Galac S, et al. Urinary corticoid:creatinine ratios in dogs with pituitary-dependent hypercortisolism during trilostane treatment. *J Vet Intern Med*. 2009;23:1214.

Hanson JM, et al. Efficacy of transsphenoidal hypophysectomy in treatment of dogs with pituitary-dependent hyperadrenocorticism. *J Vet Intern Med*. 2005;19:687.

Helm JR, et al. A comparison of factors that influence survival in dogs with adrenal-dependent hyperadrenocorticism treated with mitotane or trilostane. *J Vet Intern Med*. 2011;25:251.

Kent MS, et al. Survival, neurologic response, and prognostic factors in dogs with pituitary masses treated with radiation therapy and untreated dogs. *J Vet Intern Med*. 2007;21:1027.

Kim KH, et al. Clinical relationship between cholestatic disease and pituitary-dependent hyperadrenocorticism in dogs: a retrospective case series. *J Vet Intern Med*. 2017;31:335.

Lang JM, et al. Elective and emergency surgical management of adrenal gland tumors: 60 cases (1999-2006). *J Am Anim Hosp Assoc*. 2011;47:428.

Massari F, et al. Adrenalectomy in dogs with adrenal gland tumors: 52 cases (2002-2008). *J Am Vet Med Assoc*. 2011;239:216.

Park FM, et al. Hypercoagulability and ACTH-dependent hyperadrenocorticism in dogs. *J Vet Intern Med*. 2013;27:1136.

Schwartz P, et al. Evaluation of prognostic factors in the surgical treatment of adrenal gland tumors in dogs: 41 cases (1999-2005). *J Am Vet Med Assoc*. 2008;232:77.

Sieber-Ruckstuhl NS, et al. Cortisol, aldosterone, cortisol precursor, androgen and endogenous ACTH concentrations in dogs with pituitary-dependent hyperadrenocorticism treated with trilostane. *Domest Anim Endocrinol*. 2006;31:63.

Teshima T, et al. Central diabetes insipidus after transsphenoidal surgery in dogs with Cushing's disease. *J Vet Med Sci*. 2011;73:33.

Theon AP, et al. Megavoltage irradiation of pituitary macrotumors in dogs with neurologic signs. *J Am Vet Med Assoc*. 1998;213:225.

Vaughn MA, et al. Evaluation of twice-daily, low-dose trilostane treatment administered orally in dogs with naturally occurring hyperadrenocorticism. *J Am Vet Med Assoc*. 2008;232:1321.

Woolcock AD, et al. Evaluation of baseline cortisol concentration to monitor efficacy of twice-daily administration of trilostane to dogs with pituitary-dependent hyperadrenocorticism: 22 cases (2008-2012). *J Am Vet Med Assoc*. 2016;248:814.

Zur G, et al. Hyperadrenocorticism in 10 dogs with skin lesions as the only presenting clinical signs. *J Am Anim Hosp Assoc*. 2011;47(419).

Atypical Cushing's Syndrome in Dogs

Behrend EN, et al. Serum 17-β-hydroxyprogesterone and corticosterone concentrations in dogs with nonadrenal neoplasia and dogs with suspected hyperadrenocorticism. *J Am Vet Med Assoc*. 1762;227:2005.

Benitah N, et al. Evaluation of serum 17-hydroxyprogesterone concentration after administration of ACTH in dogs with hyperadrenocorticism. *J Am Vet Med Assoc*. 2005;227:1095.

Frank LA, et al. Serum cortisol concentrations in dogs with pituitary-dependent hyperadrenocorticism and atypical hyperadrenocorticism. *J Vet Intern Med*. 2015;29:193.

Hill KE, et al. Secretion of sex hormones in dogs with adrenal dysfunction. *J Am Vet Med Assoc*. 2005;226:556.

Hyperadrenocorticism in Cats

Daniel G, et al. Clinical findings, diagnostics and outcome in 23 cats with adrenal neoplasia (2002-2013). *J Feline Med Surg*. 2016;18:77.

Meij BP, et al. Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats. *Vet Surg*. 2001;30:72.

Mellett K, et al. Trilostane therapy for treatment of spontaneous hyperadrenocroticism in cats: 15 cases (2004-20012). *J Vet Intern Med*. 2013;27:1471.

Valentin SY, et al. Clinical findings, diagnostic test results, and treatment outcome in cats with spontaneous hyperadrenocorticism: 30 cases. *J Vet Intern Med*. 2014;28:481.

Hypoadrenocorticism

Baumstark J, et al. Use of plasma renin activity to monitor mineralocorticoid treatment in dogs with primary hypoadrenocorticism: desoxycorticosterone versus fludrocortisone. *J Vet Intern Med*. 2014;28:1471.

Burkitt JM, et al. Relative adrenal insufficiency in dogs with sepsis. *J Vet Intern Med*. 2007;21:226.

Gold AJ, et al. Evaluat5ion of basal serum or plasma cortisol concentrations for the diagnosis of hypoadrenocorticism in dogs. *J Vet Intern Med*. 1798;30:2016.

Hanson JM, et al. Naturally occurring adrenocortical insufficiency–an epidemiological study based on a Swedish-insured dog population. *J Vet Intern Med*. 2016;30:76.

Lennon EM, et al. Use of basal serum or plasma cortisol concentrations to rule out a diagnosis of hypoadrenocorticism in dogs: 123 cases (2000-2005). *J Am Vet Med Assoc*. 2007;231:413.

Thompson AL, et al. Comparison of classic hypoadrenocorticism with glucocorticoid-deficient hypoadrenocorticism in dogs: 46 cases (1985-2005). *J Am Vet Med Assoc*. 2007;230:1190.

Wenger M, et al. Ultrasonographic evaluation of adrenal glands in dogs with primary hypoadrenocorticism or mimicking diseases. *Vet Rec*. 2010;167:207.

Pheochromocytoma

Gostelow R, et al. Plasma-free metanephrine and free normetanephrine measurement for the diagnosis of pheochromocytoma in dogs. *J Vet Intern Med*. 2013;27:83.

Herrera MA, et al. Predictive factors and the effect of phenoxybenzamine on outcome in dogs undergoing adrenalectomy for pheochromocytoma. *J Vet Intern Med*. 2008;22:1333.

Kook PH, et al. Urinary catecholamine and metadrenaline to creatinine ratios in dogs with a phaeochromocytoma. *Vet Rec*. 2010;166:169.

Salesov E, et al. Urinary and plasma catecholamines and metanephrine in dogs with pheochromocytoma. *J Vet Intern Med*. 2015;27:597.

Incidental Adrenal Mass

Ash RA, et al. Primary hyperaldosteronism in the cat: a series of 13 cases. *J Feline Med Surg*. 2005;7:173.

Baum JI, et al. Prevalence of adrenal gland masses as incidental findings during abdominal computed tomography in dogs: 270 cases (2013-2014). *J Am Vet Med Assoc*. 2016;249:1165.

Cook AK, et al. Clinical findings in dogs with incidental adrenal gland lesions determined by ultrasonography: 151 cases (2007-2010). *J Am Vet Med Assoc*. 2014;244:1181.

Djajadiningrat-Laanen S, et al. Primary hyperaldosteronism: expanding the diagnostic net. *J Feline Med Surg*. 2012;13:641.

Meler EN, et al. Cyclic estrous-like behaviour in a spayed cat associated with excessive sex-hormone production by an adrenocortical carcinoma. *J Feline Med Surg*. 2011;13:473.

Syme HM, et al. Hyperadrenocorticism associated with excessive sex hormone production by an adrenocortical tumor in two dogs. *J Am Vet Med Assoc*. 1725;219:2001.

Zimmer C, et al. Ultrasonographic examination of the adrenal gland and evaluation of the hypophyseal-adrenal axis in 20 cats. *J Small Anim Pract*. 2000;41:156.



Drugs Used in Endocrine Disorders

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSAGE	
		DOG	CAT
Calcium—injectable and oral preps	Treat hypocalcemia, Treat hypoparathyroidism	See Box 53.7	See Box 53.7
Carbimazole (Neo-Mercazole)	Treat feline hyperthyroidism	NA	2.5-5 mg PO q12h initially; increase q2wk to effect
Chlorpropamide (Diabinase)	Treat partial central diabetes insipidus	5-20 mg/kg PO q12h	Unknown
Chlorothiazide (Diuril)	Treat central/renal diabetes insipidus	20-40 mg/kg PO q12h	20-40 mg/kg PO q12h
Desmopressin (DDAVP)	Treat central diabetes insipidus	1-4 drops of nasal spray in conjunctival sac q12-24h; tablets: 0.05-0.2 mg/dog PO q8-12h	1-4 drops of nasal spray in conjunctival sac q12-24h; tablets: 0.05 mg/cat PO q8-12h
Desoxycorticosterone pivalate (DOCP)	Treat hypoadrenocorticism	2.2 mg/kg, IM or SC, q25d initially	2.2 mg/kg, IM or SC, q25d initially
Dexamethasone sodium phosphate	Treat acute addisonian crisis	0.5-1 mg/kg IV, repeat q12h at 0.05-0.1 mg/kg in IV fluids	0.5-1 mg/kg IV, repeat q12h at 0.05-0.1 mg/kg in IV fluids
Diazoxide (Proglycem)	Treat hypoglycemia caused by β-cell neoplasia	5 mg/kg PO q12h initially	Unknown
Fludrocortisone acetate (Florinef)	Treat hypoadrenocorticism	0.01 mg/kg PO q12h initially	0.05-0.1 mg/cat PO
Glucagon USP	Treat hypoglycemia caused by a β-cell neoplasia	5-10 ng/kg/min as continuous IV infusion; adjust dose to effect	Unknown
Growth hormone—porcine origin	Treat pituitary dwarfism	0.1 IU/kg SC 3 times/wk for 4-6 weeks	Unknown
Insulin	Treat diabetic ketoacidosis Treat diabetes mellitus Provide supportive treatment for hyperkalemia	See Box 49.11 See Table 49.3 See Table 53.3	See Box 49.11 See Table 49.3 See Table 53.3
Ketoconazole (Nizoral	Treat hyperadrenocorticism	5 mg/kg PO q12h initially, increase to effect q2wk	Not recommended
Melatonin	Treat alopecia X syndrome	3 mg (dogs ≤ 15 kg) or 6 mg (dogs >15 kg) PO q12h for 6-8 weeks initially	NA
Methimazole (Felimazole)	Treat hyperthyroidism	2.5 mg/dog PO q12h initially; increase q2wk to effect	2.5 mg/cat PO q12h initially; increase q2wk to effect
o,p'DDD (Mitotane, Lysodren)	Treat canine hyperadrenocorticism Long-term treatment of hypoadrenocorticism	Induction: 25 mg/kg PO q12h until controlled Maintenance: 25-50 mg/kg PO per week initially divided into 2 or 3 doses	Not recommended
Phenoxybenzamine (Dibenzyline)	Supportive treatment forpheochromocytoma	0.5 mg/kg PO q12h initially, gradually increase to effect	Unknown



Drugs Used in Endocrine Disorders—cont'd

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSAGE	
		DOG	CAT
Prednisone (dogs), prednisolone (cats)	Long-term treatment of hypoadrenocorticism Provide supportive treatment for β-cell neoplasia	0.25 mg/kg PO q12h initially 0.25 mg/kg PO q12h initially; increase as needed	2.5-5 mg/cat PO q12-24h initially 2.5 mg/cat PO q12h initially; increase as needed
Sodium levothyroxine–synthetic T_4	Treat hypothyroidism	0.01-0.02 mg/kg PO q12h initially, unless formulated for q24h	0.05-0.1 mg/cat PO q12-24h initially
Somatostatin (Octreotide)	Provide supportive treatment for β-cell neoplasia	10-40 µg/dog SC q8-12h	Unknown
Trilostane (Vetoryl)	Treat hyperadrenocorticism	1 mg/kg q12h initially; adjust to effect	30 mg/cat q24h initially; adjust to effect
Vitamin D preparations	Treat hypoparathyroidism	See Box 53.7	See Box 53.7

BSA, Body surface area; *IM,* intramuscular; *IV,* intravenous; *NA,* not applicable; *PO,* by mouth; *SC,* subcutaneous.

CHAPTER 51

Weight Loss and Obesity



POLYPHAGIA WITH WEIGHT LOSS

In some dogs and cats, polyphagia with concurrent weight loss is the presenting complaint. The most common cause of polyphagia with concurrent weight loss is inadequate caloric intake (Table 51.1). Although this seems obvious, some owners are surprisingly unaware of appropriate feeding amounts and unintentionally underfeed their pets. Daily caloric needs may not be met if inadequate quantities of food are being fed, if the diet is not complete and balanced, or if the diet is of poor quality. Alternatively, the client may not recognize changes in nutritional needs (e.g., during late pregnancy and lactation, and at times of strenuous exercise, such as during hunting season) and may continue to feed the animal at previously adequate caloric levels. Likewise, the owner may switch diets and continue to feed the same volumes despite a lower energy density in the new food.

Endocrinopathies and gastrointestinal tract disorders also cause polyphagia and weight loss in some dogs and cats (see Table 51.1) as a result of an increase in basal metabolic rate (hyperthyroidism), inadequate assimilation of dietary nutrients (gastrointestinal tract disorders), or inappropriate use of nutrients (diabetes mellitus). Gastrointestinal tract disorders include parasitism, pancreatic exocrine insufficiency, infiltrative bowel disorders, lymphangiectasia, and neoplasia (most notably gastrointestinal lymphoma). In most cases the history and physical findings usually provide valuable clues to the diagnosis. For example, polyuria and polydipsia are common signs of diabetes mellitus. A thyroid nodule is usually palpable in dogs and cats with hyperthyroidism. Fatty, voluminous stools are noted in animals with pancreatic exocrine insufficiency. Diarrhea and vomiting may occur in animals with various gastrointestinal tract disorders, and palpation of the abdomen may reveal abnormal loops of intestine and mesenteric lymphadenopathy. The last condition may be discernible in animals with any of the infiltrative diseases, but it is especially noticeable in those with gastrointestinal tract lymphoma, eosinophilic enteritis, or histoplasmosis.

In addition to routine medical history and status questions posed to the client, the clinician should perform a nutritional assessment including a diet history (types and amounts of foods offered; total daily caloric intake from foods, treats, and supplements; feeding routines; and competition for food from other dogs or cats). Daily caloric requirements in individual cats and dogs are quite variable and depend on numerous factors, such as signalment, climate, and the amount of daily physical activity. The average daily caloric requirement can be calculated using the equation for the resting energy requirement (RER): 70 × body weight in kilograms$^{0.75}$. Although most people have ready access to computers and smart phones, this can also be calculated on a simple calculator with a square root button. To determine RER, the current body weight in kilograms is multiplied by itself three times, and the square root of the result is taken twice before multiplying by 70. This value for RER has a unit of kcal per day and is multiplied by a factor to derive the maintenance energy requirement (MER). The factor for a neutered cat is 1.2, an intact cat's factor is 1.4, a neutered dog's factor is 1.6, and an intact dog's is 1.8. The daily caloric requirements in any individual dog or cat may vary by as much as 50% more or less than this estimated value. Although this represents a large range for normal caloric intake, the clinician may have a greater suspicion that an inadequate amount of calories is being fed if a confident estimate of intake can be determined from the diet history, and if this amount is closer to 50% of MER. Similarly, consumption of calories closer to 150% of MER may increase the suspicion that adequate calories are being fed but that an endocrinopathy and/or gastrointestinal tract disorder may be leading to polyphagia with concurrent weight loss. It is important to note that adjustment and monitoring is the most valuable procedure for determining an individual's true calorie needs. If comparison of the actual caloric intake with

TABLE 51.1

Differential Diagnosis for Polyphagia and Weight Loss

ETIOLOGY	DEFINITIVE DIAGNOSTIC TESTS
Inadequate nutrition	Response to diet change and/or increased amounts
Hyperthyroidism	Serum T_4 and free T_4 concentrations
Diabetes mellitus	Blood glucose concentration and urinalysis
Gastrointestinal Disease	
Parasitism	Fecal examination, trial therapy
Infiltrative bowel disease: plasmacytic, lymphocytic, eosinophilic, lymphoma	Intestinal biopsy
Histoplasmosis	Intestinal biopsy, serology
Lymphangiectasia	Intestinal biopsy
Pancreatic exocrine insufficiency	Serum trypsin-like immunoreactivity, response to therapy
Protein-losing nephropathy	Urinalysis, urine protein/creatinine ratio
Hypothalamic mass	Computed tomography, magnetic resonance imaging

the calculated MER prove equivocal or cannot be attained, simply feeding more food or calories and reassessing the patient's weight may be illuminative.

A complete blood count, serum biochemistry panel, measurement of baseline thyroxine concentration, urinalysis, and fecal examination for parasites should be done if the history and physical findings are unremarkable. Results of these tests usually help identify additional specific diagnostic tests that may be required to establish a definitive diagnosis. Inadequate nutrition should be suspected if the diagnostic testing is unremarkable and especially in the face of adequate or increased appetite. Changes in the types of foods provided, daily caloric intake, and feeding routine should be made to ensure that the animal has an adequate caloric intake of a palatable and nutritionally complete and balanced food. Carefully questioning the owner regarding the feeding environment can also be important, as often subtle food guarding behaviors can be exhibited by both dogs and cats. The animal's body weight should be determined 2 and 4 weeks after the start of an appropriate diet. Resolution of signs and weight gain confirm the diagnosis. Failure to gain weight indicates problems with client compliance or the presence of occult disease, most likely disease involving the gastrointestinal tract.

BOX 51.1

Documented Potential Adverse Effects of Obesity

Decreased life span
Exacerbation of orthopedic disease, including osteoarthritis and intervertebral disk disease
Cardiopulmonary dysfunction—impaired lung compliance, Pickwickian syndrome
Exercise intolerance, heat intolerance
Insulin resistance and predisposition for diabetes mellitus
Hyperlipidemia
Hepatic lipidosis
Predisposition for pancreatitis
Problems with constipation
Predisposition for feline lower urinary tract disease
Predisposition for urinary incontinence in spayed female dogs
Predisposition for reproductive problems—dystocia
Predisposition for dermatologic problems—seborrhea, pyoderma
Increased surgical and anesthetic risk

OBESITY

Obesity is a clinical syndrome defined by the excess accumulation of body fat and its consequences. It is defined, as in people, as a body weight approximately 25% over ideal. Obesity is considered the most common form of malnutrition in small animal practice. Indeed, studies have shown that up to 59% of dogs and 63% of cats in various populations are diagnosed with overweight or obesity. The significance of obesity pertains to its role in the pathogenesis of a variety of diseases and its ability to exacerbate preexisting disease and decrease life span. Obesity has been associated with an increased incidence of osteoarthritis and other orthopedic disease, diabetes mellitus, hyperlipidemia, hepatic lipidosis, feline lower urinary tract disease (FLUTD), urine incontinence in spayed bitches, constipation, non-allergic dermatitis, cardiopulmonary dysfunction, respiratory problems, and increased anesthetic and surgical risks (Box 51.1). In addition, Scarlett et al. (1998) found a threefold increase in risk of death in obese middle-aged cats compared with the risk in lean middle-aged cats. Kealy et al. (2002) found that dogs that were kept lean throughout their life lived almost 2 years longer than control-group litter mates that were overweight. The lean dogs also did not need treatment for co-morbidities such as osteoarthritis until later in life.

Etiology

Obesity develops when daily energy intake consistently exceeds daily energy expenditure. Numerous animal and

owner factors contribute to the development of obesity (Box 51.2). These include decreased daily exercise as a result of confinement to the house and overfeeding of the pet. Clients may overfeed their pet because a good appetite is perceived as a sign of good health, they may use food as a palliative agent when they leave the pet on its own, they may replace exercise with food, and they often indulge begging behavior because they find it endearing. Clients also tend to feed the same volume of food each day despite changes in energy requirements and the energy density of foods provided. Daily energy requirements vary according to environmental temperature, the life stage of the pet (i.e., growth, pregnancy, lactation, adult maintenance, old age), neuter status, and the activity level of the pet. Therefore it is necessary to adjust the amount of food according to these factors. Feeding errors also arise when a client purchases a different type of food with a higher energy density but does not reduce the amount accordingly. It is worth noting that dry extruded foods (kibble) can range widely from approximately 200 kcal to more than 600 kcal per cup per 8-fluid ounce cup. Overfeeding may also occur if the feeding guidelines provided by pet food manufacturers are incorrect or not accurate for the individual pet. In some situations, clients are simply not aware that they are overfeeding their pet and actually perceive their overweight pet as picky or as not eating much food. Ad libitum feeding may also predispose to overeating, particularly if the pet is bored and inactive, or if there is inter-pet competition in the household. Likewise, highly palatable foods encourage overconsumption. Snacks and treats are a significant but often unappreciated contributor to excess daily caloric intake as well. It takes only about 11 extra kcal a day for a pet to gain 1 pound over the course of a year; many common treats provide between 50 and 100 extra kcal apiece.

Obese or older clients may be more likely to have obese dogs; similar findings have not been documented in cats. The client's sedentary lifestyle may contribute to lack of exercise by the pet, and the consumption of high-fat foods by the client may increase the likelihood that these energy-dense scraps are fed to the pet. In addition, it is possible that obese clients do not believe (or recognize) that obesity is a major problem for their pet. Underestimation of the pet's body condition score (BCS) is also associated with overweight and obesity in both dogs and cats; owner education of appropriate body composition may be important in prevention of obesity.

Because of genetic differences, some animals have significantly lower energy requirements and therefore require fewer calories per day to maintain their ideal body weight. Likewise, many working or sporting breeds have higher requirements for exercise, which is often not satisfied in most urban and suburban environments. In addition, some breeds tend to be more interested in food as a primary motivator for various food-seeking and consumptive behaviors. These genetic differences may be reflected by the increased propensity of certain breeds to gain excessive weight (Box 51.3).

Neutering is an important risk factor for obesity in both dogs and cats. It has been suggested that hormonal alterations secondary to neutering may alter energy expenditure,

BOX 51.2

Factors Associated with Obesity in Cats and Dogs

Primary Obesity

Excess caloric intake
- Energy-dense food
- Inappropriate feeding practices
- Inadequate feeding guidelines
- Ad libitum feeding

Reduced energy expenditure (exercise, activity)
Growth rate
Age
Neuter status
Owner income, age, and body composition
Underestimation of pet's body composition
Genetic predisposition (breed)

Secondary Obesity

Hypothyroidism
Hyperadrenocorticism
Hyperinsulinism
Acromegaly
Hypopituitarism
Hypothalamic dysfunction
Medications
- Glucocorticoids
- Progestagens
- Phenobarbital
- Primidone

BOX 51.3

Dog and Cat Breeds Associated with Higher Obesity Risk

Dogs

Labrador Retriever
Golden Retriever
Rottweiler
Cocker Spaniel
Collie
Dachshund
Cairn Terrier
Shetland Sheepdog
Beagle
Cavalier King Charles Spaniel
Basset Hound

Cats

Manx
British Short Hair
Norwegian Forest Cat
Persian
Domestic Short, Medium, and Long Hair cats

but disruptions in the regulation of food intake appears to be the most important effect. This apparently occurs rapidly, and increased food intake occurs almost immediately after neutering. Obesity has been reported to be more common in female neutered dogs and male neutered cats, and greater gains are seen with free-feeding. As such, portion control is critically important to avoid weight gain after neutering.

Obesity is less likely to result from a disease process or drug. Indeed, it has been suggested that less than 5% of obesity is due to a disease or drug. Endocrine abnormalities associated with obesity include hypothyroidism, hyperadrenocorticism, hyperinsulinism, and acromegaly. Drugs such as progestagens and corticosteroids have been associated with the development of obesity.

Diagnosis

Obesity is defined as a "pathological condition characterized by an accumulation of fat much in excess of that required for optimal body function" (Mayer, 1973). However, what is an excess amount of body fat, and what is an acceptable amount? To answer these questions, the clinician must accurately determine the amount of body fat. Body fat can be assessed by techniques such as morphometric measurements, dilutional methods, bioelectrical impedance analysis, dual energy X-ray absorptiometry (DEXA), densitometry, computed tomography, magnetic resonance imaging, determination of total body electrical conductivity, determination of total body potassium, neutron activation analysis, and morphometric measurements. Although numerous methods may be used to determine body fat, the most clinically useful techniques in small animal practice include measurement of body weight and determination of a BCS.

Measurement of body weight is a standardized, simple technique and should be included in the examination of every animal. However, body weight does not provide information regarding body composition, so additional assessments are necessary. Consideration of the potential contribution to absolute body weight of excessive adipose, decreased muscle mass, and fluid accumulation may be warranted in many cases.

Body condition scoring provides a quick and simple subjective assessment of the animal's body condition based on estimates of stored body fat (adipose tissue). It does not include assessment of lean body mass, and muscle condition scoring systems are distinct from BCS systems. The two most commonly used BCS systems in small animal practice include a 5-point system in which a score of 3 is considered ideal, and a 9-point system in which a score of 5 is considered ideal for cats and 4 or 5 is considered ideal for dogs (Figs. 51.1 and 51.2). Larger numbers are used for patients with greater adiposity. Each point above ideal on the 9-point system approximates a body weight 10% to 15% over ideal. Thus a feline patient that has a BCS of 7 out of 9 is 20% to 30% overweight as a result of the accumulation of adipose tissue. The BCS technique is subjective as it depends on operator interpretation and does not provide any precise quantitative information concerning alteration in fat-free or lean body mass relative to fat mass.

Height and circumferential measurements of the abdomen, hip, thigh, and upper arm are commonly used to estimate the percentage of body fat in humans. Body (morphometric) measurements have also been developed to estimate the percentage of body fat in dogs and cats. These tools have been promoted as one way to estimate ideal body weight to provide guidance for determining the amount to feed for weight loss plans. However, successful weight loss plans utilizing morphometric measurements to estimate ideal body weight have not been reported in the literature. Studies have demonstrated that proportion of body fat as estimated using BCS systems correlates well with that determined by DEXA measurements in both dogs and cats. However, marked individual variability was reported when using a 5-point BCS system to estimate ideal body weight in dogs (German et al., 2009). Very few clinical settings can access more precise and validated measures of body composition to more accurately estimate ideal body weight (such as DEXA). Regardless, providing an approximate quantitative assessment of a patient's degree of adiposity can be helpful in diagnosing obesity even if not exact (using either morphometric measurements or BCS or both). Ultimately, focusing the owner on the process rather than the end goal may be warranted, given that measurable benefits are seen with weight loss even before the target ideal body weight is achieved.

Treatment

After diagnosing a patient as overweight or obese, the clinician should obtain a thorough dietary history to calculate the patient's daily caloric intake. The clinician should gather the following information:

- Name, manufacturer, and type (i.e., wet versus dry, etc.) of the current food(s)
- Amount of food that is fed each day (pouches, cans, cups, or grams of food)
- Method of feeding (ad libitum versus meal fed)
- Person responsible for feeding the pet
- Additional persons who may feed the patient (children, elderly parents, or neighbors)
- Number and types of snacks, treats, or human foods given each day
- Type and amount of any supplements given each day
- Potential access to other foods (for other pets, from the garden, etc.)

The patient's current body weight should be recorded and a BCS assigned. Body weight trends should be considered as well (is the patient gaining, stable, or losing). The BCS can be used to determine the percentage of body weight that must be lost. Because each point above ideal on a 9-point scale represents an additional 10% to 15% of weight over ideal, the clinician can calculate the percentage of weight that should be lost. For example, an otherwise healthy feline



FIG 51.1
Body condition score chart for dogs from the Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association. (© The World Small Animal Veterinary Association, 2013.)

patient that has a BCS of 8 out of 9 is 30% to 45% overweight given an ideal BCS of 5. Likewise, a dog with orthopedic disease and a BCS of 7 is also 30% to 45% overweight because ideal BCS is 4 in that case. The goal rate of loss is 1% to 2% of their body weight per week. Therefore it should be expected that most overweight and obese patients will take at least several months to lose enough adipose tissue to attain their ideal body weight. Given the necessary length of time and the importance of owner persistence and compliance, it is imperative to emphasize the process goals rather than the ultimate goal of an ideal body weight. These shorter-term goals (1%-2% body weight loss per week) are typically more manageable and more motivating, and they provide additional opportunities for adjustment of the weight loss plan if needed.

The rate of weight loss of 1% to 2% of current body weight per week is typically recommended for several reasons. First, greater rates of weight loss will require that the patient receive a very small allowance of food, which is more likely to encourage begging behavior and garbage scavenging. These undesirable behaviors, along with the small volume of food to be provided, can jeopardize client compliance. Second, weight loss greater than 2% of body weight per week has been associated with greater losses of lean body mass. Third, rapid weight loss is most likely to result in a rebound weight gain effect after cessation of the program.

Given the large variation in energy requirements that can be seen in cats and dogs, the best method to determine the number of calories that one should feed a patient to induce weight loss is the use of an accurate diet history. Typically, the weight of overweight and obese patients is relatively stable at presentation; therefore feeding 80% of the patient's current caloric intake based on an accurate diet history results in weight loss at an appropriate rate. In patients in which an accurate diet history cannot be determined or that are roughly weight-stable or losing, the client may start with feeding 80% of RER for cats and RER for dogs; if the pet is gaining weight, more severe restriction is warranted. Regardless of the method used to determine the number of calories that should be fed to initiate weight loss, clients should be



FIG 51.2
Body condition score chart for cats from the Global Nutrition Committee Toolkit provided courtesy of the World Small Animal Veterinary Association. (© The World Small Animal Veterinary Association, 2013.)

told to expect to adjust the amount of food on the basis of frequent weigh-ins. Initially, some patients gain weight on the new weight loss plan, some stay weight-stable, some lose the desired amount, and some may even lose weight too quickly.

After determining the daily number of calories to feed the patient, the clinician should consider the most suitable type of food. There are essentially two main dietary options: (1) feed a reduced amount of the current diet (typically a regular maintenance food), or (2) feed a food that has been specifically formulated for weight reduction. It is not advisable to feed less of the current diet because this most likely was the food that resulted in the problem in the first place, and compliance over the long term is less likely due to habit as well as reluctance to feed low food volumes. More important, feeding a maintenance food may increase the risk of nutrient deficiency, because these are formulated for animals with normal body composition and average calorie needs. This means that if a normal dog or cat eats its daily energy requirement, it will also consume the required quantities of additional essential nutrients, such as amino acids, fatty acids, minerals, and vitamins. By feeding less of the maintenance food to induce weight loss in an obese pet, not only is the amount of energy being reduced below requirements but also the quantities of amino acids, fatty acids, minerals, and vitamins, thereby risking malnutrition, especially given the length of time often needed to achieve an ideal body condition. Conversely, diets that have been specifically formulated for weight reduction contain more essential nutrients relative to the energy content. This means that the patient is more likely to ingest the required quantities of essential nutrients even in fewer calories.

Most foods designed for weight reduction are one half to two thirds less energy-dense than typical maintenance foods. Therefore clients will not visually perceive as much of a decrease in volume when a food designed for weight reduction is used. Decreased energy density on a volume basis is achieved by decreasing the fat content of food, modifying kibble size and shape to reduce "packing" together in a cup or bowl, increasing the moisture content of wet foods, and/or increasing fiber concentration. Some of these strategies are directed at owner perceptions of volume, but others aim

to achieve a filling effect for the pet (fiber, moisture); surprisingly, even air-puffed kibble showed a satiety effect in one study of dogs, possibly by slowing food intake.

Veterinary therapeutic diets formulated specifically for weight reduction in dogs and cats typically vary according to energy density and caloric distribution (Tables 51.2 and 51.3); however, most are less energy-dense than maintenance foods. This enables greater filling of both the bowl and the bowel, which is a strategy targeted to increased compliance and satiety. Most weight reduction diets are high in fiber, as fiber is used as a bulking agent to dilute the calories as well as to provide a satiating effect. However, conflicting research findings have led to uncertainty about whether fiber reliably increases satiety. Because some patients may not respond well to higher-fiber foods, a few diets do not use this nutritional strategy, especially those formulated for cats.

Higher-protein diets not only ensure adequate amino acid intake despite caloric restriction but also help increase the proportion of fat loss while preserving or, indeed, increasing lean body mass during weight reduction. The lean body mass is the most metabolically active portion of the body and includes skeletal muscle tissues. Preservation of lean body mass in humans has been shown to facilitate successful long-term maintenance of ideal body weight after successful weight loss. Lower fat diets that provide a reduced percentage of calories from fat help reduce the energy density of the food because fat provides almost 2.5 times the calories per gram as provided by protein or carbohydrate. This is one drawback of the lower-carbohydrate diet options designed for weight reduction in cats, as they are often higher in fat; their increased energy density means that a small volume is needed to achieve the required degree of restriction, which may not be acceptable to the owner or the pet.

Once the daily caloric intake has been determined and appropriate weight reduction diet chosen, the method of feeding should be decided. Ideally, the patient should receive portion-controlled meals rather than be fed ad libitum. The number of feedings per day can be selected to suit the client's schedule, but two to four meals per day is adequate. One member of the household should be selected to feed the pet. This will reduce inadvertent overfeeding by additional family members. If treats are typically fed or are desired, the client

TABLE 51.2

Key Nutrients Concentrations in Selected Veterinary Therapeutic Diets Suitable for Weight Loss in Dogs*

	TYPE	PROTEIN (% ME)	FAT (% ME)	TOTAL DIETARY FIBER (g/Mcal)	ME (kcal/unit)
Royal Canin Veterinary Diet Canine Satiety Support Weight Management	Dry	33 (110.3 g/Mcal)	28 (34.9 g/Mcal)	103	245/cup
Royal Canin Veterinary Diet Canine Satiety Support Weight Management	Can	41 (113.2 g/Mcal)	28 (32.3 g/Mcal)	57.4	229/13.4-oz can
Royal Canin Veterinary Diet Canine Satiety Support Small Dog	Dry	36 (111.2 g/Mcal)	28 (35.2 g/Mcal)	103	225/cup
Royal Canin Veterinary Diet Canine Multifunction Urinary+Satiety	Dry	36 (109.6 g/Mcal)	38 (34.7 g/Mcal)	97.5	240/cup
Purina Veterinary Diets OM Overweight Management Canine	Dry	32.1 (102.9 g/Mcal)	18.9 (24.8 g/Mcal)	83.8	266/cup
Purina Veterinary Diets OM Select Blend Overweight Management Canine	Dry	32.4 (99.6 g/Mcal)	17.6 (22.3 g/Mcal)	81.2	235 kcal/cup
Purina Veterinary Diets OM Overweight Management Canine	Can	46.4 (129.3 g/Mcal)	30.1 (34.5 g/Mcal)	101.5	253/13.3-oz can
Hill's Prescription Diet r/d Canine	Dry	37 (105 g/Mcal)	21 (25 g/Mcal)	77	245/cup
Hill's Prescription Diet r/d Canine	Can	30 (85 g/Mcal)	24 (29 g/Mcal)	NA	257/12.3-oz can

CHO, Carbohydrate; *Mcal,* megacalories (1000 kcal); *ME,* metabolizable energy.
*Information obtained from manufacturer's product guides. Foods with less than 85 g protein/Mcal not listed.

TABLE 51.3

Key Nutrients Concentrations in Selected Veterinary Therapeutic Diets Suitable for Weight Loss in Cats*

	TYPE	PROTEIN (% ME)	FAT (% ME)	TOTAL DIETARY FIBER (g/Mcal)	ME (kcal/unit)
Royal Canin Veterinary Diet Feline Calorie Control	Can (pate)	58 (140.4g/Mcal)	32 (32 g/Mcal)	21.8	90/5.8-oz can
Royal Canin Veterinary Diet Feline Calorie Control	Can (morsels in gravy)	49 (123.3 g/Mcal)	27 (27.7 g/Mcal)	27.7	49/3-oz can
Royal Canin Veterinary Diet Feline Calorie Control	Dry	43 (109.8 g/Mcal)	25 (26.2 g/Mcal)	21.4	244/cup
Royal Canin Veterinary Diet Feline Calorie Control High Fiber	Can	31.6 (89.8 g/Mcal)	39.8 (41.9 g/Mcal)	38.3	138 kcal/6-oz can
Royal Canin Veterinary Diet Feline Satiety Support Weight Management	Dry	41 (111.1 g/Mcal)	26 (29.4 g/Mcal)	77.1	232/cup
Royal Canin Veterinary Diet Canine Multifunction Urinary+Satiety	Dry	41 (113.6 g/Mcal)	26 (30.1 g/Mcal)	78.5	238/cup
Purina Veterinary Diets OM Overweight Management Feline	Dry	57.8 (159 g/Mcal)	20.9 (23.7 g/Mcal)	46.3	321/cup
Purina Veterinary Diets OM Overweight Management Feline	Can	45.8 (121 g/Mcal)	32.9 (35.4 g/Mcal)	47.7	103/5.5-oz can
Purina Veterinary Diets OM Savory Selects Overweight Management Feline	Can	53.1 (138.3 g/Mcal)	29.5 (31.7 g/Mcal)	40.4	124/5.5-oz can
Hill's Prescription Diet r/d Feline	Dry	39 (107 g/Mcal)	23 (26 g/Mcal)	NA	265/cup
Hill's Prescription Diet r/d Feline	Can	41 (123 g/Mcal)	24 (30 g/Mcal)	NA	114/5.5-oz can
Hill's Prescription Diet m/d Feline	Dry	43 (123 g/Mcal)	41 (49 g/Mcal)	NA	493/cup
Hill's Prescription Diet m/d Feline	Can	46 (131 g/Mcal)	41 (48 g/Mcal)	NA	156/5.5-oz can
Hill's Prescription Diet Metabolic+Urinary Feline and Metabolic+Urinary Stress Feline varieties	Dry	38 (109 g/Mcal)	31 (37 g/Mcal)	NA	289/cup
Hill's Prescription Diet Metabolic+Urinary Feline: Vegetable & Chicken Stew and Vegetable & Tuna Stew varieties	Can	37 (105-107 g/Mcal)	34-35 (41 g/Mcal)	NA	60-61/2.9-oz can

Continued

TABLE 51.3

Key Nutrients Concentrations in Selected Veterinary Therapeutic Diets Suitable for Weight Loss in Cats*—cont'd

	TYPE	PROTEIN (% ME)	FAT (% ME)	TOTAL DIETARY FIBER (g/Mcal)	ME (kcal/unit)
Hill's Prescription Diet Metabolic Feline: Chicken Flavor and With Ocean Fish varieties	Dry	38 (108-109 g/Mcal)	28-31 (33-37 g/Mcal)	NA	288-297/cup
Hill's Prescription Diet Metabolic Feline	Can	39 (111 g/Mcal)	31 (36 g/Mcal)	NA	129/5.5-oz can
Hill's Prescription Diet Metabolic Feline: Vegetable & Chicken Stew and Vegetable & Tuna Stew varieties	Can	37-39 (105-110 g/Mcal)	31-32 (35-37 g/Mcal)	NA	63-65/2.9-oz can

CHO, Carbohydrate; *Mcal,* megacalories (1000 kcal); *ME,* metabolizable energy.
*Information obtained from manufacturer's product guides.

should be instructed to limit the number of treats to less than 10% of the daily caloric intake. Ideally, low-calorie treats should be selected. Commercial treats are available, but high-moisture, low-energy-density fruits (excluding grapes or raisins) and/or vegetables (no garlic or onions) can be good alternatives for dogs and even some cats. Baby carrots are an especially good vegetable treat for most dogs and provide only 4 kcal each. A small amount of lean meat, such as skinless, boneless chicken breast, can be a good alternative treat for cats. It is also important to modify the behavior of the client in such a way that the pet should not be allowed in the kitchen or dining room during meal preparation or eating, if this is typically a tempting time to respond to begging. In addition, the client should inform and enlist the support of all family members and neighbors so that they do not unknowingly give the pet additional calories. In some cases it may be useful for the client to use a food diary to record the amount of food and snacks fed each day.

Multicat households in which one cat is obese and the remainder are of normal body weight or are lean can present some management challenges. Ideally, cats should be fed in separate rooms, but this is not always possible. If this works for the family, most cats can consume their caloric needs if given at least 4 hours of access to their food daily. Thus the time that cats are separated can be minimized. Moreover, fat cats usually cannot jump very high, and it may be a useful strategy to place the food for the lean, healthy cats on an elevated bench or counter that the healthy cats can reach but the obese cat cannot. Alternatively, a hole can be cut into a cardboard box that is large enough to allow the lean cats to enter but small enough to restrict the entry of the overweight or obese cat. The lean cats are then fed in the box. Other options include boxes or pet doors controlled by collars that allow access to only one cat.

In addition to reducing daily caloric intake, every effort should be made to increase the pet's daily energy expenditure by encouraging exercise. Toys that the cat or dog can chase and play with should be encouraged. Laser pointers are particularly useful for encouraging cats to play. Ideally, dogs should receive at least two 20-minute walks per day, which include adequate sniffing opportunities; this is an important and enriching activity for dogs. Swimming is an equally effective exercise, particularly for dogs with osteoarthritis. Providing the client with written instructions for weight loss as well as scheduled rechecks will typically improve both compliance and success. Photographing the patient before institution of the weight reduction program will help clients see the effect of the weight loss on their pet. Institution of reward boards or incentive programs will also increase compliance with the weight reduction program and will help to recruit additional patients in need of weight reduction.

Patients on weight reduction programs should be reevaluated every 2 weeks initially. Body weight and BCS should be recorded. The dietary history should be reviewed to ensure compliance. Cats especially should achieve no more than a 2% body weight loss per week due to the risk of hepatic lipidosis. Dogs should achieve a weight loss rate of approximately 1% body weight loss per week (a range of 0.5%-2% is acceptable). If the rate of weight loss exceeds a 2% body weight loss per week, then the quantity of calories fed to the patient should be increased by 10% to 20%, depending on how rapidly they have lost weight. If the patient has not lost any weight, the dietary history should be reevaluated for a source of additional calories and compliance with the weight loss plan confirmed. If no such reasons are found, the daily caloric intake should be further reduced by 20%. If weight loss is being maintained at the current rate, weight checks can be performed monthly.

Once the ideal body condition has been achieved, the daily caloric intake can be adjusted to maintain an ideal body condition. The patient's weight loss diet can be maintained, or a diet with lower energy density than initially fed can be tried. Maintenance diets that are intended for weight control are widely available. Continued guidance on appropriate amounts to feed as well as types and amounts of treats should be provided. The patient should be reevaluated initially after 2 to 3 weeks, then at least every 2 to 3 months after weight loss to ensure that weight stability is maintained and that the patient is not gaining weight on its new diet regimen. Currently, medications or effective nutraceuticals for facilitating weight loss in dogs and cats are not available. Chronic energy restriction together with appropriate owner education and ideally increased activity and exercise to increase energy expenditure remain the standard strategies for achieving successful weight loss.

Prevention

Ideally, clinicians should focus more on obesity prevention than on treatment because treatment can be very challenging. Because increased food intake and overconsumption of energy resulting in the development of obesity occurs soon after gonadectomy, prevention should begin at the time that the pet is neutered. Clients should be counseled about the risk factors of obesity (e.g., male neutered cats, female neutered dogs, inactive and indoor lifestyle, free-feeding, energy-dense foods) and the consequences of obesity (e.g., increased incidence of lower urinary tract disease, diabetes mellitus, arthritis, decreased life span). It is important that clients be instructed how to properly feed their pet and how to regularly determine the pet's body condition such that they can maintain the ideal body condition of their pet. Weight education should be reinforced at least annually during the health examination.

Suggested Readings

Brooks D, et al. 2014 AAHA weight management guidelines for dogs and cats. *J Am Anim Hosp Assoc*. 2014;50:1.

Farcas AK, Michel KE. eds. Small animal obesity. *Vet Clin North Am Small Anim Pract*. 2016;46(5):761.

Freeman LM, et al. Nutritional assessment guidelines. *J Small Anim Pract*. 2011;52:385.

German AJ. Outcomes of weight management in obese pet dogs: what can we do better? *Proc Nutr Soc*. 2016;75:398.

German AJ, et al. Use of starting body condition score to estimate changes in body weight and composition during weight loss in obese dogs. *Res Vet Sci*. 2009;87:249.

Kealy RD, et al. Effects of diet restriction on life span and age-related changes in dogs. *J Am Vet Med Assoc*. 2002;220:1315.

Laflamme DP. Companion animals symposium: obesity in dogs and cats: what is wrong with being fat? *J Anim Sci*. 1653;90: 2012.

Larsen JA. Risk of obesity in the neutered cat. *J Feline Med Surg*. 2016. pii: 1098612X16660605. [Epub ahead of print].

Scarlett JM, Donoghue S. Associations between body condition and disease in cats. *J Am Vet Med Assoc*. 1998;212:1725–1731.

CHAPTER 52

Hyperlipidemia



HYPERLIPIDEMIA

Hyperlipidemia is defined as increased blood concentrations of triglycerides (hypertriglyceridemia), cholesterol (hypercholesterolemia), or both. In the fasted state (>10 hours without food), hyperlipidemia is an abnormal finding that represents accelerated production or delayed degradation of circulating lipoproteins. The lipoproteins function as a carrier system to transport water-insoluble triglycerides and cholesterol through the aqueous environment of the blood. Lipoproteins consist of a core of triglycerides and cholesterol esters surrounded by a surface layer of cholesterol, phospholipid, and apolipoproteins. The apolipoproteins (A, B, C, and E) are responsible for the structure of the lipoprotein particle, binding of the particle to cell surface receptors, and activation of enzymes. There are four major classes of lipoproteins, each differing in lipid and apoprotein content as well as physicochemical characteristics such as size, buoyant density on ultracentrifugation, and electrophoretic mobility. In order of increasing density, lipoproteins are categorized as chylomicrons, very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), or high-density lipoproteins (HDLs). The density is inversely proportional to the triglyceride content such that chylomicrons are composed largely of triglyceride, whereas HDLs have virtually no triglyceride content. It should be understood that other significant structural and functional heterogeneity exists within the classes. In addition, the system is a dynamic and progressive one, with one class becoming another during its metabolism. Chylomicrons and VLDLs are primarily involved in triglyceride metabolism, whereas HDLs and LDLs are primarily involved in cholesterol metabolism. Dogs and cats are more resistant to the development of atherosclerosis than humans because HDLs predominate in dogs and cats, as opposed to the LDLs that predominate in humans. There may also be effects related to typical life span because although atherosclerosis is slowly progressive and may begin in childhood, it typically only becomes of concern in humans when they are much older than the longest-lived dogs and cats.

Pathophysiology

After digestion and absorption occur, dietary cholesterol and triglyceride are packaged by the enterocyte into chylomicron particles. The chylomicron particles are secreted into the mesenteric lymph, through which they ultimately reach the systemic circulation via the thoracic duct. As the chylomicrons pass through adipose and muscle tissue, they are exposed to lipoprotein lipase, an enzyme that is present on the surface of capillary endothelial cells. After activation by apoprotein C-II, lipoprotein lipase hydrolyzes the triglyceride from the core of the lipoprotein to free fatty acids and glycerol. The activity of lipoprotein lipase is influenced by several factors including heparin, insulin, glucagon, and thyroid hormone. The liberated free fatty acids diffuse into adjacent tissue and may be resynthesized into triglycerides and stored (in adipocytes) or used for energy by the cell (by myocytes and other cells). Depletion of the triglyceride component of the chylomicron alters the surface such that the chylomicron is converted into a chylomicron remnant. The remnant particle is rapidly recognized by specific hepatic receptors and removed from the circulation. Within the hepatocyte the contents of the chylomicron remnant are degraded. Chylomicrons are present in plasma 30 minutes to 2 hours after consumption of a fat-containing meal, and hydrolysis is normally complete within 6 to 10 hours.

Excess free fatty acids that are not directly oxidized for energy are transformed into triglycerides by the liver. These free fatty acids may originate from residual dietary triglyceride present in chylomicron remnants, from endogenous production secondary to surplus dietary carbohydrate, and from excessive endogenous mobilization of free fatty acids. Free fatty acids can be mobilized from adipose tissue by activation of the intracellular enzyme hormone-sensitive lipase (HSL). HSL hydrolyzes stored triglycerides into free fatty acids and glycerol. Activation of HSL is a normal physiologic response that provides the body with energy during periods of fasting. Stimulators of HSL include epinephrine, norepinephrine, adrenocorticotropic hormone (ACTH), corticosteroids, growth hormone, and thyroid hormone. Of course, HSL is also activated by insulin deficiency during

normal fasting or in diabetes mellitus. In addition, HSL can be inappropriately activated in several pathologic conditions associated with an altered metabolic state.

The triglycerides produced by the hepatocyte are packaged into VLDL particles and subsequently secreted into the bloodstream. VLDL particles are produced continuously by the liver and, in the fasting state, are the main carriers of triglycerides. In addition, VLDL particles are used to export cholesterol from the liver and therefore contain a significant proportion of cholesterol. Analogous to chylomicron metabolism, endothelial lipoprotein lipase hydrolyzes the triglyceride portion of the VLDL particle into free fatty acids and glycerol. The free fatty acids can be oxidized for energy or reconstituted into triglycerides and stored. Removal of the triglyceride core converts the VLDL particle into a remnant particle, which may be removed and catabolized by the liver. Alternatively, a second endothelial lipase, hepatic lipase, can further remove any residual triglyceride and convert the VLDL remnant particle to an LDL particle.

The LDL particle is a cholesterol and phospholipid–rich entity that functions to transport cholesterol to tissues, where it may be used for membrane synthesis or steroid hormone production. Ultimately, the LDL particle can bind to LDL receptors and is removed by the liver. In addition to VLDL particles, the liver secretes nascent HDL particles into the circulation. HDL particles act to scavenge excess unesterified cholesterol from the cells and other lipoproteins and return it to the liver for excretion into bile. This process is often referred to as *reverse cholesterol transport*.

Hypertriglyceridemia can develop secondary to increased chylomicron production (excessive dietary intake of lipid), ineffective clearance of the chylomicron particle, increased VLDL production (excessive dietary intake of lipid and/or carbohydrate, excessive endogenous production or mobilization of lipids), and ineffective clearance of the VLDL particle. Hypercholesterolemia can arise from increased production of the LDL precursor particle (VLDL) or as a result of reduced clearance of the LDL or HDL particle.

Classification

Postprandial hyperchylomicronemia is the most common cause of hyperlipidemia in dogs and cats. It is a normal physiologic manifestation that is caused by the production of triglyceride-rich chylomicrons and usually resolves within 2 to 10 hours. As such, assessments of blood lipid concentrations should be done after at least a 12-hour fast. In contrast, pathologic abnormalities in plasma lipids and lipoproteins may be of genetic or familial origin (primary) or may arise as a consequence of disease (Box 52.1).

Primary hypertriglyceridemia disorders include the idiopathic hyperlipidemia of Miniature Schnauzers and the hyperchylomicronemia of cats. Idiopathic hyperlipidemia of Miniature Schnauzers is characterized by severe hypertriglyceridemia resulting from excessive VLDL particles with or without concurrent hyperchylomicronemia and hypercholesterolemia. Although the exact mechanism and genetics have not been fully elucidated, the problem progresses with age, and affected dogs have reduced activity of lipoprotein lipase but not hepatic lipase. Proteinuria is a common finding in these cases and may be due to lipid-induced injury to the glomerulus.

BOX 52.1

Causes of Hyperlipidemia in Dogs and Cats

Postprandial Hyperchylomicronemia

Primary hyperlipidemia

Idiopathic hyperlipoproteinemia (Miniature Schnauzers)
Idiopathic hyperchylomicronemia (cat)
Lipoprotein lipase deficiency (cat)
Idiopathic hypercholesterolemia

Secondary hyperlipidemia

Hypothyroidism
Diabetes mellitus
Hyperadrenocorticism
Pancreatitis
Cholestasis
Hepatic insufficiency
Nephrotic syndrome
Drug-induced hyperlipidemia
- Glucocorticoids
- Phenobarbital
- Megestrol acetate (cat)

Feline familial hyperlipidemia is characterized as a fasting hyperchylomicronemia with a slight increase in VLDL particles. The defect is due to the production of an inactive form of lipoprotein lipase resulting from a mutation in the genetic sequence such that a single amino acid is miscoded (Gly412Arg); inheritance is autosomal recessive. Idiopathic hyperchylomicronemia has also been observed in dogs. Similar to the situation with the cat, the disease in the dog is characterized by hypertriglyceridemia, hyperchylomicronemia, and normal serum cholesterol concentrations. Idiopathic hypercholesterolemia has been reported in Shetland Sheepdogs, Doberman Pinschers, and Rottweilers. Lipid derangements consist of hypercholesterolemia caused by an increased serum LDL concentration. The cause of this disorder is unknown.

Diseases commonly associated with secondary hyperlipidemia include endocrine disorders (hypothyroidism, diabetes mellitus, hyperadrenocorticism), nephrotic syndrome, and pancreatitis as well as obesity and some hepatic diseases. Some medications such as phenobarbital and glucocorticoids are also associated with hyperlipidemia. Hypothyroidism is the most common cause of hypercholesterolemia in the dog. Hyperlipidemia secondary to hypothyroidism can be attributed to both a decrease in lipid synthesis and degradation (lipid degradation is more severely affected). Decreased lipoprotein lipase activity contributes to impaired removal of triglyceride-rich lipoproteins. In addition, thyroid hormone deficiency reduces the biliary excretion of cholesterol. The resultant increase in intrahepatic cholesterol concentration

downregulates the hepatic LDL receptor, which increases the concentration of circulating LDL and HDL cholesterol–rich particles.

Insulin deficiency (diabetes mellitus) reduces the production of lipoprotein lipase, which contributes to decreased clearance of triglyceride-rich lipoproteins. Furthermore, insulin deficiency activates HSL, causing the release of large quantities of free fatty acids into the blood. These free fatty acids are ultimately converted by the liver into triglycerides, packaged into VLDL particles, and secreted back into the circulation. Therefore the hypertriglyceridemia seen with diabetes mellitus is attributed to both reduction of lipoprotein lipase and increased production and decreased clearance of VLDL particles. Insulin deficiency increases the synthesis of cholesterol in the liver. The increased intrahepatic cholesterol concentration downregulates the hepatocyte LDL receptor, consequently reducing the clearance of circulating LDL and HDL particles, which in turn causes hypercholesterolemia.

The mechanism of hypertriglyceridemia associated with hyperadrenocorticism is probably due to stimulation of HSL with release of free fatty acids into the circulation. Similar to the situation with diabetes mellitus, excess free fatty acids are converted into VLDL particles. In addition, glucocorticoids inhibit lipoprotein lipase activity, thereby reducing the clearance of triglyceride-rich lipoproteins.

Clinical Features

Waxing-and-waning vomiting, diarrhea, and abdominal discomfort are the most common clinical presentations associated with hypertriglyceridemia (Table 52.1). Severe hypertriglyceridemia (levels exceeding 1000 mg/dL) has been associated with insulin resistance, pancreatitis, lipemia retinalis, seizures, cutaneous xanthomas, peripheral nerve paralysis, and behavioral changes. Cutaneous xanthomas, which represent lipid-laden macrophages and foam cells, are the most common manifestation of hypertriglyceridemia in the cat. Severe hypercholesterolemia has been associated with arcus lipoides corneae, lipemia retinalis, and atherosclerosis (not severe enough to cause myocardial infarction).

In addition to the clinical manifestations, hypertriglyceridemia may interfere with the results of several routine biochemical tests (Table 52.2). The degree of interference depends on the specific assay used by the laboratory, the species (canine versus feline), and the severity of the hypertriglyceridemia. In addition, hyperlipidemia may cause hemolysis, which in turn can interfere with the results of some biochemical assays. Alternatively, hyperbilirubinemia may cause the cholesterol concentration to be falsely lower. These potential alterations in biochemical data must be considered when results of testing in animals with hyperlipidemia are interpreted. Fortunately, many laboratories will attempt to clear the hypertriglyceridemia by ultracentrifugation before performing biochemical assays.

TABLE 52.1

Clinical Signs and Potential Consequences of Hypertriglyceridemia and Hypercholesterolemia

HYPERTRIGLYCERIDEMIA CLINICAL SIGNS	HYPERTRIGLYCERIDEMIA CONSEQUENCES
Seizures	Seizures
Blindness	Pancreatitis
Abdominal pain	Lipid-laden aqueous humor: uveitis, blindness
Anorexia	Lipemia retinalis
Vomiting	Xanthomas
Diarrhea	
Behavioral changes	
Lipemia retinalis	
Uveitis	
HYPERCHOLESTEROLEMIA CLINICAL SIGNS	**HYPERCHOLESTEROLEMIA CONSEQUENCES**
Xanthoma formation	Corneal arcus lipoides
Peripheral neuropathy	Lipemia retinalis
Horner's syndrome	Atherosclerosis (not severe enough to cause fatal myocardial infarction)
Tibial nerve paralysis	
Radial nerve paralysis	

Diagnosis

The presence of grossly lipemic serum suggests that the animal is hypertriglyceridemic. *Lactescence* refers to the opaque, milk-like appearance of serum samples that occurs with sufficiently severe elevation of the triglyceride concentration. Animals with lactescent serum typically have triglyceride concentrations that exceed 1000 mg/dL; samples with a less opaque character than that of nonfat milk may correspond to elevated lipid content but visual inspection is not a reliable indicator of severity. Conversely, animals that are purely hypercholesterolemic do not exhibit lipemic or lactescent serum because the cholesterol-rich LDL and HDL particles are too small to refract light. Blood samples to confirm hyperlipidemia should be obtained after a fast of at least 12 hours. A serum sample rather than whole blood or plasma should be submitted for assessment. The sample can be refrigerated or frozen for several days with no effect on the assays. When assessing the sample for hypertriglyceridemia, the technician should not clear the sample before determining the triglyceride concentration. Clearing lipemic samples by centrifugation removes chylomicrons, and this will artificially lower the triglyceride result. Reference intervals for serum triglyceride concentration are typically 50 to 150 mg/dL for the adult dog and 20 to 110 mg/dL for the adult cat. Reference intervals for serum cholesterol concentration are typically 125 to 300 mg/dL for the adult dog and 95 to 130 mg/dL for the adult cat.

The chylomicron test can be helpful in delineating whether lipemia is predominantly a chylomicron or a VLDL defect. The test is performed by refrigerating a serum sample for 12 hours. Chylomicrons are less dense than the other particles and hence will float to the top of the sample to form an

TABLE 52.2

Effects of Lipemia on Clinical Chemistry Analytes in Canine and Feline Sera*

FALSE INCREASE IN VALUES		FALSE DECREASE IN VALUES	
CANINE SERA	**FELINE SERA**	**CANINE SERA**	**FELINE SERA**
Total bilirubin	Total bilirubin	Creatinine	Creatinine
Conjugated bilirubin	Conjugated bilirubin	Total CO_2	Total CO_2
Phosphorus	Phosphorus	Cholesterol	Alanine aminotransferase
Alkaline phosphatase†	Alkaline phosphatase†	Urea nitrogen	
Glucose†	Glucose†		
Total protein‡	Total protein‡		
Lipase			
Alanine aminotransferase			

*Analytes were measured using Coulter DACOS (Coulter Diagnostics, Hialeah, Fla).
†Interference occurs only at very high concentrations of lipid.
‡When measured using a refractometer.
Adapted from Jacobs RM et al: Effects of bilirubinemia, hemolysis and lipemia on clinical chemistry analytes in bovine, canine, equine and feline sera, *Can Vet J* 33:605, 1992.

opaque cream layer over a clear infranatant of serum. If hypertriglyceridemia is due to excess VLDL particles, the serum sample will remain turbid. Formation of a cream layer over a cloudy serum layer suggests excess chylomicrons and VLDL particles.

Lipoprotein electrophoresis can be used to distinguish the lipoproteins, and density gradient ultracentrifugation can provide a quantitative measurement of each of the lipoprotein classes. However, both of these procedures are time-consuming and are not routinely available for clinical application. The activity of lipoprotein lipase can be assessed by the heparin release test. Serum samples for determination of triglyceride concentrations (and, if possible, lipoprotein concentrations) are obtained before and 15 minutes after intravenous administration of heparin (100 IU/kg body weight in dogs and cats). Heparin causes the release of lipoprotein lipase from the endothelium and stimulates the hydrolysis of triglycerides. A defect in lipoprotein lipase is suspected if there is no difference between serum triglyceride concentrations before and after administration of heparin.

Treatment

Before therapy is recommended, every attempt should be made to determine whether the hyperlipidemia is primary or secondary to an underlying disease process or medication. Hyperlipidemia secondary to an underlying disorder will typically resolve or improve with correction of the metabolic disturbance. Therefore in addition to confirming fasting, each animal requires a full history, physical examination, complete blood count, serum biochemistry panel with thyroxine concentration, and urinalysis. Results of the initial diagnostic evaluation may indicate the need for additional diagnostic tests such as abdominal ultrasound, pancreatic lipase immunoreactivity assay, and low-dose dexamethasone suppression test. A recommendation to treat hyperlipidemia involves a lifelong commitment by the client and therefore must not be undertaken lightly. In general, severe hypertriglyceridemia (concentrations > 1000 mg/dL) mandates treatment. In this circumstance catabolic mechanisms can be assumed to be overwhelmed, and the triglyceride concentration is very sensitive to a small increase from the intestine or the liver. Triglyceride concentrations must be decreased to prevent possible complications, including pancreatitis. In other situations, recommendations will be influenced by additional variables, including the underlying disease process. A realistic goal of therapy is to reduce the triglyceride concentration to less than 400 mg/dL, even though such a level will still be above the reference interval.

Chylomicrons are produced from dietary fat. Therefore restriction of dietary fat relative to the current intake is the cornerstone of therapy for hypertriglyceridemia. A thorough dietary history should be reviewed, and the diet altered to one that accomplishes at least a 50% reduction in fat on a metabolizable energy (ME) basis. For dogs with moderate to severe hypertriglyceridemia, the goal is often a diet with less than 20% fat on a ME basis (Table 52.3) or lower if the patient is already on a lower-fat diet. Nutritional management of hypertriglyceridemia in cats is more difficult because of the limited availability of diets with less than 25% fat on an ME basis (Table 52.4). Care should be taken assessing fat content of pet foods. Because the guaranteed analysis reported on pet food labels requires only a minimum, rather than an average, crude fat percentage to be reported, the fat content may be significantly higher. In addition, the value is provided on an "as fed" basis, making comparisons among products challenging. This information is best converted to and expressed on a ME basis, either as a proportion of

TABLE 52.3

Key Nutrients Concentrations in Selected Veterinary Therapeutic Diets Used for the Management of Canine Hypertriglyceridemia*

		FAT (% ME)	PROTEIN (% ME)	ME (kcal/unit)
Royal Canin Veterinary Diet Canine Gastrointestinal Low Fat	Dry	17 (18.7 g/Mcal)	24 (63.3 g/Mcal)	240/cup
Royal Canin Veterinary Diet Canine Gastrointestinal Low Fat	Can	16 (18.1 g/Mcal)	29 (79.8g/Mcal)	345/13.6-oz can
Purina Pro Plan Veterinary Diets OM Overweight Management	Dry	18.9 (24.8 g/Mcal)	32.1 (102.9 g/Mcal)	266/cup
Purina Pro Plan Veterinary Diets OM Select Blend Overweight Management	Dry	17.6 (22.3 g/Mcal)	32.4 (99.6 g/Mcal)	235/cup
Hill's Prescription Diet i/d Low Fat Canine	Dry	17 (20 g/Mcal)	25 (71 g/Mcal)	333/cup
Hill's Prescription Diet i/d Low Fat Canine	Can	20 (23 g/Mcal)	24 (69 g/Mcal)	351/13-oz can

Mcal, Megacalories (1000 kcal); *ME,* metabolizable energy.
*Information obtained from manufacturer's product guides. Diets with 20% fat calories or less are listed.

TABLE 52.4

Key Nutrients Concentrations in Selected Veterinary Therapeutic Diets Used for the Management of Feline Hypertriglyceridemia*

		FAT (% ME)	PROTEIN (% ME)	ME (kcal/unit)
Royal Canin Veterinary Diet Feline Calorie Control	Dry	25 (26.2 g/Mcal)	43 (109.8 g/Mcal)	262/cup
Purina Pro Plan Veterinary Diets OM Overweight Management	Dry	20.9 (23.7 g/Mcal)	57.8 (159 g/Mcal)	321/cup
Hill's Prescription Diet w/d Feline	Dry	22 (26 g/Mcal)	41 (117 g/Mcal)	280/cup
Hill's Prescription Diet r/d Feline	Dry	23 (26 g/Mcal)	39 (107 g/Mcal)	265/cup
Hill's Prescription Diet r/d Feline	Can	24 (30 g/Mcal)	41 (123 g/Mcal)	114/5.5-oz can

Mcal, Megacalories (1000 kcal); *ME,* metabolizable energy.
*Information obtained from manufacturer's product guides. Foods with 25% fat calories or less are listed.

calories or as grams per 1000 kcal. The nutrient profiles of veterinary therapeutic foods are typically provided in product guides, and values are expressed as averages and on a ME basis, which more accurately reflects the actual fat content of the food.

Any treats or other foods used, including those needed to administer medications, should also be restricted in fat, and should contribute no more than 10% of the daily caloric intake. Fruit (other than grapes and raisins), vegetables, or some cereals and cracker snacks without seasoning are useful options. Regardless of the inclusion of treats, absolute caloric intake should be evaluated. If the animal is overweight, caloric restriction is indicated and beneficial because it decreases the production of VLDL particles from excess dietary energy. The plasma triglyceride concentration should be reevaluated after 6 to 8 weeks of a lower-fat diet. If the reduction in triglyceride concentration is less than ideal, the dietary history should be reevaluated to ensure compliance with diet and treats, no access to other pet foods, and no additional family members or neighbors who are inadvertently providing the animal with a source of dietary fat. In addition, the medical record should be reviewed to ensure the exclusion of underlying disorders that may contribute to hypertriglyceridemia. If lower-fat commercial foods are not sufficient to control hypertriglyceridemia, a complete and balanced fat-restricted (10%-14% ME for dogs, 15%-19% ME for cats) home-prepared recipe can be formulated specifically for the animal using online software (such as at balanceit.com) or with the help of a board-certified veterinary nutritionist (see www.acvn.org, or www.esvcn.eu/college).

Supplementation with omega-3 fatty acids have been suggested to improve hypertriglyceridemia in humans by decreasing the production of VLDL particles. In addition, fish oils are poor substrates for triglyceride-synthesizing enzymes, and their use leads to the formation of triglyceride-poor VLDL particles. Some clinicians have recommended the use of long-chain omega-3 fatty acids (i.e., eicosapentaenoic

acid [EPA] and docosahexaenoic acid [DHA]) in the amount of 200 to 220 mg/kg body weight/day to assist in the management of hypertriglyceridemia, especially in dogs refractory or incompletely responsive to dietary fat restriction. The efficacy is questionable in severe cases, and overall dietary fat restriction remains the priority.

Treatment with medications, all of which have the potential for toxicity, should be undertaken with particular care. In general, drugs should not be used in animals whose serum triglyceride concentration is less than 500 mg/dL. Several classes of drugs are used to treat hypertriglyceridemia in humans including statins; however, few reports have described their use in cats and dogs. Until further studies have evaluated dose, effect, and toxicity, drug therapy is indicated only in animals that have clinical signs associated with severe elevations in triglyceride concentrations that cannot be ameliorated by dietary therapy.

Niacin (100 mg/day in dogs) reduces serum triglyceride concentration by decreasing fatty acid release from adipocytes and reducing the production of VLDL particles. Adverse effects are frequent, mainly because of the associated release of the prostaglandin prostacyclin, and include vomiting, diarrhea, erythema, pruritus, and abnormalities in liver function test results. In addition, niacin has been shown to positively impact hyperlipidemia in only a small number of dogs; larger clinical trials are lacking.

Fibric acid derivatives (clofibrate, bezafibrate, gemfibrozil, ciprofibrate, fenofibrate) lower plasma triglyceride concentrations by stimulating lipoprotein lipase activity, in addition to reducing the free fatty acid concentration, which decreases the substrate for VLDL synthesis. In humans the fibrates generally lower plasma triglyceride concentrations by 20% to 40%. Gemfibrozil has been used in the dog and cat (10 mg/kg q12h), and bezafibrate has been used in the dog (4-10 mg/kg/day). Reported adverse effects in humans include abdominal pain, vomiting, diarrhea, and abnormal liver function test results. A recent study in dogs demonstrated that bezafibrate was effective in hypertriglyceridemic dogs, although ALT activity decreased over time; other adverse effects were not reported.

The statins (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin) are hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors and therefore primarily suppress cholesterol metabolism. As a consequence of lower intracellular cholesterol concentrations, the hepatic LDL receptor is upregulated, thereby increasing the removal and clearance of LDL (VLDL remnant particles) from the circulation. In addition, the statins decrease hepatic production of VLDL. In humans, the statins can lower triglyceride concentrations by 10% to 15%. Adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity. These are not commonly used, and clinical experience in dogs and cats is limited.

Chitosan has been explored as an option for controlling hyperlipidemia secondary by reducing absorption of lipids and bile salts in the intestinal lumen. It appears to be effective in lowering serum lipid concentrations in rodent models and in people. One study described positive effects of chitosan in cats with hyperlipidemia not exceeding 300 mg/dL, which was induced by feeding cholesterol orally; however, there are no studies reported in cats with naturally occurring hyperlipidemia, or in any dogs.

Hypercholesterolemia is most likely associated with the presence of an underlying disease and generally resolves with control of the altered metabolic state. Unlike the situation with humans, hypercholesterolemia is rarely a significant health concern in dog or the cat as they are at lower risk of atherosclerosis. Specific therapy is indicated only for those animals with a prolonged marked increase in the serum cholesterol concentration (i.e., >800 mg/dL) that may be associated with the development of atherosclerosis, which is typically secondary to endocrinopathy. Nutritional therapy with a diet lower in fat compared with the current and historical intake is the initial treatment of choice for severe hypercholesterolemia. The addition of soluble fiber to the diet may also help to reduce plasma cholesterol concentrations by as much as 10%, because it interferes with the enteric reabsorption of bile acids. Consequently, the fecal excretion of cholesterol increases and the liver uses intrahepatic cholesterol to increase the synthesis of bile acids.

Pharmacologic agents that can be considered for the management of severe hypercholesterolemia include bile acid sequestrates, HMG-CoA reductase inhibitors, and probucol. Bile acid sequestrates are ion exchange resins that interrupt the enterohepatic circulation of bile acids. Decreased reabsorption of bile acids stimulates the liver to synthesize bile acids, thereby reducing intrahepatic cholesterol stores. Depletion of intrahepatic cholesterol stores stimulates the hepatic LDL receptor to increase the removal of LDL and HDL particles from the circulation. Cholestyramine (1-2 g, administered orally q12h) is effective for lowering cholesterol concentrations; however, its use has been associated with constipation, it interferes with the absorption of several oral medications, and it may increase hepatic VLDL synthesis, resulting in an increase in plasma triglyceride concentrations. It may also increase the dietary requirement for sulfur amino acids because they serve as precursors for taurine synthesis in the dog, which conjugates bile acids exclusively with taurine. In cats the requirement for dietary taurine may be similarly increased. HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis. The HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, and atorvastatin) are the most potent cholesterol-lowering agents, and in humans may reduce cholesterol concentrations by 20% to 40%. Lovastatin (10-20 mg, administered orally q24h) may be tried in dogs with persistent, severe idiopathic hypercholesterolemia that does not respond to diet alone. Potential adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity. Lovastatin should not be administered to dogs with hepatic disease. Probucol is a cholesterol-lowering agent whose mechanism of action is not completely clear. Probucol is no longer recommended for the management of hypercholesterolemia because its effect on lowering cholesterol

concentrations is variable and it has been associated with the development of arrhythmias. As of 1995, it was withdrawn from the market in the United States.

Suggested Readings

Barrie J, et al. Quantitative analysis of canine plasma lipoproteins. *J Small Anim Pract*. 1993;34:226.

Bauer JE. Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. *J Am Vet Med Assoc*. 1995;206:1684.

Bhatnagar D. Lipid-lowering drugs in the management of hyperlipidaemia. *Pharmacol Ther*. 1998;79:205.

De Marco V, et al. Therapy of canine hyperlipidemia with bezafibrate. *J Vet Intern Med*. 2017;[Epub ahead of print].

Furrow E, et al. Proteinuria and lipoprotein lipase activity in Miniature Schnauzer dogs with and without hypertriglyceridemia. *Vet J*. 2016;212:83.

Jacobs RM, et al. Effects of bilirubinemia, hemolysis, and lipemia on clinical chemistry analytes in bovine, canine, equine, and feline sera. *Can Vet J*. 1992;33:605.

Jones BR. Inherited hyperchylomicronaemia in the cat. *J Small Anim Pract*. 1993;34:493.

Jones BR, et al. Peripheral neuropathy in cats with inherited primary hyperchylomicronaemia. *Vet Rec*. 1986;119:268.

Watson TDG, et al. Lipoprotein metabolism and hyperlipidaemia in the dog and cat: a review. *J Small Anim Pract*. 1993;34:479.

Whitney MS, et al. Ultracentrifugal and electrophoretic characteristics of the plasma lipoproteins of miniature schnauzer dogs with idiopathic hyperlipoproteinemia. *J Vet Intern Med*. 1996;7:253.

Xenoulis PG, Steiner JM. Canine hyperlipidemia. *J Small Anim Pract*. 2015;56:595.

CHAPTER 53

Electrolyte Imbalances



HYPERNATREMIA

Etiology

Hypernatremia exists if the serum sodium concentration exceeds the reference interval, which may vary between laboratories (in general >160 mEq/L). It most commonly develops after water loss exceeds sodium loss (Box 53.1). The water loss may be pure (i.e., not accompanied by loss of electrolytes, such as that which occurs with diabetes insipidus), or it may be hypotonic (i.e., loss of both water and sodium but with the water loss predominating, such as that which occurs with gastrointestinal fluid loss and chronic kidney disease). Insufficient water intake and an abnormal thirst mechanism are usually facets of an excessive water loss. Rarely, hypernatremia may occur in animals with hypodipsia caused by neurologic disease, an abnormal thirst mechanism, or defective osmoregulation of vasopressin release.

Less commonly, hypernatremia develops after sodium retention, such as that which occurs with iatrogenic sodium overload or primary hyperaldosteronism. Primary hyperaldosteronism is caused by an aldosterone-secreting adrenal tumor or idiopathic bilateral adrenal hyperplasia but is uncommon in dogs and cats. Increased serum aldosterone concentrations cause variable hypernatremia, hypokalemia, and systemic hypertension.

Clinical Features

Clinical signs of hypernatremia originate in the central nervous system (CNS) and include lethargy, weakness, muscle fasciculations, disorientation, behavioral changes, ataxia, seizures, stupor, and coma. Clinical signs typically become apparent when the plasma osmolality exceeds 350 mOsm/kg (serum sodium concentration >170 mEq/L). Clinical signs are caused by neuronal dehydration. Hypernatremia and hyperosmolality cause fluid to shift from the intracellular to the extracellular space. As the brain shrinks, meningeal vessels are damaged and torn, causing hemorrhage, hematoma, venous thrombosis, infarction of cerebral vessels, and ischemia. This gradient flow of water from the intracellular to the extracellular compartment often maintains adequate skin turgor and gives a false impression of hydration, even though the animal has experienced a detrimental loss of fluid.

The severity of clinical signs is related to the absolute increase in serum sodium concentration and especially to the rapidity of onset of hypernatremia and hyperosmolality. Clinical signs usually do not develop until the serum sodium concentration approaches 170 mEq/L. If hypernatremia is rapid in onset, clinical signs may develop at a lower sodium concentration and vice versa. With a gradual increase in the serum sodium concentration, the cells in the CNS can adapt by producing osmotically active solutes (idiogenic osmoles) intracellularly within a few hours of cell shrinkage to reestablish osmotic equilibration between extracellular and intracellular compartments, thereby minimizing cell shrinkage.

Diagnosis

Measurement of the serum sodium concentration identifies hypernatremia. After it has been identified, the underlying cause should be sought. Careful evaluation of the history, physical examination findings, and results of complete blood count (CBC), serum biochemistry panel, and urinalysis usually yield clues to the cause. Evaluation of the urine specific gravity is especially helpful. Hypernatremia and hyperosmolality stimulate the release of vasopressin, resulting in hypersthenuria. A urine specific gravity of less than 1.008 in a dog or cat with hypernatremia is consistent with central or nephrogenic diabetes insipidus. A urine specific gravity greater than 1.030 in a dog and 1.035 in a cat implies a normal vasopressin–renal tubular axis and indicates the existence of sodium retention, primary hypodipsia-adipsia, or gastrointestinal or insensible water loss. A urine specific gravity of between 1.008 and 1.030 (dog) or 1.035 (cat) indicates the presence of partial vasopressin deficiency or impaired renal tubular response to vasopressin, most likely secondary to a primary kidney disorder.

Treatment

The goals in treating patients with hypernatremia are to restore the extracellular fluid (ECF) volume to normal, to

BOX 53.1

Causes of Hypernatremia in Dogs and Cats

Caused by Pure Water Loss

Central diabetes insipidus*
Nephrogenic diabetes insipidus*
Hypodipsia-adipsia
- Neurologic disease
- Abnormal thirst mechanism
- Defective osmoregulation of vasopressin release

Inadequate access to water
High environmental temperature (heatstroke)
Fever

Hypotonic Fluid Loss

Gastrointestinal fluid loss*
- Vomiting
- Diarrhea

Chronic kidney disease*
Polyuric acute kidney injury*
Osmotic diuresis
- Diabetes mellitus
- Mannitol infusion

Diuretic administration
Postobstructive diuresis
Cutaneous burns
Third-space loss
- Pancreatitis
- Peritonitis

Excess Sodium Retention

Primary hyperaldosteronism
Iatrogenic causes
- Salt poisoning
- Hypertonic saline infusion
- Sodium bicarbonate therapy
- Sodium phosphate enemas
- Parenteral nutrition

*Common causes.
Modified from DiBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid, electrolyte and acid-base disorders in small animal practice*, ed 4, St Louis, 2012, Saunders Elsevier.

correct water deficits at a fluid rate that avoids significant complications, and to identify and correct the underlying cause of the hypernatremia. The initial priority is to restore ECF volume to normal. Hypernatremic animals should be resuscitated with a balanced electrolyte solution with NaCl added to the suspension to bring the solution's sodium content up to that of the animal (±6 mEq/L). To achieve this, 23.4% NaCl can be added to the fluid solution; it contains 4 mEq NaCl/mL of solution. In deficit replacement, rapid administration of fluids is contraindicated unless signs of significant hypovolemia are noted. Any fluid should be administered cautiously at a volume only large enough to correct hypovolemia. In animals with mild to moderate hypernatremia ($[Na^+]$ <180 mEq/L), sodium should be decreased at a rate of 1 mEq/L/h. With severe hypernatremia (Na >180), sodium should be corrected at a rate of 0.5 to 1 mEq/L/h. Multiple fluid solutions can be used to successfully decrease sodium safely (Table 53.1). In the presence of hemorrhagic shock, whole blood, plasma, or a colloid suspension is the ideal fluid to administer. Serum sodium concentration should be measured frequently (q4-6h) to assess response to treatment, and the status of the CNS should be evaluated frequently to observe for changes in clinical signs. Worsening neurologic status or sudden onset of seizures during fluid therapy is generally indicative of cerebral edema and the need for hypertonic saline solution or mannitol therapy (see Drugs Used in Metabolic and Electrolyte Disorders, p. 934). Once ECF deficits have been replaced, the serum sodium concentration should be reevaluated and water deficits corrected if hypernatremia persists. An approximation of the free water deficit in liters may be calculated using the following formula:

$$(\text{current}[Na^+] \div \text{normal}[Na^+] - 1) \times (0.6 \times \text{bodyweight in kg})^2$$

Because the brain adjusts to hypertonicity by increasing the intracellular solute content via the accumulation of "idiogenic osmoles," the rapid repletion of body water with ECF dilution causes translocation of water into cells and may cause cerebral edema. If slower water repletion is undertaken, brain cells lose the accumulated intracellular solutes, and osmotic equilibration can occur without cell swelling.

Maintenance crystalloid solutions (e.g., half-strength [0.45%] saline solution with 2.5% dextrose, half-strength lactated Ringer's solution with 2.5% dextrose) or 5% dextrose in water can be used to correct the water deficit in hypernatremic animals with normal perfusion and hydration, and can also be used in dehydrated animals with persistent hypernatremia after fluid deficits have been corrected.

Oral fluid administration is preferable for correcting water deficits, and fluid is administered through an intravenous (IV) route if oral administration is not possible. The water deficit should be replaced slowly. Approximately 50% of the water deficit should be corrected in the first 24 hours, and the remainder corrected over the following 24 to 48 hours. The serum sodium concentration should decline slowly, preferably at a rate of 0.5 to 1 mEq/L/h. The rate of fluid administration should be adjusted as needed to ensure an appropriate decrease in the serum sodium concentration. A gradual reduction in the serum sodium concentration minimizes the fluid shift from the extracellular to the intracellular compartment, thereby minimizing neuronal cell swelling and cerebral edema and increasing intracranial pressure. Deterioration in CNS status after the start of fluid therapy indicates the presence of cerebral edema and the immediate need to reduce the rate of fluid administration. Frequent monitoring of serum electrolyte concentrations, with appropriate adjustments in the type of fluid administered and the rate of fluid

TABLE 53.1

Parenteral Fluid Solutions

SOLUTION	ELECTROLYTE CONCENTRATION (mEq/L) Na	K	Cl	BUFFER (mEq/L)	OSMOLALITY (mOsm/L)	CALORIES (kcal/L)
Electrolyte Replacement Solutions						
Lactated Ringer's	130	4	109	Lactate 28	273	9
Ringer's	147	4	156	—	310	—
Normal saline	154	—	154	—	308	—
Normosol R	140	5	98	Acetate 27	296	18
Plasmalyte 148*	140	5	98	Acetate 27	295	—
Maintenance Solutions						
2½ Dextrose/0.45% saline	77	—	77	—	203	85
2½ Dextrose/½ strength LRS	65	2	55	Lactate 14	265	89
Normosol M*	40	13	40	Acetate 16	112	—
Normosol M in 5% dextrose*	40	13	40	Acetate 16	364	175
Plasmalyte 56*	40	13	40	Acetate 16	110	—
Colloidal Solutions						
Dextran 70 (6% w/v in 0.9% saline)	154	—	154	—	310	—
Hetastarch /Hespan 6% 670/0.75	154	—	154	—	310	—
Hextend 6% 670/0.75	143	3	124	Lactate 28	307	9
Vetstarch 6% 130/0.4	154	—	154	—	308	
Plasma (average values, dog)	145	4	105	24	300	—
Other						
5% Dextrose in water	—	—	—	—	252	170

Cl, Chloride; *K,* potassium; *LRS,* lactated Ringer's solution; *Na,* sodium.
*Contains magnesium 3 mEq/L.
Modified from DiBartola SP, Bateman S: Introduction to fluid therapy. In DiBartola SP, editor: *Fluid, electrolyte and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Saunders Elsevier.

administration, is important in the successful management of hypernatremia.

On rare occasions, a hypernatremic animal presents with an increase in ECF volume. Such animals are difficult to treat. The goal is to lower the serum sodium concentration without exacerbating an increase in ECF volume and causing pulmonary congestion and edema. To slowly correct hypernatremia in these animals, the clinician should administer loop diuretics (e.g., furosemide, 1-2 mg/kg orally or intravenously q8-12h) to promote sodium loss in the urine; this is done in conjunction with the judicious administration of D_5W.

HYPONATREMIA

Etiology

Hyponatremia is present if the serum sodium concentration is less than the reference interval (145 mEq/L, although reference ranges may vary between laboratories). It can result from excessive sodium loss, primarily through the kidney, or from increased water conservation, or both. The latter condition may be an appropriate response to a reduction in ECF volume or may be inappropriate (e.g., syndrome of inappropriate antidiuretic hormone secretion [SIADH]). In most cases hyponatremia results from abnormalities in water

balance (principally a defect in renal water excretion) rather than from abnormalities in sodium balance. Causes of hyponatremia in dogs and cats are listed in Box 53.2.

Hyponatremia must be differentiated from pseudohyponatremia, which is a decrease in the serum sodium concentration that results from laboratory methods used in the presence of normal plasma osmolality. Pseudohyponatremia occurs in the presence of hyperlipidemia or severe hyperproteinemia. An increase in the concentration of triglycerides or proteins in plasma reduces the sodium concentration in the total plasma volume, but the sodium concentration in plasma water remains the same. Methods that measure the amount of sodium in a specific volume of plasma (e.g., flame photometry) result in falsely low sodium values, whereas methods that determine the sodium concentration in the aqueous phase of plasma (e.g., direct potentiometry using ion-specific electrodes) yield an accurate sodium value. Pseudohyponatremia can usually be identified if the method used to measure the sodium concentration is known, a blood sample is examined for the presence of gross lipemia, and a CBC and a serum biochemistry panel are performed.

Hyponatremia may also occur after the concentration of osmotically active solutes (e.g., glucose, mannitol) in the ECF is increased. An increase in the concentration of osmotically active solutes in the ECF causes a fluid shift from the intracellular to the extracellular compartment and a corresponding decrease in the serum sodium concentration. For example, the serum sodium concentration decreases by approximately 1.6 mEq/L for every 100-mg/dL increase in serum glucose concentration, and this decrease may become more severe when the blood glucose concentration exceeds 500 mg/dL. Estimation of the plasma osmolality is helpful in differentiating the cause of hyponatremia. Hyponatremia is usually associated with hypo-osmolality (<290 mOsm/kg), whereas pseudohyponatremia is associated with normal plasma osmolality, and hyponatremia caused by an increase in osmotically active solutes in the ECF is associated with hyperosmolality. Plasma osmolality can be estimated using the following formula:

$$\text{Plasma osmolality (mOsm/kg)} = (2 \times \text{Na [mEq/L]}) + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{Ureanitrogen (mg/dL)}}{2.8}$$

Normal plasma osmolality in dogs and cats is approximately 280 to 310 mOsm/kg.

BOX 53.2

Causes of Hyponatremia in Dogs and Cats

With Normal Plasma Osmolality

Hyperlipidemia
Hyperproteinemia

With High Plasma Osmolality

Hyperglycemia*
Mannitol infusion
Severe azotemia

With Low Plasma Osmolality

And hypervolemia
- Advanced liver failure*
- Advanced chronic kidney disease*
- Nephrotic syndrome*
- Congestive heart failure
- Accidental water injection or ingestion (water intoxication)

And normovolemia
- Primary (psychogenic) polydipsia
- Inappropriate antidiuretic hormone (ADH) secretion (SIADH)
- Myxedema coma of hypothyroidism
- Iatrogenic causes
  - Hypotonic fluid administration
  - Antidiuretic drugs (e.g., barbiturates, β-adrenergics)

And hypovolemia
- Hypoadrenocorticism*
- Gastrointestinal fluid loss*
- Third-space loss
  - Pleural effusions (e.g., chylothorax)
  - Peritoneal effusions
  - Pancreatitis
- Cutaneous burns
- Diuretic administration
- Salt losing nephropathy
- Cerebral salt wasting syndrome
- Shock
- Renal insufficiency

*Common causes.
Modified from DiBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Saunders/Elsevier.

Clinical Features

Clinical signs of hyponatremia include lethargy, anorexia, vomiting, weakness, muscle fasciculations, obtundation, disorientation, seizures, and coma. CNS signs are the most concerning, occur when hyponatremia is severe (<120 mEq/L), and develop as changes in plasma osmolality cause fluid to shift from the extracellular to the intracellular space, resulting in neuronal swelling and lysis. The onset and severity of clinical signs depend on the rapidity with which hyponatremia develops as well as on the degree of hyponatremia. The more chronic the hyponatremia and the more slowly it develops, the more capable the brain is of compensating for changes in osmolality through the loss of potassium and organic osmolytes from cells. Clinical signs develop when the decrease in plasma osmolality occurs faster than the brain's defense mechanisms can counter the influx of water into the neurons.

Diagnosis

Hyponatremia is readily evident from measurement of serum electrolyte concentrations. However, hyponatremia

must be differentiated from pseudohyponatremia (discussed in a previous section). Hyponatremia is not a diagnosis per se but rather a manifestation of an underlying disorder. As such, a diagnostic evaluation to identify the cause, as well as appropriate therapy to correct the hyponatremia, should be initiated. In most dogs and cats the cause of hyponatremia is readily apparent after evaluation of the history, physical examination findings, CBC, serum biochemistry panel, and urinalysis findings, but further diagnostic tests may be necessary. Careful assessment of urine specific gravity and plasma osmolality and of the hydration status of the animal will help to localize the problem (see Box 53.2).

Treatment

The goals of therapy are to treat the underlying disease and, if necessary, to increase serum sodium concentration and plasma osmolality. The goals of treatment directed at the hyponatremia are to correct body water osmolality and restore cell volume to normal by raising the ratio of sodium to water in ECF using IV fluid therapy, water restriction, or both. The increase in ECF osmolality draws water from cells, thereby reducing their volume. The approach to treatment and the type of fluid used depend on the underlying cause, the severity of the hyponatremia, and the presence or absence of clinical signs (see Table 53.1). Chronic hyponatremia in an asymptomatic animal is best treated conservatively. Lactated Ringer's or Ringer's solution can be used for mild hyponatremia (serum sodium concentration >130 mEq/L) and physiologic saline solution for more severe hyponatremia (serum sodium concentration <130 mEq/L). Physiologic saline solution is typically used in symptomatic animals with severe hyponatremia.

Fluid and electrolyte balance should gradually be restored over 24 to 48 hours, with periodic assessment of serum electrolyte concentrations and the patient's CNS status. The general goal is to increase the serum sodium concentration slowly toward the lower end of the reference range at a rate no greater than 0.5 to 1.0 mEq/L/h. The more acute and severe the hyponatremia, the more slowly the serum sodium concentration should be corrected. A rapid increase in the serum sodium concentration to levels greater than 125 mEq/L is potentially dangerous and should be avoided in animals with acute, severe hyponatremia (serum sodium concentration <120 mEq/L) and neurologic signs. For these animals, the serum sodium concentration should be gradually increased to 125 mEq/L or higher over 6 to 8 hours. Because loss of brain solute represents one of the compensatory mechanisms for preserving brain cell volume during dilutional states, an increase in serum sodium concentration toward normal is relatively hypertonic to brain cells that are partially depleted of solute as a result of hyponatremia. Consequently, raising the serum sodium concentration rapidly to greater than 125 mEq/L can cause CNS damage.

The major complication of treatment of hyponatremia is myelinosis, which results from neuronal shrinkage away from the myelin sheath as water moves out of the neuron during correction of hyponatremia. Clinical signs include paresis, ataxia, dysphagia, and obtundation and often do not manifest until several days after treatment of hyponatremia. The prognosis for recovery is guarded.

HYPERKALEMIA

Etiology

Hyperkalemia is present if the serum potassium concentration exceeds 5.5 mEq/L (although reference ranges may vary between laboratories) and is considered severe and potentially life-threatening when it exceeds 7.5 mEq/L. Hyperkalemia can develop after increased potassium intake (uncommon) or translocation of potassium from the intracellular to the extracellular space (uncommon), or as a result of impaired potassium excretion in the urine (common; Box 53.3). Impaired urinary excretion of potassium is usually caused by chronic kidney disease or hypoadrenocorticism. Iatrogenically induced hyperkalemia is also common in dogs and cats, typically resulting from excessive IV administration of potassium-containing fluids. Generally the IV rate of potassium administration should not exceed 0.5 mEq/kg body weight per hour. Pseudohyperkalemia refers to an increase in potassium in vitro and can occur in the setting of severe hypernatremia (if dry reagent methods are used), leukocytosis (white blood cell count >100,000/μL), or thrombocytosis (>1 × 10^6/μL), and in the setting of hemolysis in Akitas (and possibly Shiba Inus and Kindos) and in English Springer Spaniels with phosphofructokinase deficiency. Collection of blood in heparinized tubes rather than in clot tubes and prompt separation of plasma from cells help to prevent pseudohyperkalemia. Obtaining blood from fluid lines or catheters contaminated with potassium-containing fluids may yield falsely increased potassium concentrations.

Clinical Features

The clinical manifestations of hyperkalemia reflect changes in cell membrane excitability and the magnitude and rapidity of onset of hyperkalemia. Mild to moderate hyperkalemia (serum potassium concentration <6.5 mEq/L) is typically asymptomatic. Generalized skeletal muscle weakness develops as the hyperkalemia worsens. Weakness occurs after a hyperkalemia-induced decrease in resting cell membrane potential to the level of the threshold potential, thereby impairing repolarization and subsequent cell excitation. The most prominent manifestations of hyperkalemia are cardiac in nature. Hyperkalemia causes decreased myocardial excitability, an increased myocardial refractory period, and slowed conduction—effects that may cause potentially life-threatening cardiac rhythm disturbances (Box 53.4).

Diagnosis

Measurement of serum potassium concentration or evaluation of an electrocardiogram (ECG) can identify hyperkalemia. Once it has been identified, a careful review of the history, physical findings, CBC, serum biochemistry panel, and urinalysis usually yields clues to the cause. The most

BOX 53.3

Causes of Hyperkalemia in Dogs and Cats

Transcellular Shifts (ICF to ECF)

Metabolic and respiratory acidosis
Insulin deficiency—DKA
Acute tumor lysis syndrome
Reperfusion post–thrombus dissolution
Crush injuries

Decreased Urinary Excretion

Hypoadrenocorticism*
Acute oliguric-anuric kidney disease*
End-stage chronic kidney disease
Urethral obstruction*
Ruptured bladder—uroabdomen*
Selected gastroenteritis (e.g., trichuriasis, salmonellosis)
Chylothorax with repeated pleural fluid drainage
Hyporeninemic hypoaldosteronism

Iatrogenic Causes†

Excessive administration of potassium-containing fluids*
Expired RBC transfusion
Potassium-sparing diuretics (e.g., spironolactone)
Angiotensin-converting enzyme inhibitors (e.g., enalapril)
Angiotensin-receptor blockers (e.g., losartan)
β-Blockers (e.g., propranolol)
Cardiac glycosides (e.g., digitalis)
Prostaglandin inhibitors (e.g., indomethacin)
α-Adrenergic agonists (e.g., phenylpropanolamine)
Cyclosporine
Heparin
Nonsteroidal antiinflammatory drugs

Pseudohyperkalemia

Hemolysis (Akita)
Thrombocytosis (>10^6/μL)
Leukocytosis (>10^5/μL)
Hypernatremia (dry reagent methods)

DKA, Diabetic ketoacidosis; *ECF,* extracellular fluid; *ICF,* intracellular fluid.
*Common causes.
†Require contributing factors to cause hyperkalemia.
Modified from DiBartola SP, Autran de Morais H: Disorders of potassium: hypokalemia and hyperkalemia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Saunders Elsevier.

BOX 53.4

Electrocardiographic Alterations Associated With Hyperkalemia and Hypokalemia in Dogs and Cats

Hyperkalemia

Serum potassium: 5.6-6.5 mEq/L
- Bradycardia
- Tall, narrow T waves

Serum potassium: 6.6-7.5 mEq/L
- Decreased R-wave amplitude
- Prolonged QRS interval

Serum potassium: 7.0-8.5 mEq/L
- Decreased P-wave amplitude
- Prolonged P-R interval

Serum potassium: >8.5 mEq/L
- Invisible P wave
- Deviation of ST segment
- Complete heart block
- Ventricular arrhythmias
- Cardiac arrest

Hypokalemia

Depressed T-wave amplitude
Depressed ST segment
Prolonged QT interval
Prominent U wave
Arrhythmias
- Supraventricular
- Ventricular

common causes of hyperkalemia in the dog and cat are iatrogenic, most notably excessive potassium administration in IV fluids; renal dysfunction, especially acute oliguric-anuric kidney disease, urethral obstruction (tomcats), and rupture within the urinary system leading to uroabdomen; and hypoadrenocorticism. It can be a diagnostic challenge to differentiate renal dysfunction from hypoadrenocorticism because both disorders can result in a similar clinical picture. A baseline serum cortisol concentration can be used to rule out hypoadrenocorticism, but an adrenocorticotropic hormone (ACTH) stimulation test is needed to confirm hypoadrenocorticism when the baseline cortisol concentration is less than 2 μg/dL (55 nmol/L). Small rents in the urinary bladder can be difficult to identify, and contrast-enhanced diagnostic imaging studies (i.e., radiographic, computed tomography [CT], magnetic resonance imaging [MRI]) or surgical exploration is frequently necessary to confirm their presence.

Treatment

For most animals, therapy for hyperkalemia is directed at treating the underlying cause. Symptomatic therapy for hyperkalemia should be initiated if the serum potassium concentration is greater than 7 mEq/L, or if pronounced cardiac toxicity (i.e., complete heart block, premature ventricular contractions, arrhythmias) is identified on an ECG (Table 53.2). Rapid institution of therapy in animals with marked hyperkalemia could mean the difference between

TABLE 53.2

Treatment Options for Hyperkalemia in the Dog and Cat

TREATMENT	DOSAGE	ROUTE OF ADMINISTRATION	DURATION OF EFFECT
Physiologic saline	≥60-100 mL/kg/day	IV	Hours
Dextrose	5%-10% in IV fluids *or* 1-2 mL of 50% dextrose/kg	IV, continuous IV, slow bolus	Hours Hours
Regular insulin and dextrose	0.5-1 U/kg in parenteral fluids plus 2 g dextrose/U insulin administered	IV IV	Hours Monitor blood glucose
Sodium bicarbonate	1-2 mEq/kg	IV, slow bolus	Hours
10% Calcium gluconate	0.5 mL/kg to 1.5 mL/kg over 5-10 minutes with ECG monitoring	IV, slow bolus	30-60 minutes Monitor heart
β_2 adrenergic agonist	Terbutaline 0.01 mg/kg	IV slowly	2 hours

IV, Intravenous.

life and death. The goals of symptomatic therapy are to reverse the cardiotoxic effects of hyperkalemia and, if possible, to reestablish normokalemia. Asymptomatic animals with normal urine output and chronic hyperkalemia (<7 mEq/L) may not require immediate treatment, but a search for the underlying cause should be initiated.

IV fluid administration in amounts designed to correct fluid deficits and to cause volume expansion rehydrates the animal, improves renal perfusion and potassium excretion, and dilutes the blood potassium concentration. Physiologic saline solution is the fluid of choice for this purpose. Potassium-containing fluids (e.g., lactated Ringer's solution) can be used if physiologic saline solution is not available because the low potassium concentration in these fluids (see Table 53.1) in relation to that in blood will still have a dilutional effect on the blood potassium concentration. Dextrose can be added to the fluids to make a 5% to 10% dextrose-containing solution, or 1 to 2 mL/kg of 50% dextrose can be administered by slow IV bolus. Dextrose stimulates insulin secretion, which in turn promotes the movement of glucose and potassium from the extracellular to the intracellular space. Fluids containing more than 5% dextrose should be given into a central vein to minimize the risk of phlebitis.

Rarely, additional therapy may be required to block the cardiotoxic effects of hyperkalemia (see Table 53.2). Sodium bicarbonate and regular insulin given with dextrose act to shift potassium from the extracellular to the intracellular space. IV calcium infusions block the effects of hyperkalemia on cell membranes but do not lower the blood potassium concentration. β_2 adrenergic agonists (e.g., albuterol, terbutaline) can be administered as an adjunct treatment, driving potassium intracellularly by increasing sodium and potassium adenosine triphosphatase (ATPase) activity. These therapies constitute aggressive, short-term, life-saving measures that can reestablish normal cardiac conduction until more conventional therapy (i.e., IV fluids) has the time to become effective.

For more chronic, mild to moderate hyperkalemia due to kidney disease, especially those with proteinuria and/or on ACE inhibitors, a potassium-restricted homemade diet can be effective in controlling serum potassium concentrations. In these cases, consultation with a board-certified veterinary nutritionist should be pursued to ensure a balanced and appropriate diet (see www.acvn.org or www.esvcn.eu/college).

HYPOKALEMIA

Etiology

Hypokalemia is present when the serum potassium concentration is less than 3.5 mEq/L, although reference ranges may vary between laboratories. Hypokalemia can develop after decreased dietary potassium intake (uncommon), translocation of potassium from the ECF to the intracellular fluid (common), or increased potassium loss in urine or gastrointestinal secretions (common; Box 53.5). Iatrogenic hypokalemia is also common in dogs and cats. Pseudohypokalemia is uncommon and depends on the method used to measure the serum potassium concentration. Hyperlipidemia, hyperproteinemia (>10 g/dL), hyperglycemia (>750 mg/dL), and azotemia (urea nitrogen concentration >115 mg/dL) can potentially cause pseudohypokalemia.

Clinical Features

Most dogs and cats with mild to moderate hypokalemia (i.e., 3.0-3.5 mEq/L) are asymptomatic. Clinically severe hypokalemia primarily affects the neuromuscular and cardiovascular systems owing to hypokalemia-induced initial hyperpolarization followed by hypopolarization of cell membranes. The

BOX 53.5

Causes of Hypokalemia in Dogs and Cats

Transcellular Shifts (ECF to ICF)

Metabolic alkalosis
Hypokalemic periodic paralysis (Burmese cats)

Increased Loss

Gastrointestinal fluid loss (vomiting, diarrhea)*
Chronic kidney disease, especially in cats*
Diabetic ketoacidosis*
Diet-induced hypokalemic nephropathy in cats
Distal (type I) renal tubular acidosis
Proximal (type II) renal tubular acidosis after sodium bicarbonate treatment
Postobstructive diuresis
Primary hyperaldosteronism
Chronic liver disease
Hyperthyroidism
Hypomagnesemia

Iatrogenic Causes*

Potassium-free fluid administration (e.g., 0.9% saline)
Parenteral nutritional solutions
Insulin- and glucose-containing fluid administration
Sodium bicarbonate therapy
Loop (e.g., furosemide) and thiazide diuretics
Low dietary intake

Pseudohypokalemia

Hyperlipidemia (dry reagent methods; flame photometry)
Hyperproteinemia (dry reagent methods; flame photometry)
Hyperglycemia (dry reagent methods)
Azotemia (dry reagent methods)

ECF, Extracellular fluid; *ICF,* intracellular fluid.
*Common causes.
Modified from DiBartola SP, Autran de Morais H: Disorders of potassium: hypokalemia and hyperkalemia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Saunders Elsevier.

most common clinical sign of hypokalemia is generalized skeletal muscle weakness. In cats ventroflexion of the neck (see Chapter 67), forelimb hypermetria, and a broad-based hindlimb stance may be observed. The timing of onset of hypokalemia-induced weakness is extremely variable among animals. Cats seem more susceptible than dogs to the deleterious effects of hypokalemia. In dogs, signs may not be evident until the serum potassium concentration is less than 2.5 mEq/L, whereas in cats signs can be seen when the serum potassium concentration is between 3 and 3.5 mEq/L.

Cardiac consequences of hypokalemia include decreased myocardial contractility, decreased cardiac output, and disturbances in cardiac rhythm. Cardiac disturbances assume a variable clinical expression, often evidenced only by electrocardiography (see Box 53.4). Other metabolic effects of hypokalemia include hypokalemic nephropathy, which is characterized by chronic tubulointerstitial nephritis, impaired renal function, and azotemia and manifests clinically as polyuria, polydipsia, and impaired urine concentrating capability; hypokalemic polymyopathy, which is characterized by increased serum creatine kinase activity and electromyographic abnormalities; and paralytic ileus, which manifests clinically as abdominal distention, anorexia, vomiting, and constipation. Hypokalemic nephropathy and polymyopathy are most notable in cats.

Diagnosis

Measurement of the serum potassium concentration identifies hypokalemia. Once it has been identified, a careful review of the history, physical findings, CBC, serum biochemistry panel, and urinalysis usually provides clues to the cause (see Box 53.5). If the cause is not readily apparent after review of this information, other less likely causes for hypokalemia should be considered, such as renal tubular acidosis, or another renal potassium-wasting disorder, primary hyperaldosteronism, and hypomagnesemia. To help differentiate renal from nonrenal sources of potassium loss, the clinician may need to determine the fractional excretion of potassium on the basis of a single urine and serum potassium and creatinine concentration or may need to evaluate 24-hour urine potassium excretion (see Chapter 39).

Treatment

Therapy is indicated if the serum potassium concentration is less than 3.5 mEq/L, if clinical signs related to hypokalemia are present, or if a serum potassium loss is anticipated (e.g., insulin therapy in diabetic ketoacidosis [DKA]) and the animal's ability to compensate for the loss is impaired. The goal of therapy is to reestablish and maintain normokalemia without inducing hyperkalemia.

Potassium chloride is the compound most commonly used for parenteral potassium supplementation, in part to help promote chloride as well as potassium repletion. IV administration is preferred, although potassium chloride can be given subcutaneously as long as the concentration of potassium does not exceed 30 mEq/L. In dogs and cats with normal renal function, the maintenance amount of potassium supplementation is approximately 20 mEq/L of fluids. The amount of potassium first added to fluids depends on the animal's serum potassium concentration (Table 53.3) and the amount of potassium already present in the fluids (see Table 53.1). The rate of IV potassium administration should not exceed 0.5 mEq/kg/h. The rate of potassium administration can be increased cautiously to 1.0 mEq/kg/h in patients with profound hypokalemia and normal or increased urine output. Close ECG monitoring is recommended.

It is difficult to estimate the amount of potassium required to reestablish normal potassium balance on the basis of the serum potassium concentration because potassium is primarily an intracellular cation. As such, serial measurement

TABLE 53.3

Guidelines for Potassium Supplementation in IV Fluids

SERUM K^+ (mEq/L)	TOTAL mEq OF K^+/L OF FLUIDS	MAXIMUM FLUID INFUSION RATE (mL/kg/h)*
>3.5	20	25
3.0-3.5	30	16
2.5-3.0	40	12
2.0-2.5	60	8
<2.0	80	6

*Total hourly potassium administration should not exceed 0.5 mEq/kg body weight.

of the serum potassium concentration is important during treatment and should initially be done every 6 to 12 hours depending on the severity of the hypokalemia and the rate of potassium administration. Adjustments in potassium therapy should be made accordingly, with the goal of establishing a normal serum potassium concentration and then maintaining the serum potassium concentration in the normal range as treatment is withdrawn. Clinical signs of hypokalemia usually resolve within 1 to 5 days after correction of hypokalemia.

Depending on the underlying cause, long-term oral potassium supplementation may be required to prevent recurrence of hypokalemia. Potassium gluconate powder or capsules are commonly used as an oral dietary potassium supplement for dogs and cats with minimal gastrointestinal side effects. The recommended dose is 2.2 mEq of potassium per 100 calories of required energy intake per day or 2 mEq of potassium per 4.5 kg of body weight twice a day. Subsequent adjustments in dosage are made on the basis of clinical response and serum potassium concentrations. Fruits such as kiwi and bananas are also a good source of potassium. Ten inches (25 cm) of banana contains approximately 10 mEq of potassium.

HYPERCALCEMIA

Identification

Hypercalcemia is present if the serum calcium concentration is greater than 12 mg/dL (dog) and 11 mg/dL (cat) or if the serum ionized calcium concentration is greater than 1.5 mmol/L (dog) and 1.3 mmol/L (cat), although reference ranges may vary between laboratories. The serum total and ionized calcium concentrations are higher in puppies than in adult dogs. A mild increase in serum total calcium (i.e., <13 mg/dL), ionized calcium (i.e., <1.55 mmol/L), and phosphorus (i.e., <10 mg/dL) concentrations in a clinically healthy puppy, together with an increase in serum alkaline phosphatase activity and normal urea nitrogen and creatinine concentrations, should be considered normal. The serum total calcium concentration does not fluctuate with age in cats, but the serum ionized calcium concentration may be higher (<0.1 mmol/L) in cats younger than 2 years of age than in older cats.

Most automated and in-house serum chemistry analyzers measure the total serum calcium concentration, which consists of biologically active, ionized calcium (55%), protein-bound calcium (35%), and calcium complexes (10%). A drawback to this is that alterations in the plasma protein concentration may alter the total serum calcium concentration, yet the ionized calcium concentration remains normal. For this reason, serum albumin and total protein concentrations should be measured when the total serum calcium concentration is determined in the dog. Simple quantitative changes in albumin and total plasma proteins do not cause hypocalcemia or hypercalcemia in dogs, even though total serum calcium levels may appear to be low or high on the biochemistry panel. Historically, the following formulas have been used to estimate the total serum calcium concentration in dogs with hypoalbuminemia or hypoproteinemia:

$$\text{Adjusted calcium (mg/dL)} = \text{Serum calcium (mg/dL)} - \text{Serum albumin (g/dL)} + 3.5$$

or

$$\text{Adjusted calcium (mg/dL)} = \text{Serum calcium (mg/dL)} - (0.4 \times \text{Serum total protein [g/dL]}) + 3.3$$

These formulas are not used in dogs younger than 24 weeks of age, because high values may be obtained, nor are they used in cats, because there is no linear relationship between serum total calcium and serum albumin and total protein concentration in cats. These formulas yield a rough estimate of the total serum calcium concentration and were developed without verification by serum ionized calcium measurements. Subsequent studies identified a poor correlation between adjusted total calcium results and corresponding serum ionized calcium concentrations, suggesting that adjusted total serum calcium concentrations are not reliable indicators of calcium homeostasis, and that measurement of serum ionized calcium concentration is preferred, especially in animals with hypoproteinemia.

The biologically active, ionized fraction of calcium can be determined directly; this approach bypasses the influence of plasma proteins on the total serum calcium concentration. Ionized calcium measurements are superior to serum total calcium measurements for assessing calcium in dogs and cats. Automated equipment that uses a calcium ion-selective electrode allows accurate measurement of ionized calcium in blood, plasma, or serum. Ionized calcium results can be affected by many variables, including method of sample collection (samples collected anaerobically provide more precise results); amount and type of heparin, if used (may underestimate or overestimate ionized calcium results);

and change in sample pH (ionized calcium decreases as pH increases). Protocols established by the clinical chemistry laboratory for submitting blood samples for ionized calcium determination should be followed to ensure accurate results. Handheld point-of-care analyzers typically report ionized calcium values that are less than those reported from bench-top machines.

Etiology

Hypercalcemia is relatively common in dogs and cats. Persistent hypercalcemia usually results from increased calcium resorption from bone or kidney or increased calcium absorption from the gastrointestinal tract. Humoral hypercalcemia of malignancy (HHM), the most common cause of hypercalcemia, occurs when the tumor produces substances that promote osteoclastic activity and renal calcium reabsorption. These substances include parathyroid hormone (PTH); PTH–related peptide (PTHrP); 1,25-dihydroxyvitamin D; cytokines, such as interleukin-1 and tumor necrosis factor; prostaglandins; and humoral factors that stimulate renal 1α-hydroxylase. Tumors may also induce hypercalcemia through local osteolytic activity after they metastasize to bone. Less commonly, hypercalcemia develops as the result of impaired loss of calcium from the serum (e.g., reduced glomerular filtration) or reduced plasma volume (e.g., dehydration).

The list of differential diagnoses for hypercalcemia in dogs and cats is relatively short (see Table 47.2, p. 761). In the dog HHM (especially lymphoma), hypoadrenocorticism, chronic kidney disease, hypervitaminosis D, and primary hyperparathyroidism are the most common diagnoses. In the cat, idiopathic hypercalcemia, HHM (especially lymphoma and squamous cell carcinoma), and chronic kidney disease are the most common diagnoses. Calcium oxalate urolithiasis and consumption of acidifying diets are commonly identified in cats with hypercalcemia, but their role, if any, in causing the disorder is unknown.

Hypercalcemia can develop in dogs and cats with chronic kidney disease and, less commonly, acute kidney injury. The pathogenesis of hypercalcemia associated with chronic kidney disease is complicated. The development of autonomously functioning parathyroid glands or an alteration of the set point for PTH secretion after prolonged stimulation of renal secondary hyperparathyroidism, decreased PTH degradation by renal tubular cells, increased PTH-mediated intestinal absorption of calcium, increased PTH-mediated osteoclastic bone resorption, decreased renal excretion of calcium, and increased protein-bound or complexed fractions of calcium is believed to contribute to the hypercalcemia of renal failure. Prolonged hypercalcemia, especially in conjunction with concurrent high-normal to increased serum phosphorus concentration, can also cause nephrocalcinosis and exacerbate kidney disease and azotemia. Determining whether the kidney disease is primary or secondary in a dog with hypercalcemia, hyperphosphatemia, and azotemia poses an interesting diagnostic challenge (see the Diagnosis section).

Clinical Features

Although all tissues can be affected by hypercalcemia, the neuromuscular, gastrointestinal, renal, and cardiac systems are the most important clinically. Secondary nephrogenic diabetes insipidus, loss of the renal concentration gradient, and metastatic mineralization of the kidney cause polyuria and polydipsia. Decreased excitability of the central and peripheral nervous systems in conjunction with decreased excitability of gastrointestinal smooth muscle causes lethargy, anorexia, vomiting, constipation, weakness, and (rarely) seizures. In rare instances, cardiac arrhythmias may develop in animals with severe hypercalcemia (i.e., >18 mg/dL). Prolongation of the PR interval and shortening of the QT interval may be found on electrocardiographic readings recorded in animals with milder hypercalcemia.

Clinical signs are often absent with mild increases in the serum calcium concentration, and hypercalcemia is discovered only after a serum biochemistry panel is performed, often for unrelated reasons. When clinical signs do develop, they initially tend to be insidious in onset. The severity of clinical signs depends in part on the severity, rate of onset, and duration of the hypercalcemia. Clinical signs become more severe as the magnitude of the hypercalcemia increases, regardless of the rate of onset or duration. Clinical signs are usually mild with serum calcium concentrations less than 14 mg/dL, are readily apparent with concentrations greater than 14 mg/dL, and become potentially life-threatening (i.e., cardiac arrhythmias) when the serum calcium concentration exceeds 18 to 20 mg/dL. Clinical signs resulting from the development of calcium phosphate or calcium oxalate uroliths may be noted.

Diagnosis

Hypercalcemia should always be reconfirmed, preferably from a nonlipemic blood sample obtained from the dog or cat after a 12-hour fast, before an extensive diagnostic evaluation is undertaken. Results of CBC, serum biochemistry panel, and urinalysis, in conjunction with the history and physical examination findings, often provide clues to the diagnosis (see Table 47.2). Special attention should be paid to serum electrolytes and renal parameters. Hypoadrenocorticism-induced hypercalcemia typically occurs in conjunction with mineralocorticoid deficiency; hyponatremia, hyperkalemia, and prerenal azotemia should be present. The serum phosphorus concentration is in the lower half of the normal range or low with HHM and primary hyperparathyroidism (Fig. 53.1). If the serum phosphorus concentration is increased and renal function is normal, hypervitaminosis D and bone osteolysis from metastatic or primary bone neoplasia are the primary differentials.

Determining whether kidney disease is primary or secondary to hypercalcemia caused by another disorder when hyperphosphatemia and hypercalcemia coexist with azotemia can be difficult. Chronic, and less commonly acute, kidney disease can cause hypercalcemia. Alternatively, disorders that cause persistent hypercalcemia with a concurrent high-normal to increased serum phosphorus concentration

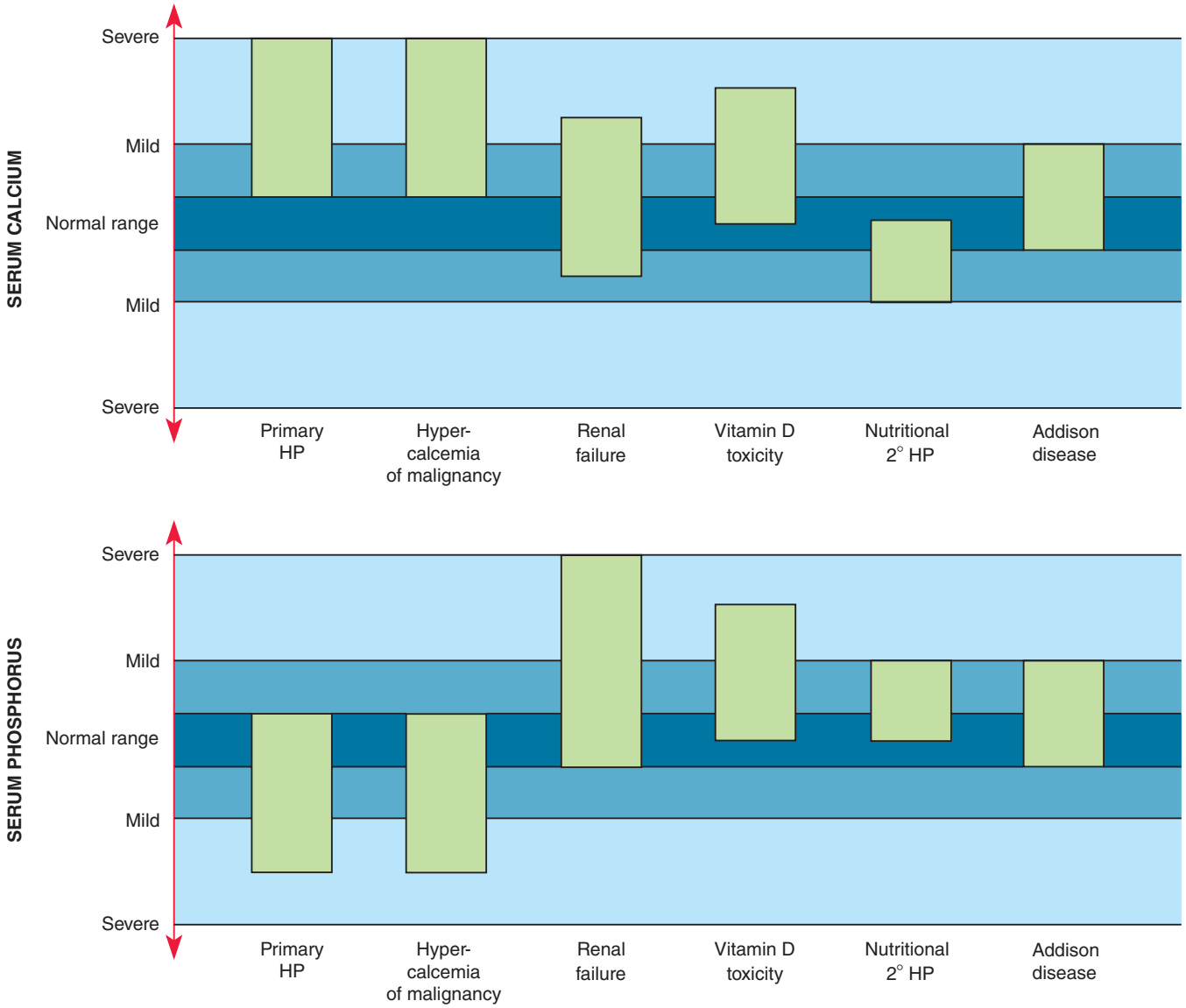


FIG 53.1
The range in serum calcium and phosphorus concentrations for the more common causes of hypercalcemia and/or hyperparathyroidism in the dog. *HP,* Hyperparathyroidism; *2° HP,* secondary hyperparathyroidism. (From Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction,* ed 4, St Louis, 2015, Saunders Elsevier.)

can cause progressive mineralization of the kidney and eventual chronic kidney disease. Measurement of the serum ionized calcium concentration may help identify dogs and cats with kidney disease–induced hypercalcemia; serum ionized calcium concentrations are typically normal or decreased in kidney disease and increased in hypercalcemia caused by other disorders. However, autonomous hypersecretion of PTH by the parathyroid gland and an increase in serum ionized calcium (i.e., tertiary hyperparathyroidism) may occur albeit uncommonly in dogs and cats with chronic kidney disease and long-standing renal secondary hyperparathyroidism.

Hypercalcemia of malignancy and primary hyperparathyroidism are the primary differentials when hypercalcemia and normal to low serum phosphorus concentrations are identified. The most common malignancy is lymphoma. A careful review of the history and physical examination findings may provide clues to the diagnosis. Systemic signs of illness suggest hypercalcemia of malignancy. Dogs and cats with primary hyperparathyroidism are usually healthy, and clinical signs are mild. The appendicular skeleton, peripheral lymph nodes, abdominal cavity, and rectum should be carefully palpated for masses, lymphadenopathy, hepatomegaly, splenomegaly, or pain on digital palpation of the long bones. Diagnostic tests helpful in identifying an underlying malignancy include thoracic and abdominal radiographs; abdominal ultrasound; cytologic evaluation of aspirates of the liver, spleen, lymph nodes, and bone marrow; determination of

serum ionized calcium, PTH, and PTHrP concentrations; and cervical ultrasound.

Sternal and hilar lymphadenopathy is common with lymphoma-induced hypercalcemia and can be readily identified with thoracic radiographs. Radiographs of the thorax and abdomen can also be used to evaluate bones; discrete lytic lesions in the vertebrae or long bones suggest multiple myeloma. Hyperproteinemia, proteinuria, and plasma cell infiltration in the bone marrow suggest multiple myeloma. Cytologic evaluation of peripheral lymph node, bone marrow, and splenic aspirates can be helpful in identifying lymphoma; involvement of the peripheral lymph nodes or spleen by lymphoma can be present without causing their enlargement. Ideally, the largest lymph node should be evaluated. Normal lymph node, bone marrow, and splenic aspirates do not rule out lymphoma.

Measurement of serum ionized calcium, PTH, and PTHrP levels from the same blood sample is helpful in differentiating primary hyperparathyroidism from HHM. Excessive secretion of biologically active PTHrP plays a central role in the pathogenesis of hypercalcemia in most forms of HHM. An increased serum ionized calcium concentration, a detectable serum PTHrP concentration, and a nondetectable serum PTH concentration are diagnostic for HHM. Lymphoma is the most common cause of detectable PTHrP concentrations, but other tumors, including apocrine gland adenocarcinoma and various carcinomas (e.g., mammary gland, squamous cell, bronchogenic), can also cause hypercalcemia by this mechanism. In contrast, an increased serum ionized calcium concentration, a normal to increased serum PTH concentration, and a nondetectable PTHrP concentration are diagnostic of primary hyperparathyroidism. Ultrasonographic examination of the parathyroid complex may reveal enlargement of one or more parathyroid glands (see Fig. 47.2, and Video 47.1). Most parathyroid adenomas measure 4 to 8 mm in greatest diameter, although parathyroid adenomas can exceed 2 cm. In contrast, the parathyroid glands should be small (<2 mm in diameter) or undetectable with hypercalcemia of malignancy.

Trial therapy to determine the cause of hypercalcemia is strongly discouraged. If the dog or cat is stable, eating, and not significantly ill, it is recommended to wait a few days to weeks and retest. Most of the causes of hypercalcemia are not occult, so the veterinarian is reminded to complete a thorough history (including toxin and supplement exposure), physical exam, cervical and abdominal ultrasonography, and assessment of PTH and PTHrP assays. Very rarely in dogs the clinician is left with nebulous results and must consider surgical exploration of the neck or trial therapy with L-asparaginase to see if hypercalcemia is alleviated.

Idiopathic hypercalcemia is a common diagnosis in young and middle-aged cats established by ruling out other causes of hypercalcemia. Hypercalcemia is usually mild (<13 mg/dL), and cats are usually asymptomatic. Serum phosphorus concentration and renal parameters are normal. The cause is unknown. Results of a complete diagnostic evaluation, as described previously, are unremarkable. Serum PTH concentrations are in the normal range or low; primary hyperparathyroidism has not been confirmed in any of these cats. Increased serum PTHrP, 25-hydroxyvitamin D, or calcitriol concentrations have not been identified. Nephrocalcinosis and urolithiasis may develop, presumably secondary to increased urinary calcium excretion. Consistently effective treatment has not been identified primarily because the pathogenesis of this problem remains unknown. In addition, the course of the disease is sometimes waxing and waning, which complicates confident correlation of improvement to treatments. Serum calcium concentrations have decreased in some cats following a dietary change to a high-fiber diet, a diet designed for kidney disease, or a diet designed to manage calcium oxalate urolithiasis, or after prednisolone treatment (initial dose, 5 mg q24h), but the response has been unpredictable and often short-lived. Preliminary trials with oral bisphosphonates (e.g., alendronate) have been promising in some cats with idiopathic hypercalcemia (see Treatment section). Serum calcium, phosphorus, and renal parameters should be monitored periodically in affected cats and appropriate therapy initiated if hypercalcemia progressively worsens, deterioration in renal function occurs, or both (see Chapter 41).

Treatment

Medical therapy should be directed at eradicating the underlying cause of the hypercalcemia. Supportive therapy to decrease the serum calcium concentration to less toxic levels is indicated if clinical signs are severe, if serum calcium concentration is greater than 17 mg/dL (dog) or 16 mg/dL (cat), if serum ionized calcium is greater than 1.8 mmol/L (dog) or 1.7 mmol/L (cat), if the calcium-phosphorus solubility product ([Ca] × [Pi]) is greater than 60 to 70 (implying metastatic mineralization of soft tissues), or if azotemia is present. In dogs and cats, correction of fluid deficits, saline diuresis, diuretic therapy with furosemide, and corticosteroids are the most commonly used modes of therapy (Box 53.6). Prerenal azotemia is common in dogs with hypercalcemia secondary to water restriction imposed by owners concerned about the polyuria and polydipsia. Therefore diuretics should never be administered before volume replenishment is completed.

The supportive therapy implemented should not interfere with attempts to establish a definitive diagnosis. As a general rule, saline diuresis followed by diuretic therapy can be initiated without compromising the results of diagnostic tests. Because of the high incidence of lymphoma in animals with hypercalcemia, glucocorticoids should not be administered unless the cause of the hypercalcemia has been identified.

Calcitonin may be useful in the treatment of animals with severe hypercalcemia and could be used in lieu of prednisone for treating hypercalcemia in animals without a definitive diagnosis. Calcitonin inhibits osteoclast activity. It has been used most commonly to treat hypercalcemia in dogs with cholecalciferol rodenticide toxicosis. The decrease in serum total calcium concentration after calcitonin administration is relatively small (≤3 mg/dL), and adverse reactions

BOX 53.6

Nonspecific Therapy for Control of Hypercalcemia

Acute Therapy

1. Correct fluid deficits
2. Physiologic saline diuresis, 60-180 mg/kg/day IV
3. Furosemide, 1-2 mg/kg IV, PO q6-12h
4. Once diagnosis has been established: prednisone, 1-2 mg/kg q12h PO or dexamethasone 0.1-0.2 mg/kg IV q12h

Additional Therapy if Above Fails

1. Calcitonin-salmon, 4-6 IU/kg SC q8-12h
2. Pamidronate, 1-2 mg/kg in 150 mL of 0.9% NaCl IV over 2-4 hours
3. Peritoneal dialysis, hemodialysis

Long-Term Therapy

1. Furosemide (see above)
2. Prednisone (see above)
3. Low-calcium-containing diet
4. Intestinal phosphate binders if hyperphosphatemia present (see Chapter 41)
5. Bisphosphonates (pamidronate [see previous]; etidronate, 5-15 mg/kg once to twice daily PO)

IV, Intravenous; *IM,* intramuscular; *PO,* by mouth; *SC,* subcutaneous.

include anorexia and vomiting. Although the onset of action of calcitonin may be rapid, its effect may be short-lived (hours), and resistance often develops within a few days, presumably because of downregulation of calcitonin receptors. The transitory effect of calcitonin and its expense have limited its usefulness for treating hypercalcemia.

Bisphosphonates inhibit bone resorption by decreasing osteoclast activity and function and inducing osteoclast apoptosis. Pamidronate has been used to treat dogs and cats with a variety of disorders causing hypercalcemia, including cholecalciferol rodenticide toxicosis, hypercalcemia caused by lymphoma, myeloma, osteosarcoma, primary hyperparathyroidism, and nocardiosis. The IV administration of pamidronate has a rapid onset of action and is effective in lowering serum total and ionized calcium concentrations. The only adverse reaction reported with pamidronate is renal toxicity, which appears to be uncommon. Factors that affect onset of renal toxicity in humans include type of bisphosphonate administered, rate of infusion, and hydration status of the patient. Administration of pamidronate before a definitive diagnosis has been obtained should not adversely affect establishing the cause of the hypercalcemia.

The oral bisphosphonate alendronate has been used to treat idiopathic hypercalcemia in cats that have failed to respond to changes in diet and oral prednisolone. Alendronate is not recommended until the serum calcium concentration exceeds 13 mg/dL. Oral alendronate is not as effective as injectable. The currently recommended treatment protocol developed by Dr. Dennis Chew is one 10-mg capsule per cat administered once weekly after a strict 12-hour fast, immediately followed by 6 mL of water taken orally and placement of butter on the nose to promote salivation and swallowing. The cat should not be fed for 2 hours or longer after administration of alendronate. Food interferes with absorption of the medication, and alendronate can cause esophageal erosions. Serum ionized calcium concentration should be measured initially 2 to 3 weeks after treatment is begun and the blood sample obtained just before the next treatment is given, to assess efficacy and to monitor for hypocalcemia. Increasing the dose to 20 mg once a week should be considered if minimal improvement in hypercalcemia is noted after 6 to 8 weeks of treatment.

If prolonged supportive therapy is required (e.g., in an animal with nontreatable malignancy), furosemide, corticosteroids, and a low-calcium diet (consult with a board-certified veterinary nutritionist for current options) can be used to help control the hypercalcemia. Non–calcium-containing intestinal phosphorus binders (e.g., aluminum hydroxide) should be administered if hyperphosphatemia is present. Oral or IV administration of bisphosphonates, as needed to control hypercalcemia, may also be considered.

HYPOCALCEMIA

Etiology

Hypocalcemia is present if the serum total calcium concentration is less than 9 mg/dL in adult dogs and less than 8 mg/dL in adult cats, or if the serum ionized calcium concentration is less than 1.0 mmol/L, although reference ranges may vary between laboratories. Hypocalcemia develops with increased demands of reproduction (e.g., preparturient or puerperal tetany), decreased calcium resorption from bone or kidney (e.g., primary hypoparathyroidism), decreased calcium absorption from the gastrointestinal tract (e.g., malassimilation syndromes), or increased precipitation-chelation of serum calcium (e.g., ethylene glycol toxicity, acute pancreatitis). The acute onset of hyperphosphatemia can also cause hypocalcemia. The most common causes of hypocalcemia in dogs and cats are hypoalbuminemia, puerperal tetany, acute and chronic kidney disease, malassimilation syndromes, critical illness (e.g., sepsis, systemic inflammatory response syndrome [SIRS]), and primary hypoparathyroidism (especially after thyroidectomy in hyperthyroid cats; see Table 47.3). The serum total calcium concentration is typically decreased in animals with concurrent hypoalbuminemia for reasons discussed in the section on hypercalcemia. Depending on the underlying cause, the serum ionized calcium concentration may or may not be decreased. Serum ionized calcium should be measured before a diagnosis of hypocalcemia is rendered in an animal, especially if a decreased serum albumin concentration is present.

Clinical Features

Animals with hypocalcemia range from being asymptomatic to showing severe neuromuscular dysfunction. Serum total

calcium concentrations between 7 and 9 mg/dL are usually clinically silent; dogs and cats with clinical signs usually have serum calcium values less than 7 mg/dL (ionized calcium <0.8 mmol/L), but severity of hypocalcemia and the presence of clinical signs are unpredictable and depend on the magnitude, rapidity of onset, and duration of hypocalcemia.

The most common clinical signs are directly attributable to a hypocalcemia-induced increase in neuronal excitability and include nervousness, behavioral changes, focal muscle twitching (especially ear and facial muscles), muscle cramping, stiff gait, tetany, and seizures. Seizures are not usually associated with loss of consciousness or urinary incontinence. Early indicators of hypocalcemia, especially in cats, include lethargy, anorexia, intense facial rubbing, and panting. Exercise, excitement, and stress may induce or worsen clinical signs. Additional physical examination findings may include fever, a "splinted" abdomen, cardiac abnormalities (e.g., weak femoral pulses, bradycardia, tachycardia), and cataracts.

Diagnosis

Hypocalcemia should be confirmed before diagnostic tests are begun to identify the cause, preferably by measuring the serum ionized calcium concentration. The list of differential diagnoses for hypocalcemia is relatively short, and the history, physical examination findings, CBC, serum biochemistry panel, urinalysis, and tests for pancreatitis (e.g., canine pancreatic lipase immunoreactivity [cPLI], abdominal ultrasound) usually provide the clues necessary to establish the diagnosis (see Table 47.3, p. 765). Primary hypoparathyroidism is the most likely diagnosis in the nonazotemic, nonreproductive dog or cat with clinical signs of hypocalcemia and normal serum magnesium concentration. The finding of a low or undetectable baseline serum PTH concentration confirms this diagnosis. Hypermagnesemia and hypomagnesemia can impair the secretion of PTH and PTH actions on its receptor, so measurement of serum magnesium (preferably ionized magnesium) is important, especially in animals with refractory hypocalcemia.

Treatment

Therapy should be directed at eradicating the underlying cause of the hypocalcemia. Administration of calcium may not be indicated if the patient is stable, no clinical signs of hypocalcemia are noted, and the serum calcium concentration is stable. Vitamin D, calcium, or both are indicated if clinical signs of hypocalcemia are present, if the serum total calcium concentration is less than 7.5 mg/dL, if the serum ionized calcium concentration is less than 0.8 mmol/L, or if hypocalcemia has developed quickly and is progressively decreasing. If hypocalcemic tetany is present, calcium should be administered intravenously slowly to effect (Box 53.7). Calcium gluconate is the preferred agent because it is not caustic if administered outside of the vein, unlike calcium chloride. Auscultation and electrocardiographic monitoring are advisable during calcium administration; if bradycardia or shortening of the QT interval occurs, the IV infusion should be stopped briefly. Calcium-rich fluids should be infused with caution in dogs or cats with hyperphosphatemia because these fluids can increase the probability of mineralization of soft tissues, most notably in the kidney.

Once signs of hypocalcemic tetany have been controlled with IV calcium, oral vitamin D, oral calcium, or both may be needed to prevent the recurrence of clinical signs. If the cause of hypocalcemia is readily reversible and the hypocalcemia is anticipated to be short-lived (e.g., weaning puppies from a bitch with puerperal tetany), oral calcium combined with IV calcium gluconate as needed may be all that is

BOX 53.7

Treatment of Hypocalcemia in Dogs and Cats

Immediate Treatment of Symptomatic Hypocalcemia

Calcium gluconate 10% solution
Dosage: 0.5-1.5 mL/kg IV slowly to effect
Monitor for bradycardia and arrhythmias
Goal: to resolve clinical signs of hypocalcemia

Parenteral Treatment to Prevent Symptomatic Hypocalcemia

Continuous IV infusion of 10% calcium gluconate
- Initial dosage: 60-90 mg elemental calcium/kg/day
- 10 mL of 10% calcium gluconate provides 93 mg of elemental calcium
- Administer via syringe pump in separate IV line
- Do not add to fluids containing lactate, acetate, bicarbonate, or phosphates
- Monitor serum ionized or total calcium q8-12h, and adjust infusion rate accordingly
- Goal: to avoid clinical signs of hypocalcemia while correcting the cause and/or waiting for oral calcium and vitamin D therapy to take effect

Oral Vitamin D and Calcium Treatment for Hypocalcemia

1,25-Dihydroxyvitamin D_3 (calcitriol) is preferred because of its fast onset of action
- Available as 0.25-µg and 0.50-µg capsules
- Initial dosage: 0.02-0.03 µg/kg/day
- Monitor serum ionized or total calcium q12-24h, and adjust dosage or frequency of administration accordingly
- Goal: to avoid clinical signs of hypocalcemia and development of hypercalcemia; target total calcium concentration is between 9 and 10 mg/dL

Oral calcium gluconate, calcium lactate, or calcium carbonate tablets
- Various tablet strengths available, ranging from 30-500 mg calcium/tablet
- Initial dosage: approximately 25-50 mg of Ca/kg q24h, dose often divided
- Typically used in conjunction with vitamin D
- Dosage and frequency of administration adjusted on the basis of serum ionized or total calcium concentration

IV, Intravenous.

necessary to prevent the recurrence of clinical signs. An IV continuous-rate infusion (CRI) of calcium, in addition to oral calcium, vitamin D, or both, is recommended for animals with disorders causing prolonged severe hypocalcemia (e.g., primary hypoparathyroidism, postparathyroidectomy for primary hyperparathyroidism). For IV CRI, calcium gluconate should be administered at an initial dosage of 60 to 90 mg of elemental calcium/kg/day. Ten milliliters of 10% calcium gluconate provides 93 mg of elemental calcium. Approximately 1, 2, or 3 mg/kg/h elemental calcium is provided when 10, 20, or 30 mL of 10% calcium gluconate, respectively, is added to 250 mL of fluids and administered at a maintenance rate of 60 mL/kg/day (2.5 mL/kg/h). Calcium salts should not be added to fluids that contain lactate, acetate, bicarbonate, or phosphates because calcium salt precipitates can result. The serum calcium concentration should be monitored every 8 to 12 hours and the calcium infusion adjusted accordingly with the goal of gradually decreasing and then discontinuing the infusion once the serum total calcium concentration is consistently greater than 8 mg/dL, or the serum ionized calcium concentration is greater than 0.9 mmol/L.

Long-term maintenance therapy may be necessary to control hypocalcemia. It is most commonly required for the control of primary hypoparathyroidism and hypoparathyroidism after bilateral thyroidectomy in cats with hyperthyroidism. Oral vitamin D administration is the primary mode of treatment for the management of chronic hypocalcemia (see Box 53.7). Vitamin D works by stimulating intestinal calcium and phosphorus absorption and, together with parathyroid hormone, by mobilizing calcium and phosphorus from bone. Oral calcium supplements are needed early in maintenance therapy in addition to vitamin D.

The aim of maintenance therapy is to keep the serum calcium concentration between 9 and 10 mg/dL (dog) and between 8 and 9 mg/dL (cat), which controls clinical signs, lessens the risk of hypercalcemia, and provides some stimulus for remaining or ectopic parathyroid tissue to become functional. The serum calcium concentration should be monitored closely (initially q24-48h) and adjustments in therapy made accordingly. Vitamin D therapy is required permanently in animals with primary hypoparathyroidism and in animals that have undergone total parathyroidectomy. Vitamin D therapy usually can be tapered and discontinued if only partial or transient parathyroid damage has occurred. Regardless, calcium supplementation often may be tapered and stopped. (See Chapter 47 for more information on the treatment of hypocalcemia.) Appropriate use and selection of diets to support gestation and lactation are critical for optimizing successful reproduction in cats and dogs and to help prevent and treat calcium imbalances.

HYPERPHOSPHATEMIA

Etiology

Hyperphosphatemia is present when the serum phosphorus concentration is greater than 6.0 mg/dL in the adult dog and cat, although reference ranges may vary between laboratories. Young dogs (<12 months) especially of large and giant breeds and young cats (<6 months) have higher serum phosphorus concentrations than adults, which should gradually decrease to adult values (e.g., typical laboratory reference ranges) by 12 months of age. Bone growth and an increase in renal tubular reabsorption of phosphorus mediated by growth hormone are believed to contribute to this age effect. Hyperphosphatemia can result from increased intestinal phosphorus absorption, decreased phosphorus excretion in the urine, or a shift in phosphorus from the intracellular to the extracellular compartment. Translocation of phosphorus between intracellular and extracellular compartments is similar to that of potassium. The most common cause of hyperphosphatemia in dogs and cats is decreased renal excretion secondary to kidney disease (Box 53.8).

BOX 53.8

Causes of Hyperphosphatemia in Dogs and Cats

Physiologic Causes

Young growing animal*

Increased Input

Hypervitaminosis D*
- Excess supplementation
- Cholecalciferol rodenticides

Jasmine toxicity
Excess dietary intake
Osteolytic bone lesions (neoplasia)

Decreased Loss

Acute or chronic kidney disease*
Uroabdomen
Hypoparathyroidism*
Hyperthyroidism
Hyperadrenocorticism
Acromegaly

Transcellular Shifts (ICF to ECF)

Metabolic acidosis
Tumor cell lysis syndrome
Tissue trauma or rhabdomyolysis
Hemolysis

Iatrogenic Causes

IV phosphorus administration
Phosphate-containing enemas
Diuretics: furosemide and hydrochlorothiazides

Laboratory Error

Lipemia
Hyperproteinemia

ECF, Extracellular fluid; *ICF,* intracellular fluid; *IV,* intravenous.
*Common causes.
Modified from DiBartola SD, Willard MD: Disorders of phosphorus: hypophosphatemia and hyperphosphatemia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice,* ed 4, St Louis, 2012, Saunders Elsevier.

Clinical Features

Hyperphosphatemia is a marker of underlying disease. By itself, hyperphosphatemia usually does not cause clinical signs. An acute increase in serum phosphorus may cause hypocalcemia and its associated neuromuscular signs. Sustained hyperphosphatemia can cause secondary hyperparathyroidism, fibrous osteodystrophy, and mineralization of soft tissues. Fortunately, most causes of hyperphosphatemia cause a decrease in serum calcium concentration so that the calcium-phosphorus solubility product ([Ca] × [Pi]) remains less than 60. The risk of soft tissue mineralization increases when the [Ca] × [Pi] solubility product exceeds 60. Chronic kidney disease is the most common cause of sustained hyperphosphatemia and an increase in the solubility product above 60. History, physical examination, and results of CBC, serum biochemistry panel, urinalysis, and serum T_4 concentration (cats) will usually reveal the cause.

Treatment

Hyperphosphatemia usually resolves with correction of the underlying disease. In dogs and cats with kidney disease, hyperphosphatemia can initially be lowered with aggressive fluid therapy. Low-phosphorus diet with orally administered phosphate binders is the most effective way to treat sustained hyperphosphatemia caused by kidney disease (see Chapter 41).

HYPOPHOSPHATEMIA

Etiology

Hypophosphatemia is present when the serum phosphorus concentration is less than 3 mg/dL in the dog and cat, although reference ranges may vary between laboratories. Hypophosphatemia usually is not clinically worrisome until the serum phosphorus concentration is less than 1.5 mg/dL. Hypophosphatemia results from decreased phosphorus absorption in the intestinal tract, increased urinary phosphorus excretion, or translocation from the extracellular to the intracellular compartment. Hypophosphatemia is commonly associated with humoral HHM (i.e., lymphoma), primary hyperparathyroidism, and aggressive therapy for DKA (Box 53.9). Clinically significant hypophosphatemia is most likely to occur within the first 24 hours of therapy for diabetic ketoacidosis, when a shift of potassium and phosphorus from the extracellular to the intracellular compartment occurs. The nature of the translocation of phosphorus between intracellular and extracellular compartments is similar to that seen with potassium. Factors that promote a shift of potassium into the intracellular compartment (e.g., alkalosis, insulin, glucose infusion) promote a similar shift in phosphorus. During therapy for DKA, the serum phosphorus concentration can decline to severe levels (i.e., <1 mg/dL) as a result of the dilutional effects of fluid therapy and the intracellular shift of phosphorus after initiation of insulin and bicarbonate therapy. It is interesting to note that the initial serum phosphorus concentration usually is normal or only mildly decreased because metabolic acidosis of DKA results in a shift of phosphorus from the intracellular to the extracellular compartment.

BOX 53.9

Causes of Hypophosphatemia in Dogs and Cats

Decreased Intestinal Absorption

Phosphate binders*
Vitamin D deficiency
Decreased dietary intake
Malabsorption, steatorrhea

Increased Urinary Excretion

Primary hyperparathyroidism*
Humoral hypercalcemia of malignancy*
DKA*
Renal tubular disorders (Fanconi syndrome)
Diuretics
Eclampsia

Transcellular Shifts

Insulin administration, especially for DKA*
Respiratory and metabolic alkalosis
Sodium bicarbonate administration*
Parenteral glucose administration*
Parenteral nutritional solutions
Hypothermia

Laboratory Error

DKA, Diabetic ketoacidosis.
*Common causes.
Modified from DiBartola SD, Willard MD: Disorders of phosphorus: hypophosphatemia and hyperphosphatemia. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice*, ed 4, St Louis, 2012, Saunders Elsevier.

Clinical Features

Clinical signs may develop when the serum phosphorus concentration is less than 1.5 mg/dL, although signs are variable and severe hypophosphatemia is clinically silent in many animals. Hypophosphatemia primarily affects the hematologic and neuromuscular systems in the dog and cat. Hemolytic anemia is the most common sequela to hypophosphatemia. Hypophosphatemia decreases the erythrocyte concentration of adenosine triphosphate (ATP), which increases erythrocyte fragility, leading to hemolysis. Hemolysis usually is not identified until the serum phosphorus concentration is 1 mg/dL or less. Hemolytic anemia can be life-threatening if not recognized and treated. Neuromuscular signs include weakness, ataxia, and seizures, as well as anorexia and vomiting secondary to intestinal ileus.

Treatment

For most dogs and cats, hypophosphatemia resolves after correction of the underlying cause. Phosphate therapy

probably is not indicated for asymptomatic animals in which the serum phosphorus concentration is greater than 1.5 mg/dL and is unlikely to decrease further. Phosphate therapy is indicated if clinical signs or hemolysis is identified, or if the serum phosphorus concentration is less than 1.5 mg/dL, especially if a further decrease is possible. Phosphate supplementation is not indicated in dogs and cats with hypercalcemia, oliguria, or suspected tissue necrosis. If renal function is in question, phosphorus supplementation should not be provided until the status of renal function and the serum phosphorus concentration are known.

The goal of therapy is to maintain the serum phosphorus concentration greater than 2 mg/dL without causing hyperphosphatemia. Injectable potassium phosphate solution is available; however, unless urgent due to severity, oral phosphate supplementation is preferred (e.g., K-Phos Neutral or Phospha 250 Neutral); bovine milk contains 0.032 mmol/mL of elemental phosphorous and can be used for oral phosphate supplementation, balanced commercial diets, or a combination of these. IV phosphate supplementation is usually required to correct severe hypophosphatemia, especially in animals with diabetic ketoacidosis. Potassium phosphate solutions are typically used. If potassium supplementation is contraindicated, sodium phosphate solutions can be substituted. Potassium and sodium phosphate solutions contain 3 mmol of phosphate per milliliter and either 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The initial dosage of phosphate is 0.01 to 0.03 mmol/kg/h, preferably administered by constant-rate infusion in calcium-free IV fluids (i.e., 0.9% sodium chloride). In dogs and cats with severe hypophosphatemia, it may be necessary to increase the dosage to 0.03 to 0.12 mmol/kg/h. Because the dose of phosphate necessary to replete an animal and the animal's response to therapy cannot be predicted, it is important to initially monitor the serum phosphorus concentration every 4 to 8 hours and adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, mineralization of soft tissues, and renal failure. Serum total or preferably ionized calcium concentration should be measured at the same time as serum phosphorus concentration and the rate of phosphate infusion decreased if hypocalcemia is identified.

HYPOMAGNESEMIA

Etiology

Hypomagnesemia is present if serum total and ionized magnesium concentrations are less than 1.5 mg/dL and 0.4 mmol/L, respectively, although reference ranges may vary between laboratories. Hypomagnesemia results from decreased oral intake, increased loss from the gastrointestinal tract (e.g., malabsorption syndromes), increased renal loss (e.g., postobstructive diuresis), endocrine causes (e.g., diabetes mellitus), or translocation of the cation from the extracellular to the intracellular compartment. The most common causes of clinically significant hypomagnesemia in dogs and cats include disorders leading to small intestinal malassimilation; renal disorders associated with high urine output; the osmotic diuresis of diabetic ketoacidosis; and the shift of potassium, phosphorus, and magnesium from the extracellular to the intracellular compartment that occurs within the first 24 hours of therapy for DKA (Box 53.10). Magnesium is predominantly an intracellular cation. The nature of the translocation of magnesium between intracellular and extracellular compartments is similar to that of potassium in that factors that promote a shift of potassium into the intracellular compartment (e.g., alkalosis, insulin, glucose infusion) promote a similar shift of magnesium.

Clinical Features

Hypomagnesemia is reported to be the most common electrolyte disorder in critically ill dogs and cats, and magnesium deficiency may predispose animals to a variety of cardiovascular, neuromuscular, and metabolic complications. Clinical signs of hypomagnesemia do not usually occur until serum total and ionized magnesium concentrations are less than 1.0 mg/dL and 0.4 mmol/L, respectively, and even at these low levels many animals remain grossly asymptomatic. However, magnesium deficiency can result in several nonspecific clinical signs, including lethargy, anorexia, muscle weakness (including dysphagia and dyspnea), muscle fasciculations, seizures, ataxia, and coma. Concurrent hypokalemia, hyponatremia, and hypocalcemia occur in animals with hypomagnesemia, although the prevalence of these electrolyte abnormalities may differ between species. These electrolyte abnormalities may also contribute to the development of clinical signs. Magnesium is a co-factor for all enzyme reactions that involve ATP, most notably the sodium-potassium ATPase pump. Deficiencies in magnesium may cause potassium-losing nephropathy and increased urinary potassium losses, and the resultant hypokalemia may be refractory to appropriate potassium replacement therapy unless hypomagnesemia is corrected. Magnesium deficiency may inhibit PTH secretion from the parathyroid gland and may promote calcium uptake into bone, resulting in hypocalcemia. Magnesium deficiency also causes the resting membrane potential of myocardial cells to be decreased and leads to increased Purkinje fiber excitability, with consequent generation of arrhythmias. Electrocardiographic changes include a prolonged PR interval, a widened QRS complex, a depressed ST segment, and peaked T waves. Cardiac arrhythmias associated with magnesium deficiency include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation. In addition, hypomagnesemia predisposes animals to digitalis-induced arrhythmias.

Diagnosis

Many disorders and predisposing factors in dogs and cats are associated with hypomagnesemia (see Box 53.10). However, measurement of serum total vs. ionized magnesium is somewhat controversial. Serum total magnesium represents 1% of

BOX 53.10

Causes of Hypomagnesemia and Magnesium Depletion in Dogs and Cats

Gastrointestinal Causes

Inadequate intake
Chronic diarrhea and vomiting*
Malabsorption syndromes
Acute pancreatitis
Cholestatic liver disease
Nasogastric suction

Renal Causes

Chronic kidney disease
Renal tubular acidosis
Postobstructive diuresis
Drug-induced tubular injury (e.g., aminoglycosides, cisplatin)
Post–renal transplant
Prolonged intravenous fluid therapy*
Diuretics*
Digitalis administration
Concurrent electrolyte disorders
- Hypercalcemia
- Hypokalemia
- Hypophosphatemia

Endocrine Causes

Diabetes mellitus and diabetic ketoacidosis*
Hyperthyroidism
Primary hyperparathyroidism
Primary hyperaldosteronism

Miscellaneous Causes

Acute administration of insulin, glucose, or amino acids
Sepsis
Hypothermia
Massive blood transfusion
Peritoneal dialysis, hemodialysis
Parenteral nutrition

*Common causes.
Modified from Bateman S: Disorders of magnesium: magnesium deficit and excess. In DiBartola SP, editor: *Fluid, electrolyte, and acid-base disorders in small animal practice*, ed 4, St Louis, 2012, Saunders/Elsevier.

the body's magnesium stores, and serum ionized magnesium represents 0.2% to 0.3% of total body magnesium stores. As a result, serum total and ionized magnesium concentrations do not always reflect total body magnesium status. A normal serum magnesium concentration may exist despite an intracellular magnesium deficiency. However, a low serum magnesium concentration would support the presence of a total body magnesium deficiency, especially when clinical signs or concurrent electrolyte abnormalities are consistent with hypomagnesemia. A serum ionized magnesium concentration determined with the use of an ion-selective electrode has been recommended based on the assertion that it more accurately assesses total body magnesium content than measurement of serum total magnesium. However, some lines of evidence in dogs, cats, and humans indicate that evaluation of total magnesium or the ratio or ionized to total magnesium is indicated with suspected chronic deficiency, because ionized magnesium may be preserved at the expense of total magnesium concentrations. Assessing an animal's magnesium status is problematic because no simple, rapid, and accurate laboratory test is available to gauge total body magnesium status. A parenteral magnesium tolerance test involving IV infusion and measurement of magnesium in urine to estimate retention has been described in dogs to identify those with poor total body status, but this has not been standardized in clinical practice. In dogs and cats with low serum magnesium concentration, a review of the history, physical examination, CBC, serum biochemistry panel, and urinalysis usually provides clues to the underlying cause (see Box 53.10).

Treatment

Treatment of hypomagnesemia usually involves ill dogs and cats that are hospitalized and have inappetence and/or excessive fluid loss from the gastrointestinal tract or kidneys. Treatment of hypomagnesemia may also be indicated during treatment of DKA in dogs and cats with refractory hypokalemia, hypocalcemia, or both, in dogs and cats with refeeding syndrome, and in dogs or cats in heart failure with concurrent ventricular arrhythmias that are being treated with loop diuretics, digitalis, or both.

Parenteral solutions of magnesium sulfate (8.12 mEq of magnesium per gram of salt) and magnesium chloride (9.25 mEq of magnesium per gram of salt) are available commercially. The IV dose for rapid and slow magnesium replacement is 0.5 to 1 mEq/kg/day and 0.3 to 0.5 mEq/kg/day, respectively, administered by constant-rate infusion in 5% dextrose in water or 0.9% sodium chloride. Magnesium is incompatible with solutions containing bicarbonate or calcium. Kidney function should be assessed before magnesium is administered, and the magnesium dose should be reduced by 50% to 75% in azotemic animals. The use of magnesium with digitalis cardioglycosides may cause serious conduction disturbances. Serum magnesium, calcium, and potassium concentrations should be monitored every 8 to 12 hours. The goal of magnesium therapy is the resolution of clinical signs or refractory hypokalemia and hypocalcemia. Parenteral administration of magnesium sulfate may cause significant hypocalcemia due to the chelation of calcium with sulfate; therefore, magnesium chloride should be given if hypocalcemia is also present or a calcium infusion may be necessary. Other adverse effects of magnesium therapy include hypotension; atrioventricular and bundle branch blocks; and, in the event of overdose, respiratory depression and cardiac arrest. Overdoses are treated with IV calcium gluconate (see Box 53.7). Oral supplementation for more chronic or less severe cases is indicated and often well tolerated although a laxative effect may be seen; magnesium oxide, citrate, gluconate, chelate, or a mix of forms in an oral

tablet supplement product to provide 1 to 2 mEq/kg body weight per day has been sufficient to maintain total magnesium in the normal range in dogs in the experience of the authors.

HYPERMAGNESEMIA

Etiology

Hypermagnesemia is present if serum total and ionized magnesium concentrations are greater than 2.5 mg/dL and 1.5 nmol/L, respectively, although reference ranges may vary between laboratories. It is an uncommon clinical problem owing to the remarkable ability of the kidney to efficiently eliminate excessive magnesium. Hypermagnesemia may occur in dogs and cats with kidney disease and post–renal azotemia and iatrogenically after excessive intake of magnesium (e.g., IV administration). Because excess magnesium is rapidly excreted by the healthy kidney, iatrogenic hypermagnesemia usually occurs in animals with chronic kidney disease. Hypermagnesemia has also been reported in cats with thoracic neoplasia and pleural effusion and in dogs with hypoadrenocorticism, primary hyperparathyroidism, and hypothyroidism. The mechanism involved in the development of hypermagnesemia in these cats and dogs is unknown.

Clinical Features

Hypermagnesemia usually results in varying degrees of neuromuscular blockade. Nonspecific clinical manifestations of hypermagnesemia include lethargy, weakness, and hypotension. Loss of deep tendon reflexes and electrocardiographic changes, consisting of prolonged PR intervals, widening QRS complexes, and heart block, occur at higher serum magnesium concentrations. Serious complications, including respiratory depression, apnea, cardiac arrhythmias, and cardiac arrest, occur when serum magnesium concentrations exceed 12 mg/dL. At these high levels, magnesium acts as a nonspecific calcium channel blocker.

Diagnosis

Measurement of the serum magnesium concentration identifies hypermagnesemia. Unlike magnesium depletion, serum concentrations cannot be normal if there is an increase in magnesium stores. A correlation between increased serum magnesium concentrations and the severity of total body excess has not been reported.

Treatment

Treatment begins with discontinuation of all exogenous sources of magnesium. Additional treatment depends on the severity of the hypermagnesemia, the clinical presentation, and the status of renal function. Most dogs and cats with healthy kidneys require only supportive care and observation. Treatment aimed at improving renal function is indicated in animals with concurrent chronic kidney disease (see Chapter 41). Saline diuresis and administration of loop diuretics (e.g., furosemide) will accelerate renal magnesium excretion. Administration of IV calcium gluconate is indicated in dogs and cats with cardiac arrhythmias or significant hypotension (see Box 53.7).

Suggested Readings

Bolliger AP, et al. Detection of parathyroid hormone-related protein in cats with humoral hypercalcemia of malignancy. *Vet Clin Pathol*. 2002;31:3.

DiBartola SP, ed. *Fluid, electrolyte and acid-base disorders in small animal practice*. ed 4. St Louis: Saunders Elsevier, 2006.

Fan TM, et al. Evaluation of intravenous pamidronate administration in 33 cancer-bearing dogs with primary or secondary bone involvement. *J Vet Intern Med*. 2005;19:74.

Fincham SC, et al. Evaluation of plasma ionized magnesium concentration in 122 dogs with diabetes mellitus: a retrospective study. *J Vet Intern Med*. 2004;18:612.

Graham-Mize CA, et al. Absorption, bioavailability and activity of prednisone and prednisolone in cats. *Adv Vet Dermatol*. 2005;5:152.

Holowaychuk MK, et al. Ionized hypocalcemia in critically ill dogs. *J Vet Intern Med*. 2009;23:509.

Hostutler RA, et al. Uses and effectiveness of pamidronate disodium for treatment of dogs and cats with hypercalcemia. *J Vet Intern Med*. 2005;19:29.

Mellema MS, Hoareau GL. Hypomagnesemia in brachycephalic dogs. *J Vet Intern Med*. 2014;28:1418.

Midkiff AM, et al. Idiopathic hypercalcemia in cats. *J Vet Intern Med*. 2000;14:619.

Norris CR, et al. Serum total and ionized magnesium concentrations and urinary fractional excretion of magnesium in cats with diabetes mellitus and diabetic ketoacidosis. *J Am Vet Med Assoc*. 1999;215:1455.

Ramsey IK, et al. Hyperparathyroidism in dogs with hyperadrenocorticism. *J Small Anim Pract*. 2005;46:531.

Savary KCM, et al. Hypercalcemia in cats: a retrospective study of 71 cases (1991-1997). *J Vet Intern Med*. 2000;14:184.

Schenck PA, et al. Prediction of serum ionized calcium concentration by serum total calcium measurement in dogs. *Am J Vet Res*. 2005;66:1330.

Sharp CR, et al. A comparison of total calcium, corrected calcium, and ionized calcium concentrations as indicators of calcium homeostasis among hypoalbuminemic dogs requiring intensive care. *J Vet Emerg Crit Care*. 2009;19:571.

Silverstein DC, Hopper KK, eds. *Small animal critical care medicine*. St Louis: Saunders Elsevier; 2009.

Stern JA, et al. Cutaneous and systemic blastomycosis, hypercalcemia, and excess synthesis of calcitriol in a domestic shorthair cat. *J Am Anim Hosp Assoc*. 2011;47:116.

Toll J, et al. Prevalence and incidence of serum magnesium abnormalities in hospitalized cats. *J Vet Intern Med*. 2002;16:217.

Whitney JL, et al. Use of bisphosphonates to treat severe idiopathic hypercalcemia in a young Ragdoll cat. *J Fel Med Surg*. 2011;13:129.

Drugs Used in Electrolyte Disorders

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Alendronate	Treat hypercalcemia	Unknown	10 mg PO, after 12-hour fast, once weekly
Calcitonin—salmon	Treat hypercalcemia	4-6 IU/kg SC q8-12h	Unknown
Calcium—injectable and oral preparations	Treat hypocalcemia	See Box 53.7	See Box 53.7
Calcium gluconate 10%	Treat hyperkalemia Treat hypocalcemia	2-10 mL IV, slow bolus 0.5-1.5 mL/kg IV, slow bolus to effect	1-5 mL IV, slow bolus 0.5-1.5 mL/kg IV, slow bolus to effect
Furosemide (Lasix)	Treat hypercalcemia and hypermagnesemia	1-4 mg/kg IV, PO q6-12h	1-4 mg/kg IV, PO q6-12h
Hypertonic (7.2%) saline	Treat cerebral edema	3-5 mL/kg over 20 minutes in central vein	Same
Insulin—regular crystalline	Treat hyperkalemia	0.5-1 U/kg plus 2 g dextrose/U of insulin in parenteral fluids IV	0.5-1 U/kg plus 2 g dextrose/U of insulin in parenteral fluids IV
Magnesium—injectable and oral preparations	Treat hypomagnesemia	See p. 932	See p. 932
Mannitol 20%	Treat cerebral edema	1-3 mg/kg over 20 minutes in central vein	Same
Pamidronate	Treat hypercalcemia	1-2 mg/kg in 150 mL 0.9% saline IV over 2-4 h	Recommend alendronate
Potassium gluconate (Kaon Elixir, Tumil-K)	Treat hypokalemia	2.2 mEq K/100 kcal food consumed per day or 2 mEq K/4.5 kg PO q2h	2.2 mEq K/100 kcal food consumed per day or 2 mEq K/4.5 kg PO q12h
Prednisone (dog), Prednisolone (cat)	Treat hypercalcemia	1-2 mg/kg PO q12h	1-2 mg/kg PO q12h
Sodium bicarbonate	Treat hyperkalemia	1-2 mEq/kg IV, slow bolus	1-2 mEq/kg IV, slow bolus
Vitamin D preparations	Treat hypocalcemia	See Box 53.7	See Box 53.7

IV, Intravenous; *PO,* oral; *SC,* subcutaneous.

PART EIGHT ▪ Reproductive System Disorders

Autumn P. Davidson

CHAPTER 54

The Practice of Theriogenology



Theriogenology is the branch of veterinary medicine concerned with reproduction, including the physiology and pathology of male and female reproductive systems of animals and the clinical practice of veterinary obstetrics, gynecology, and andrology. Clinical small animal theriogenology primarily revolves around the production of healthy purebred puppies and kittens from privately owned breeding stock. Less commonly, veterinary participation in large-scale commercial breeding programs is sought. Generally, small animal theriogenology is a rewarding subspecialty in veterinary internal medicine. Although demanding of the clinician's time and expertise, the breeder client tends to be very loyal and compliant. A good reproductive practice generates its own referrals and usually is quite busy. Obstetrics and pediatrics are undeniably rewarding parts of the specialty for veterinarians and their staff. Reproductive practice incorporates the fields of physiology, endocrinology, embryology, genetics, metabolism, nutrition, pediatric and maternal critical care, anesthesia, pharmacology, and anatomy. The field is uniquely both medical and surgical, and involves both intact and neutered dogs and cats (Boxes 54.1 and 54.2).

THE PREBREEDING CONSULTATION

Veterinary participation benefits dog and cat breeding programs not only by providing medical and surgical intervention when indicated but also by promoting good animal husbandry with preventive medicine. Proper genetic counseling and screening for selection of breeders minimizes inherited defects. Optimizing the prebreeding condition of the dam and sire involves health and reproductive system examinations, nutrition evaluation, parasite control, and infectious disease prevention. Ovulation timing and breeding management improve conception rates and litter size. Obstetrics promotes eutocia and improves neonatal survival. Postpartum preventive medicine minimizes morbidity and mortality of both the dam and her offspring. Periodic physical examination and semen evaluation is advised in the valuable stud dog.

Breeding soundness consultations for canine or feline breeding animals should include evaluation of the temperament, physical condition, health and breeding history, infectious disease status (canine brucellosis, herpes virus; feline leukemia virus [FeLV], feline immunodeficiency virus [FIV], feline infectious peritonitis [FIP], and feline toxoplasmosis), vaccination status, diet, current medications, and any supplements, as well as available genetic screening appropriate for the breed (Box 54.3). A review of kennel or cattery husbandry should be completed (canine: housing, parasite control, diet, supplements, medications; feline: light cycles, housing, cat density, diet, parasite control, supplements, medications). Proper perinatal nutrition and body condition for the prospective dam should be addressed. In bitches, a change from an adult diet to a diet formulated for pregnancy and lactation (usually labeled as nutritionally complete for all life stages or complete nutrition for growth, pregnancy, and lactation) should occur at the fourth to sixth week of gestation and continue through weaning. Bitches' energy requirements during pregnancy increase in the last trimester. A change to a diet high in essential fatty acids at the time of breeding has been advocated to improve litter size and neonatal viability (Kelley et al., 2004). The amount fed must be managed to maintain proper body condition, because obesity negatively impacts labor. Supplements should be discouraged because they generally unbalance a commercially prepared diet. The pregnancy and lactation diet should be one previously tested and found to be adequate by the Association of American Feed Control Officials (AAFCO) standards, not one simply "formulated to meet AAFCO standards." A protein level of 27% to 34% dry matter (preferably animal-based sources), at least 18% fat with a balanced supply of both n-6 and n-3 fatty acids, and 20% to 30% carbohydrates with optimum vitamins and minerals (avoiding deficiencies and excesses) is advisable. Queens uniquely experience linear weight gain during pregnancy; they should

BOX 54.1

Basic Reproductive Practice Job Tasks

Canine ovulation timing
Canine semen collection and evaluation
Chilled canine semen collection and processing
Canine artificial insemination, vaginal and transcervical; fresh and chilled semen
Ultrasonographic pregnancy diagnosis in the bitch and queen
Obstetrics
Elective cesarean section (timing and performance)
Emergency cesarean section
Neonatal resuscitation
Pediatrics
Infertility evaluation/management
Diagnosis and therapy of disorders of the reproductive tract (canine, feline, male and female) while preserving breeding potential
Estrus induction
Pregnancy termination

BOX 54.2

Advanced Reproductive Practice Job Tasks

Canine cryopreservation
Frozen semen insemination (transcervical, surgical)
Feline semen collection and evaluation
Feline artificial insemination
Transcervical diagnostics (intrauterine cytology, biopsy)

BOX 54.3

Infectious Disease Screening

Canine

Brucella canis
Screen: Rapid slide/tube agglutination (RSAT, RTAT), 2-mercaptoethanol modified RSAT or TAT
Confirmatory: Agar Gel Immunodiffusion (AGID), culture, PCR
± Herpes canis serology (to guide quarantine)

Feline

FeLV, FIV serology
(FIP real time PCR on tissue or body fluids of abortions)
Toxoplasmosis IgM, IgG serology/PCR

be placed on a diet designed to support gestation and lactation before breeding and continue through weaning, and queens should be fed free choice. Stud dogs and toms should be fed AAFCO-tested commercial maintenance diets and be kept in good body condition.

Veterinarians should not be hesitant to advise against breeding individuals with undesirable temperament, physical

BOX 54.4

Veterinary Resources for Genetic Disease and Genetic Variability Screening

http://www.caninehealthinfo.org/
https://www.ofa.org/breedtests.html?btnSearch=Tests+by+Breed
http://www.fabcats.org/breeders/inherited_disorders/index.php
http://omia.angis.org.au
www.vet.cam.ac.uk/idid/
https://www.vetgen.com/



FIG 54.1
Vaginoscopy performed in a proestrual bitch with a pediatric proctoscope.

conditions, or genetic traits. To increase access to information on diagnosing hereditary diseases in dogs and cats, a web application has been developed to collect, organize, and display information on available DNA tests and other supporting information, including gene and chromosomal locations, mutations, primary research citations, and disease descriptions. There are currently 131 molecular genetic tests available for hereditary diseases in dogs and cats offered by 43 laboratories worldwide (Box 54.4).

The physical examination should pay specific attention to the external genitalia. Bitches and queens should be evaluated for vestibule-vaginal malformations that could interfere with copulation or whelping, either via digital or vaginoscopic examination (Fig. 54.1). Abnormalities of the development of the müllerian duct or with the normal fusion between the müllerian duct and the urogenital sinus during embryogenesis can result in atresia of the tubular genitalia or formation of septa. Septa can be circumferential (hymen-like) or dorsoventral bands, both usually located just cranial to the urethral papilla. Dorsoventral bands, if narrow, can usually be easily resected with vaginoscopy before breeding and whelping, even during proestrus (Fig. 54.2). Sedation of a short general anesthetic is sometimes required. Thicker bands and circumferential strictures are difficult to resolve

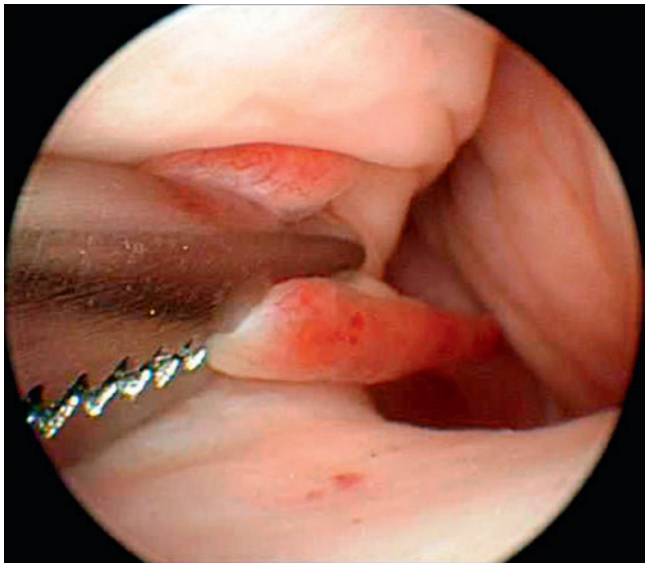


FIG 54.2
Endoscopic-guided revision of a vaginal septum.

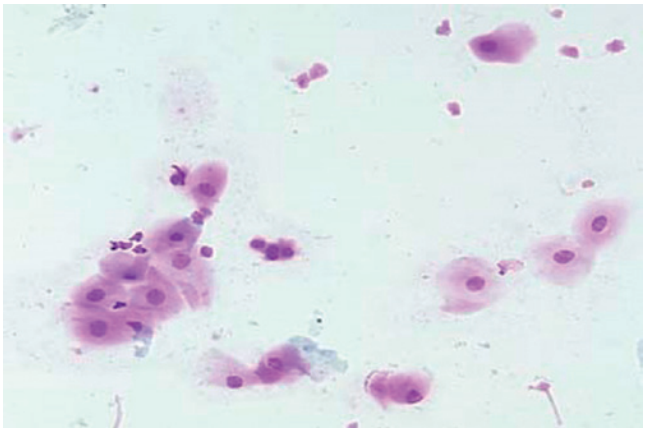


FIG 54.3
Anestrus vaginal cytology showing scant cellularity, parabasal cells, and occasional neutrophils.

surgically because they require an episiotomy and commonly reform and restrict. Artificial insemination and elective cesarean section are usually advised. Rarely anomalous uterine structures (agenesis, duplication) accompany vaginal septa and preclude breeding. The heritability of these septa is not known. Both bitches and queens should be evaluated for mammary gland normalcy and nipple duct patency. Dogs and toms should be evaluated for normal testicular descent into the scrotum, lack of a persistent penile frenulum, or penile hair ring (tom) (see Chapter 56), and normal testicular, epididymal, and prostatic (dog) palpation. In both species the prepuce should be retracted to inspect the penile mucosa. Semen evaluation should be performed in the dog (see later).

ESTROUS CYCLE OF THE BITCH

Puberty occurs between 6 and 24 months in the bitch, later in large breeds. The normal canine reproductive cycle can be categorized into four phases: anestrus, proestrus, estrus, and diestrus, each having characteristic behavioral, physical, and endocrinologic patterns (Table 54.1). The interestrous interval is normally 4 to 13 months, with 7 months as the average. The anestrus phase of the estrous cycle is marked by uterine involution and endometrial repair. The normal bitch is not attractive or receptive to male dogs. No overt vulvar discharge is present, and the vulva is small. Vaginal cytology is predominated by small parabasal cells, with occasional neutrophils and small numbers of mixed bacteria (Fig. 54.3). The endoscopic appearance of vaginal mucosal folds is flat, thin, and red. The physiologic controls terminating anestrus are still under investigation but involve spontaneous deterioration of luteal function and decline of prolactin secretion. It has been shown that the administration of dopamine agonists shortens the interestrous interval, which in some instances is associated with inhibition of prolactin release (prolactin is luteotrophic). The natural termination of anestrus is induced by an increase in the pulsatile gonadotropin-releasing hormone (GnRH)–induced secretion of pituitary gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Hypothalamic GnRH secretion is itself pulsatile, its intermittent secretion a physiologic requirement of gonadotropin release. Mean concentrations of FSH are moderately elevated and those of LH slightly elevated during anestrus. At late anestrus, the pulsatile release of FSH increases, causing proestrus folliculogenesis. Estrogen concentration is basal (2-10 pg/mL) and progesterone at nadir (<1 ng/mL) at late anestrus. Anestrus normally lasts from 1 to 6 months.

During proestrus, the bitch becomes attractive to male dogs but is still not receptive to breeding, although she may become more playful. A serosanguineous to hemorrhagic vulvar discharge of uterine origin is present, and the vulva is mildly enlarged. Vaginal cytology shows a progressive shift from small parabasal cells to small and large intermediate cells, superficial-intermediate cells, and finally superficial (cornified) epithelial cells, reflecting the degree of estrogen influence (Fig. 54.4). Red blood cells (RBCs) are usually but not invariably present. The vaginal mucosal folds appear edematous, pink, and round (Fig. 54.5). FSH and LH are low during most of proestrus, rising during the preovulatory surge. Estrogen rises from basal anestrus concentration (2-10 pg/mL) to a peak (50-100 pg/mL) at late proestrus, whereas progesterone remains basal (<1 ng/mL) until rising at the LH surge (1.5-4 ng/mL). Proestrus lasts from 3 days to 3 weeks, with a 9-day average. The follicular phase of the ovarian cycle coincides with proestrus and very early estrus.

During estrus, the normal bitch displays receptive or passive behavior, enabling breeding. This behavior correlates with decreasing estrogen and increasing progesterone concentrations. Serosanguineous to hemorrhagic vulvar discharge may diminish to variable degrees. Vulvar edema

TABLE 54.1

Salient Characteristics of the Canine Estrous Cycle

STAGE	LENGTH	BEHAVIOR	IMPORTANT HORMONES	VAGINAL CYTOLOGY	VAGINOSCOPY	REPRODUCTIVE ACTIVITY	DISCHARGE, VULVA
Anestrus	1-6 months	Asexual	E baseline (2-10 pg/mL) P nadir (<1 ng/mL) GnRH pulsatile increase FSH moderate elevation LH slight elevation	Scant parabasals	Flat, white	Uterine involution/ repair	None Small
Proestrus	3 days-3 weeks	Attractive Not receptive	E peaks (50-100 pg/mL) P rises (1.5-4 ng/mL) GnRH pulsatile FSH increases LH surges (>1)	RBCs, parabasals transitioning to intermediates and superficials	Edematous, pink	Folliculogenesis	Hemorrhagic Enlarged
Estrus	3 days-3 weeks	Receptive	E declines P rises (4-35+ ng/mL)	Superficials ± bacteria, RBCs	Progressive crenulation	Ovulation Ova maturation Copulation Fertilization	Serosanguineous Enlarged
Diestrus	2-3 months	Not receptive, diminished attractiveness	E low P elevated (15-80 mg/mL) then declines LH pulsatile Prolactin rises	Parabasals Neutrophils ±Bacteria	Flat	Implantation Pregnancy or pseudopregnancy	Diminishing sanguineous Modest enlargement

E, Estrogen; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone; *P,* progesterone.

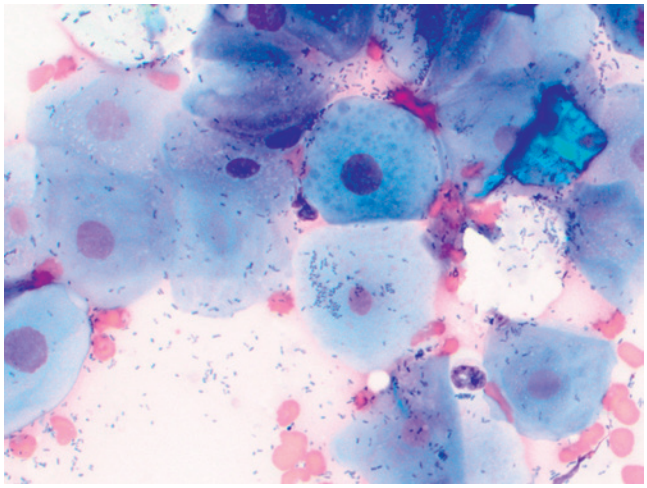


FIG 54.4
Proestrus vaginal cytology, showing intermediate cells and red blood cells, with numerous extracellular opportunistic bacteria.

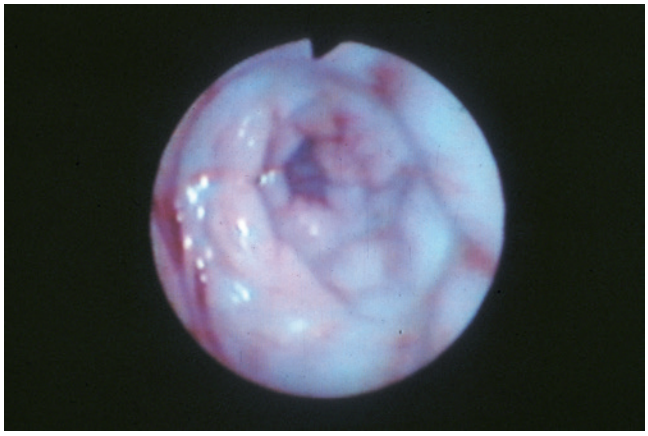


FIG 54.5
Vaginoscopic appearance of edematous vaginal folds during proestrus.



FIG 54.6
Vulvar appearance,estrus.

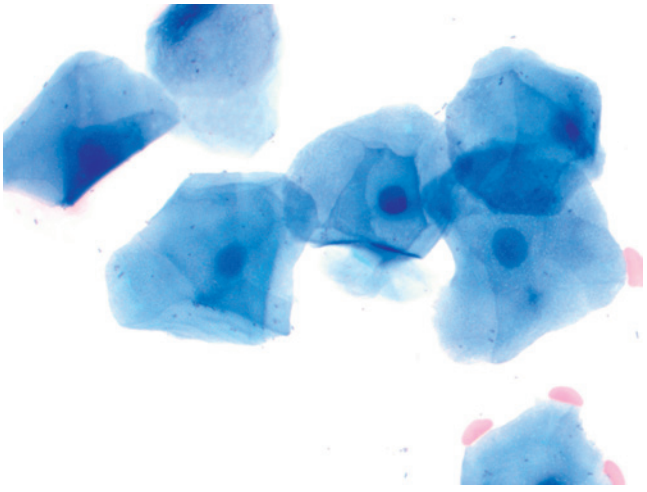


FIG 54.7
Estrus vaginal cytology, showing superficial cells with both pyknotic nuclei and anuclear cells.

tends to be maximal (Fig. 54.6). Vaginal cytology remains predominated by superficial cells; RBCs tend to decrease but may persist throughout (Fig. 54.7). Vaginal mucosal folds become progressively wrinkled (crenulated) in conjunction with ovulation and oocyte maturation (Fig. 54.8). Estrogen concentrations reduce markedly after the LH peak, while progesterone concentrations steadily increase (usually 4-10 ng/mL at ovulation), marking the luteal phase of the ovarian cycle. Estrus lasts 3 days to 3 weeks, with an average of 9 days. Estrous behavior may precede or follow the LH surge; its duration is variable and may not coincide precisely with the fertile period. Ovulation of primary oocytes occurs 2 days after the LH surge; oocyte maturation occurs 2 to 3 days later. The life span of secondary oocytes is 2 to 3 days.

During diestrus, the normal bitch becomes refractory to breeding, with diminishing attraction of male dogs. Vulvar discharge diminishes and edema slowly resolves. Vaginal cytology is abruptly altered by the reappearance of parabasal epithelial cells and frequently neutrophils (Fig. 54.9). The appearance of vaginal mucosal folds becomes flattened and flaccid. Estrogen concentrations are variably low, and progesterone concentrations steadily rise to a peak of 15 to 80 ng/mL before progressively declining in late diestrus. Progesterone secretion is dependent on both pituitary LH

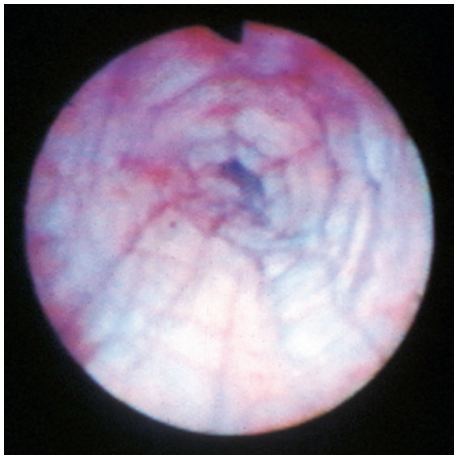


FIG 54.8
Vaginoscopic appearance of crenulated vaginal mucosal folds during estrus.

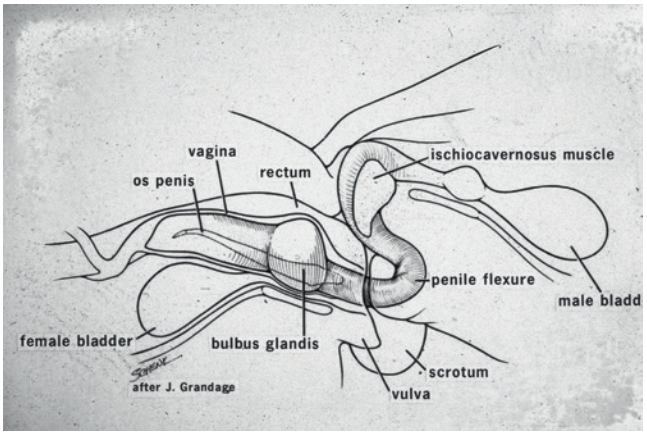


FIG 54.10
Schematic of the canine copulatory lock.

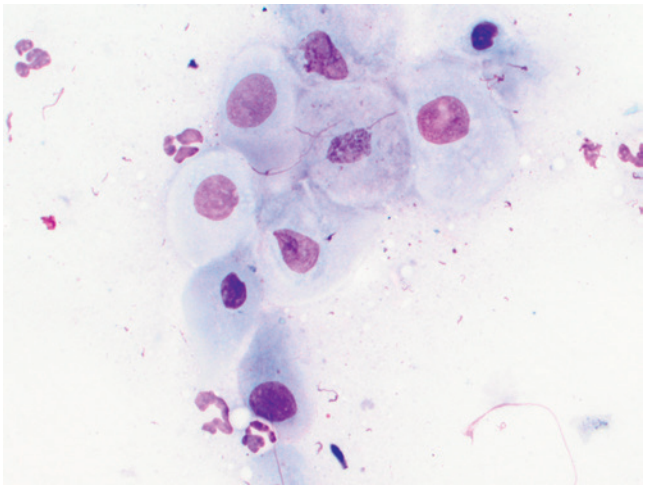


FIG 54.9
Diestrus vaginal cytology showing parabasal and intermediate cells and neutrophils.

and prolactin secretion. Proliferation of the endometrium and quiescence of the myometrium occur under the influence of elevated progesterone. Diestrus usually lasts 2 to 3 months in the absence of pregnancy. Parturition terminates pregnancy 64 to 66 days after the LH peak. Prolactin concentrations increase in a reciprocal fashion to falling progesterone at the termination of diestrus or gestation, reaching much higher values in the pregnant state. Mammary ductal and glandular tissues increase in response to prolactin levels.

CANINE OVULATION TIMING: EVALUATION OF THE ESTROUS CYCLE TO IDENTIFY THE OPTIMAL TIME TO BREED

Individual bitches can have nonproblematic variations of the normal estrous cycle, be presented at variable times during their estrous cycle for evaluation, or exhibit pathologic variations in their cycle. Each of these scenarios requires veterinary interpretation. Considerable variation exists within the normal range of events in the reproductive cycle. The clinician must differentiate between bitches with normal estrous cycles but unexpected patterns and those with true abnormalities. This usually entails monitoring a bitch during an entire estrous cycle. Detection of individual variation within the normal range of events in a fertile bitch can be crucial to providing effective counseling concerning breeding management. Evaluation of the estrous cycle for true abnormalities is an important part of the workup of the apparently infertile bitch (see Chapter 55).

SERUM HORMONE INTERPRETATION

Estrogen

During the follicular phase of the ovarian cycle, increasing estrogen causes an increased turnover rate of vaginal epithelial cells, resulting in the progressive cornification seen on vaginal cytology and thickening of the vaginal wall in preparation for copulation with an interlocking tie (Fig. 54.10). Also seen is progressive edema of the vaginal mucosa, seen with endoscopic examination. Estrogen assays are performed by many commercial laboratories. However, the information given is of little value for ovulation timing, because peak estrogen levels are variable from bitch to bitch, and even relative changes do not correlate to ovulation or the fertile period. Estrogen is best assessed by serial vaginal cytologies and vaginoscopy. Estrogen levels do not indicate the fertile period, because ovulation is triggered by the LH surge, not an estrogen peak. Examination of the cells on the surface of the vaginal epithelium will give information about the stage of the estrous cycle, primarily by showing the presence or absence of an estrogen effect. It is important to always begin ovulation timing with vaginal cytologic evaluation to confirm the bitch is actually in heat and to identify the proper time to initiate cost-effective serial progesterone testing. Serum

hormone testing during proestrus—when vaginal cytology is primarily parabasal and intermediate cells—is costly and not contributory to actual ovulation timing.

Competence in vaginal cytologic analysis should be acquired by any clinician offering reproductive services, because commercial laboratory interpretation of serial cytologies is costly and not timely. Proper technique is important to obtain cells representative of the hormonal changes occurring. The sample should be collected from the cranial vagina, because cells from the clitoral fossa, vestibule, urethral papilla, or vestibulovaginal junction are not as indicative of the stage of the cycle (Figs. 54.11 and 54.12). The vaginal cytology swab should be rolled onto a slide without overlap or smearing (Fig. 54.13). Under the influence of increased estrogen levels, the number of layers making up the vaginal epithelium increases dramatically, presumably to provide protection to the mucosa during copulation. As estrogen rises during proestrus, the maturation rate of the epithelial cells increases, as does the number of keratinized cornified epithelial ("superficial") cells seen on a vaginal smear. Full cornification continues throughout estrus until the diestrual shift occurs, signifying the first day of diestrus. The vaginal smear then changes abruptly from full cornification to 40% to 60% immature (parabasal and intermediate) cells over a 24- to 36-hour period, accompanied by neutrophils. If vaginal cytologic examination is performed until the diestrual shift is observed, a retrospective analysis of the date of the LH surge (7-10 days previously), ovulation and ova

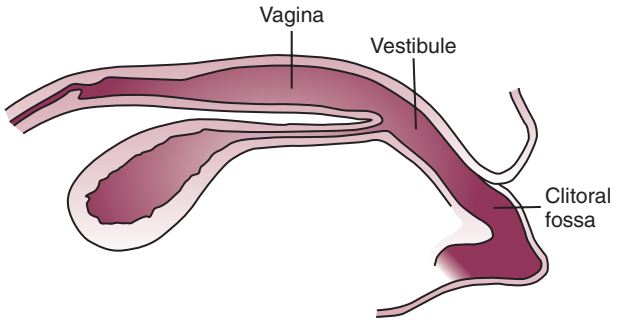


FIG 54.11
Schematic showing the anatomic orientation of the vestibule and vagina of the bitch.

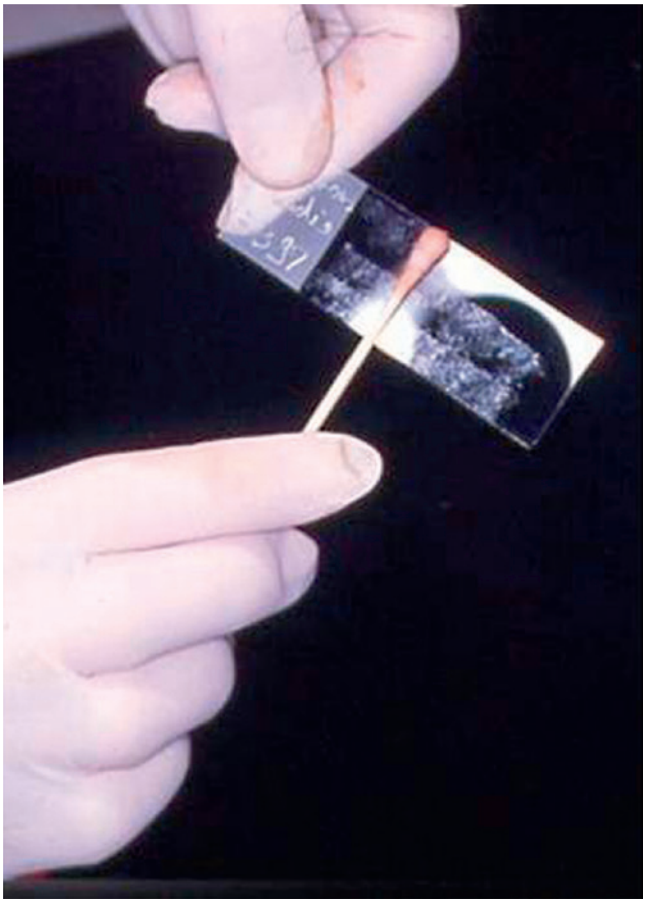


FIG 54.13
Rolling the vaginal swab onto a slide results in a single layer of cells to stain and evaluate.

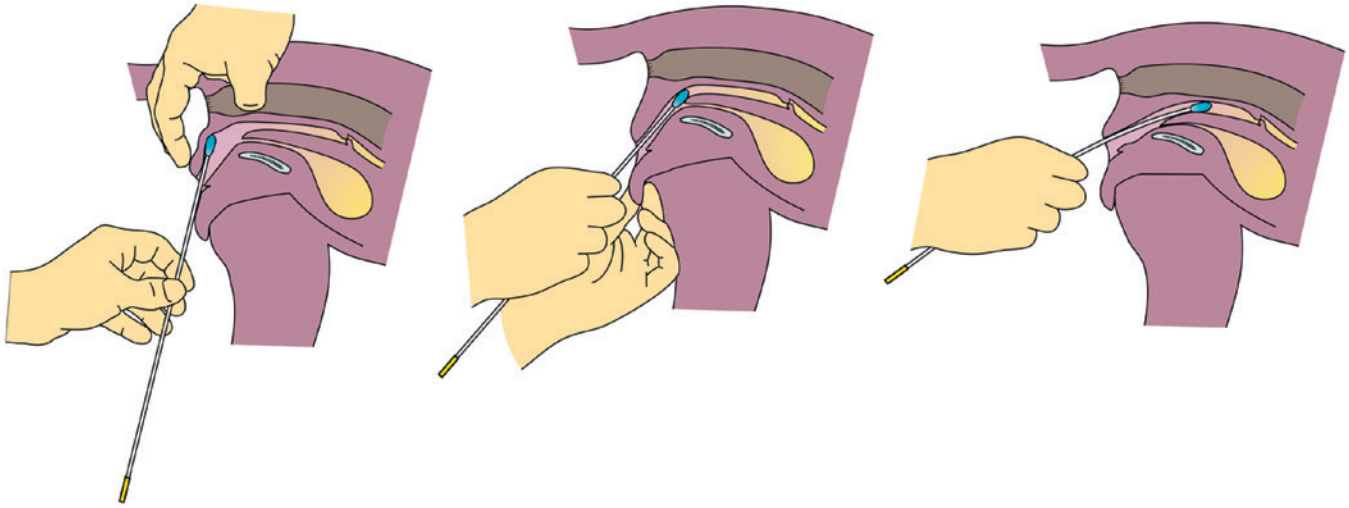


FIG 54.12
Schematic illustrating proper placement of the cotton-tipped swab for vaginal cytology.

maturation (~24-48 hours after the LH surge), and the fertile period (~3-6 days after the LH surge) can be obtained. It is the least expensive way to perform ovulation timing, albeit retrospective. It can also be very useful if evaluation of gestational age becomes important, because parturition occurs 56 to 58 days from the diestrual shift.

Luteinizing Hormone

At the end of the follicular phase of the estrous cycle, a marked increase in LH over its usual basal values occurs over a 24- to 48-hour period, followed by a return to baseline. This surge in LH is thought to take place in response to the decline in estrogen/progesterone ratio that occurs as estrogen levels decrease and progesterone rises. The LH surge triggers ovulation and thus makes it the central endocrinologic event in the reproductive cycle of the bitch, with all events after being consistent between bitches. Daily serial measurement of LH to identify the exact date of the LH surge is therefore the most accurate diagnostic tool for timing breedings. Affordable semiquantitative in-house kits (Status-LH [Synbiotics/Pfizer/Zoetis]) are available for measuring serum LH levels in the dog, identifying the preovulatory LH surge and thus the time of ovulation and the true fertile period. LH testing is the most accurate means of ovulation timing and should be considered the gold standard. However, samples must be drawn daily at about the same time of day, because the LH surge may have a duration of only 24 hours in many bitches and could be missed if even one day was skipped. Commercially available LH kits can be subject to variable operator interpretation, so the same person should run the tests if possible. Serum progesterone testing must always be done in concert with LH testing in the event that the LH surge is missed.

Progesterone

Unique to the bitch, progesterone begins to rise at approximately the time of the LH surge (actually before ovulation), enabling indirect detection of the LH surge. Rising progesterone acts synergistically with declining estrogen to reduce edema of the vulva and vagina, which can be appreciated on vaginoscopic exam, and to cause the bitch to accept copulation. Other observable clinical signs of ovarian luteinization (production of progesterone) are minimal. Serial blood samples performed every 2 days once vaginal cytology is roughly 70% superficial cells can be used to identify the initial rise in progesterone (usually > 1.5 ng/mL), which indicates the LH surge has occurred. Progesterone can be assayed by radioimmunoassay (RIA) or chemiluminescence at most veterinary commercial laboratories. Several in-house semiquantitative kits are also available. Human laboratories are acceptable if previously cross-checked with a veterinary laboratory for comparability. By examination of the range and overlap of progesterone values at different points in proestrus and estrus, it becomes clear that no one absolute value of progesterone correlates to any particular event. Progesterone varies at the point of the LH surge from 0.8 to 3.0 ng/mL, from 1.0 to 8.0 ng/mL at ovulation, and from 4.0 to more than 30.0 ng/mL during the fertile period. However, if accurate serial quantitative progesterone assays are obtained, the LH surge may be estimated as the first day a distinct increase in progesterone concentration is seen, commonly between 1.5 and 4.0 ng/mL. This will not be as accurate as actual identification of the LH surge by use of an LH assay, but estimation of the LH surge using progesterone results is still very useful and often more widely available, less costly, and more convenient. When timing breedings using semiquantitative in-clinic progesterone assays, only a range of progesterone is obtained, not an actual number, making it difficult to accurately identify the exact day of the initial rise in progesterone or the true fertile period. Technical problems with these kits have occurred, so these assays should only be used for ovulation timing for routine natural or fresh artificial breedings involving fertile dogs, where a wider margin of error is acceptable. A safe rule of thumb to follow is that when kit testing indicates progesterone has risen above 2.0 ng/mL, breeding should begin. Optimal ovulation timing for chilled semen breedings, breedings involving subfertile bitches or stud dogs, or frozen semen breedings should utilize quantitative progesterone assays from commercial laboratories; the cost difference is minimal. Regardless of which assay is used, an additional test should always be performed 2 to 4 days after the initial rise is detected to indicate that the cycle has progressed as expected, functional corpora lutea have formed, and ovulation has occurred; progesterone concentration should be over 5.0 ng/mL.

Vaginoscopy may be performed throughout the cycle as an adjunct to vaginal cytologic analysis and hormonal assays, especially when evaluating an unusual cycle or if only one breeding is planned. Vaginoscopy is especially useful if a bitch is initially presented late, after the day of the LH surge, with greater than 90% superficial cells on vaginal cytology and progesterone of above 3.0 ng/mL. Maximal crenulation (puckering of the vaginal mucosa) occurs when the ova are mature and most fertilizable, and can be judged quickly with vaginoscopy. The vagina of the bitch is relatively long compared with other domestic animals; the total length from the cervix to the vulva (including the vestibule) has been reported to be 10 to 14 cm in an 11-kg bitch. The canine cervix is not accessible by digital palpation per vaginam nor can it be visualized with an ordinary vaginal speculum or otoscope; both are too short. Consequently, equipment for visualizing the entire vagina and approaching the canine cervix or accessing the uterus from the vagina must be long (e.g., up to 29 cm for large breeds, 33 cm for giant breeds) (Fig. 54.14). In addition, the presence of vaginal mucosal folds and the position of the cervix in the bitch require the use of rigid equipment to access the cervix; pediatric proctoscopes suffice for visualization of the vaginal mucosa, but fiberoptic vaginoscopes permit superior optics and multiple channels for sampling and insemination (Figs. 54.15, 54.16, 54.17). Hormone-induced changes in the vaginal mucosa enable estrual bitches to tolerate vaginoscopy without sedation or anesthesia.



FIG 54.14
Image showing the appropriate length of vaginoscope required to visualize the canine cervix for transcervical insemination.



FIG 54.15
Endoscopic vaginoscope Karl Storz Hopkins Telescope with protective external sheath, 30-degree telescope, 3.5-mm width, 3 ports, and 29-cm working length.



FIG 54.16
Endoscopic vaginoscope Karl Storz Uretero-renoscope with telescope and instrument sheath combined into one 8F to 13.5F unit with 3 ports and 34-cm working length.



FIG 54.17
Norwegian rigid transcervical catheters.

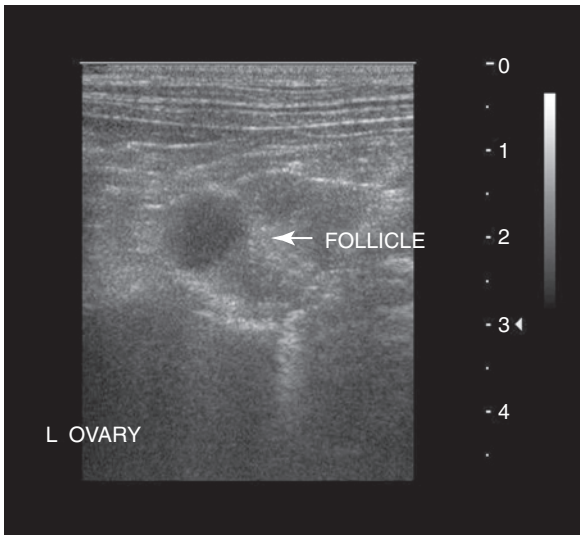


FIG 54.18
Normal sagittal canine left ovary in the follicular phase of the estrous cycle. The developing follicles *(arrow)* will increase in size over time to the point of ovulation.

Ultrasonography can be used to identify ovulation in the bitch, but early attempts were discouraging. The small size of the ovaries and their similarity to close structures make them difficult to visualize. Recent improvements in scanhead technology and operator expertise have made ovarian ultrasound more effective. During proestrus, multiple anechoic follicular cystic structures can be identified, enlarging with time (up to 1.0 cm in diameter). These structures ultimately have distinct thin walls and anechoic fluid centers with distal enhancement (Fig. 54.18). The surface of the ovary may become irregular or lumpy. The anechoic fluid-filled follicles acutely become hypoechoic to hyperechoic corpora hemorrhagica at the time of ovulation, progressing over several days to a thicker walled corpora lutea (Fig. 54.19). The ovarian follicles do not collapse in the bitch and queen. During diestrus the ovaries may be lobular; the corpora lutea are obvious hypoechoic structures of variable size. Results show a close correlation to ovulation as predicted by LH and progesterone testing. The main drawback is that imaging must be performed 2 to 3 times daily when ovulation is anticipated.

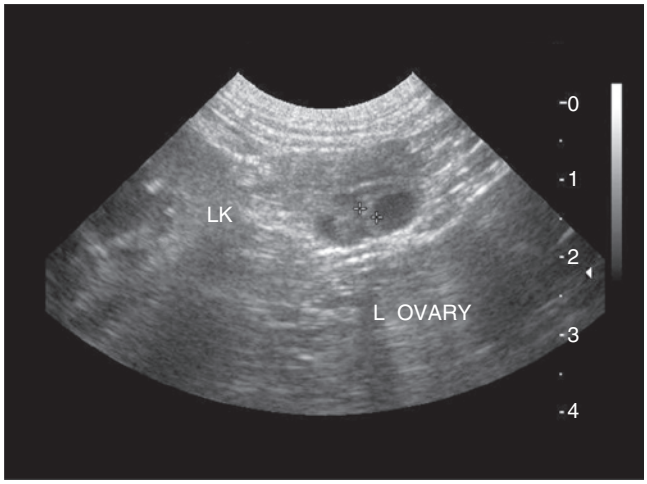


FIG 54.19
Normal sagittal canine left ovary in the luteal phase of the estrous cycle. The corpora lutea have thicker walls *(cursors)* and anechoic contents, and will persist for >45 days postovulation. *LK,* Left kidney.

CLINICAL PROTOCOL: VETERINARY BREEDING MANAGEMENT

Clients usually delay breeding the maiden bitch until after 2 years of age for ethical reasons and to complete genetic screening; bitches are physiologically capable of breeding in their first estrous cycle. Breeder clients should be advised to notify the clinic when they first notice a bitch for which timing is planned is in season, based on vaginal discharge or vulvar swelling/attraction to males. Even the most astute owner can fail to notice the true onset of proestrus for a few days, so early clinical evaluation (on day 3-5 after the onset of the heat cycle) with vaginal cytology is advised. The type of breeding anticipated should be determined because it dictates the types of testing to be done. Early proestrus should be documented by vaginal cytologic analysis (<50% cornification/superficial cells). A baseline progesterone level might be informative if the true onset of the cycle is unknown (baseline is < 1.0 ng/mL). Vaginal cytology should be performed every 2 to 4 days until a significant progression in the percent of superficial cells is seen, usually above 70% superficial cells. At that point, appropriate serial hormonal assaying should begin. For routine breedings (natural, fresh, or fresh chilled artificial insemination with fertile dogs), progesterone testing may be done every other day until a rise in progesterone above 2.0 ng/mL is identified. The day of the initial rise in progesterone is identified as "day zero." Two natural breedings or artificial inseminations are advised between days 3 through 6, ideally 48 hours apart. Which 2 days are chosen depends upon overnight chilled semen shipping options and the involved clients' and veterinarians' schedules. As described, confirmation of progesterone rise above 5.0 ng/mL by the time of breeding is optimal. Vaginal cytologic examination should always be performed on the day of artificial insemination to confirm previous timing; 90% to 100% superficial cells should be present. If clients delay in bringing dogs to the veterinarian for assistance with breeding until after several days of failed attempts, vaginal cytology must still be performed to confirm the bitch is still in estrus. Progesterone testing will then confirm whether she is postovulatory and breeding is timely, but an initial artificial insemination is advised while awaiting progesterone results. A shift to less than 50% superficial cells indicates diestrus has begun. Only intrauterine inseminations performed on the first day of diestrus have been successful in producing pregnancy.

When increased accuracy of ovulation timing is necessary (i.e., for frozen semen breedings or breedings with subfertile stud dogs or brood bitches), LH testing is recommended. Once the LH surge is identified, breeding days may be planned. The day of the LH surge is also day zero. Two natural, fresh, or chilled semen artificial breedings are advised from days 3 through 6. Frozen semen inseminations are advised on day 5 or 6 of the fertile window owing to the short life span of cryopreserved thawed sperm. In addition, at least one progesterone assay should be performed after the LH surge is identified to document that progesterone levels continue to rise and are above 5.0 ng/mL before breeding. If client economics dictate minimal testing, serum can be batched on a daily basis and quantitative progesterone tests performed initially as advised earlier. When the initial rise in progesterone is identified, the batched serum can be specifically evaluated for the day of the LH surge, confirming identification of day zero.

Clinicians may be questioned about using vaginal glucose content and electrical conductivity for ovulation timing. Increased glucose has been identified in vaginal secretions as an inconsistent finding; it is thought to be a result of insulin antagonism that occurs secondary to altered hormone concentrations at the time of the progesterone rise. This finding is not reliable, however, and is not recommended for ovulation timing. Measurement of electrical conductivity of vaginal mucus is used routinely to time breedings in foxes and has been studied in several other species, including the dog. It was found that electrical resistance increases as estrus approaches and then plateaus at a maximal level for several days, changes that may be due to rising estrogen. Although it appeared that ovulation occurred at some point during this period of maximum electrical resistance, it has not been shown to be correlated to the LH surge or the fertile period, so it cannot be recommended for accurate ovulation timing. Ovulation timing is not usually performed in the queen whose estrual behavior is obvious; in fact vaginal swabbing can induce ovulation. Estrus cytology in the queen is similar to the bitch, but superficial cells retain their nuclei (Fig. 54.20). Serum progesterone can be used to confirm ovulation if >5.0 ng/mL.

Behavior and other observations (flagging, attractiveness to males) should also be made at each examination, but less weight should be put on these parameters (Videos 54.1 and 54.2). The clinician should keep in mind that the most accurate ovulation timing occurs when information from several

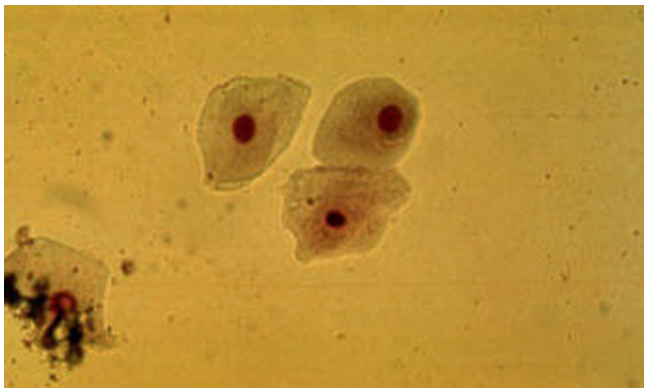


FIG 54.20
Feline vaginal cytology, estrus showing nucleated superficial cells.

BOX 54.5

Semen Collection Equipment

Teaser bitch (estrual)
Artificial vagina (AV)
Test tube rack
Plastic collection tubes
Pipettes
Nonskid rug or floor mat
Slide warmer turned on and loaded with slides
Slide covers, glass pipettes
Fresh semen extender solution, warmed to body temperature
Lubrication jelly, not spermicidal
Light microscope 10×, 40×, 100×

tests is pooled (vaginal cytologies, vaginoscopy, and progesterone or LH tests).

THE DOG AND TOM

SEMEN COLLECTION

If a natural breeding cannot be accomplished (mismatched mate size, geriatric or inexperienced stud) or is precluded by geography (shipped extended and chilled semen), or frozen semen is to be used, veterinary participation may be sought for artificial insemination. Both intravaginal and intrauterine artificial insemination techniques are successful in the bitch. Neither is commonly performed clinically in the queen, hampered by the technical demands of semen collection in the tom (special training to an artificial vagina [AV], electroejaculation, or chemically [100 µg/kg medetomidine IM]-induced ejaculation with urethral catheterization) and ovulatory status (usually induced) of the queen (Zambelli et al., 2006; Zambelli et al., 2007). Most veterinarians have not developed semen collection and insemination skills in school. Successful artificial insemination requires proper collection technique, appropriate semen handling, and correct insemination procedure. Semen evaluation should be performed regularly in valuable stud dogs. Special training is required to develop additional skills in semen chilling, advanced methods of artificial insemination, and semen freezing (cryopreservation). Cryopreservation of canine semen is routinely performed both by veterinarians and technicians. According to the American Kennel Club (AKC) only a licensed veterinarian should perform artificial insemination of cryopreserved semen. Several proprietary programs train individuals for canine cryopreservation. Research and debate concerning semen extenders, freeze buffers, and the role of prostatic fluid in sperm function are ongoing.

Successful collection of fresh canine semen usually requires a quiet room, a rug or mat for good footing, an estrual or teaser bitch, and minimal special equipment (Box 54.5). Attempts to put the dog at ease before the collection may include simple measures like the veterinarian and assistant not wearing their white laboratory coats. Medical procedures (vaccination, temperature evaluation, rectal examinations, venipuncture) should be performed *after* the collection or by another veterinarian. When performing semen collections, one should try to approximate the stud dog's usual breeding environment as closely as possible. Collection should be performed on the floor except in toy breeds accustomed to being collected on a table. Repeat visits allow the stud dog to relax, and he will soon learn what he is there for. Semen quality is generally better when an estrous teaser bitch is present and cooperative, and the stud's libido is highest. Stud dogs can withhold the sperm-rich (middle or second) portion of the ejaculate if they are uncomfortable. Semen collection equipment (AVs, semen collection tubes) is commercially available. Make sure all collection equipment is at room temperature, dry and clean, and free of spermicidal agents.

Support the teaser bitch in a standing position, restraining her head as necessary. Allow the stud to familiarize himself with the surroundings, the bitch, and the handlers. Position yourself next to the stud as he approaches the bitch. Right-handed people usually work best on the stud's left side. Allow the stud to mount, placing the AV in front of his penis with the left hand as he thrusts toward the bitch. If he does not mount or thrust, gently massaging the penis through the prepuce with the right hand will stimulate an erection. When he is 50% erect or less, push the prepuce behind the bulbus glandis. If this cannot be done easily, pull the dog off the bitch, walk him away to allow detumescence, and bring him back to the bitch to try again. Ejaculation within the prepuce is painful. During thrusting, reposition your hands to provide gentle constant pressure just behind and incorporating the bulbus glandis, keeping the AV over the penis. Rapid thrusting coincides with penetration. After achieving full erection, coinciding with the tie, the stud will dismount and try to step over the bitch and your arm to turn. Help the stud by lifting his leg over your arm and swinging the penis 180 degrees so it is directed backwards between his legs. Keep the dogs standing near each other during the ejaculation phase so the stud believes a breeding is occurring. Visualize the semen as

it flows into the clear tubes. There are three fractions in the ejaculate. The first is clear, from seminal vesicles. The second fraction is white sperm-rich fluid (SRF). The third fraction is clear and is prostatic fluid. The SRF is usually released at the end of rapid thrusting after the dog has turned. Semen evaluation requires the collection of only the first and second fractions. Evaluation of a small amount of the more voluminous prostatic fluid is adequate. If collecting for fresh artificial insemination, avoid collecting the clear prostatic fluid.

The total volume of SRF in a large dog is generally no more than 1 to 2.5 mL. After collection is complete, leave the AV on the stud until his erection has diminished. This keeps the penis more comfortable. Apply some water-soluble lubrication to the base of the penis, under the AV, to facilitate return of the penis within the prepuce. Always check to make sure the paraphimosis (penis extruded outside of the prepuce) resulting from artificial semen collection resolves. It is not necessary to walk the dog; he will lose the erection in 5 to 15 minutes. Care must be taken to ensure that the stud dog has adequately recovered from his erection before he is retired; preputial skin and hair can strangulate the tip of the penis.

SEMEN ANALYSIS

Semen analysis should include evaluation of sperm morphology, motility, and concentration. If the clinician is uncomfortable with semen evaluation, the sample or a representative aliquot can be submitted to a commercial laboratory for analysis, but motility must be judged immediately postcollection. Normal canine semen has 70% (or greater) progressively forward-moving sperm with moderate speed and good-quality motility. To evaluate motility, place a drop of the sperm-rich fraction (second) on a warmed slide, using a pipette. Top with a coverslip and observe under ×10 to ×40 magnification. Sperm should swim across the slide in a relatively straight path, with minimal gyrations (good-quality motility) and brisk speed (moderate to fast motility). No sperm-to-sperm agglutination should occur, but agglutination to egg yolk particles in extenders or other cells in semen can be normal. If motility is poor, prepare another drop on a new slide and double-check. Observe individual live, unstained sperm cells under ×40 magnification for morphology. Abnormal sperm can have coiled tails, proximal droplets, abnormal shape to heads, double tails or heads, and altered acrosomes (Figs. 54.21 and 54.22). The acrosome is difficult to visualize without phase contrast microscopy. Iatrogenic damage can cause detached heads and bent tails. Observing fresh sperm before staining permits evaluation for stain-induced morphologic abnormalities. Prepare another slide with the pipette as you would a peripheral blood smear, air dry, and stain for morphologic analysis. Both Wright-Giemsa and eosin-nigrosin stains are commonly used. At least 100 to 200 sperm should be tallied for morphology, noting both normal cells and sperm cells with head abnormalities (misshapen, double), neck abnormalities (proximal droplets), and tail abnormalities (distal droplets, coiled, double). Using a differential cell counter labeled for



FIG 54.21
Canine spermatozoa, phase contrast microscopy.

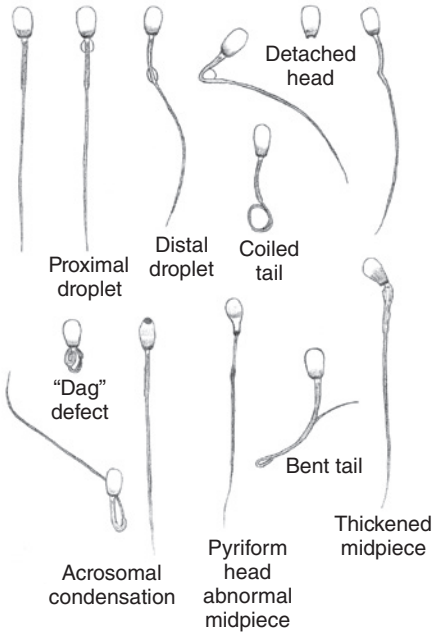


FIG 54.22
Schematic of sperm morphology showing common abnormalities.

semen morphology with the previously mentioned categories is helpful. If a high number of morphologic abnormalities occur poststaining, a different methodology may be advisable. Note the presence of epithelial cells, white blood cells (WBCs), and RBCs as well (record as 1-4+/HPF). Sperm counts can be performed by using a hemocytometer and Unopette. Alternatively, the automated Spermcue (MOFA Inc.) produces a very accurate automated sperm count. Multiply the number of sperm per milliliter by the volume of the SRF to obtain the number of sperm per ejaculate. Normal dogs have 200 to 400 million (up to a billion) sperm per ejaculate. Normal toms' average semen volume varies by the method of collection (10.5-233 μ/L); sperm count 21 to 57

million per ejaculate. Higher numbers of morphologically normal sperm can be associated with the breeding season in cats. In general, felids are frequently affected by teratospermia, with normal toms having ~40% abnormal spermatozoa. This is thought to be a result of decreased genetic variation (Pukazhenthi et al., 2006).

FRESH, FRESH CHILLED, AND FROZEN ARTIFICIAL INSEMINATIONS (AI)

VAGINAL AI

With the bitch standing and comfortably restrained, using digital guidance or a pediatric proctoscope, an insemination pipette is passed dorsal to the urethral papilla and as far into the vaginal vault as it will comfortably go. Vaginal inseminations are best accomplished using a clean mare uterine infusion pipette, which is rigid and allows placement of the semen near the cervix in the cranial vagina. Care must be taken to not contaminate the semen with water, disinfectant chemicals, or spermicidal lubricants. A 5F to 10F polypropylene urinary catheter can also be used. Nonlatex syringes are advised when handling semen.

Maneuvering the pipette over and under vaginal mucosal folds usually must be done. Once the pipette is in place, the bitch's hindquarters are elevated onto an assistant's lap in a wheelbarrow position. The bitch's abdomen should not be compressed; the assistant should restrain the bitch by firmly holding her hocks in a comfortable position. The syringe of semen is then attached to the pipette, elevated, and slowly infused. If the semen will not infuse, back the pipette out slightly. A small amount of air in the syringe will empty the pipette contents into the vagina. It is not necessary to continue elevating the bitch's hindquarters after insemination as this does not impact conception or litter size; walking the bitch for 10 minutes without allowing her to sit or urinate is optimal.

INTRAUTERINE AI

Cryopreservation and subsequent thawing diminish semen quality and longevity post-thaw, necessitating special insemination technology. Frozen thawed semen has to be placed close to the site of fertilization (fallopian tubes) for acceptable conception rates; intrauterine insemination is highly recommended. The process and resultant quality of canine cryopreservation have improved with time; insemination techniques remained challenging until transcervical endoscopic intrauterine access was developed. Data supporting the benefit of intrauterine deposition of frozen thawed semen exists (40%-90% conception rates). We extrapolate that better conception rates will occur with intrauterine insemination of chilled, extended, or otherwise compromised (subfertile) semen as well.

The normal anatomy of the vagina and cervix in the bitch hampered transcervical access to the canine uterus until rigid cystourethroscopes were developed and adapted for vaginoscopy. Historically, intrauterine insemination required an invasive procedure (laparotomy or laparoscopy) in the bitch. In addition to its invasiveness, laparotomy requires general anesthesia, which many clinicians and clients find objectionable for an elective procedure such as artificial insemination (Fig. 54.23). Laparoscopic approach to the canine uterus has been used infrequently, especially in the practice setting, because of its relative invasiveness (multiple incisions, insufflation) and because it requires special equipment, expertise, and anesthesia. In some countries, elective surgeries such as these are not considered ethical.

Transcervical insemination is becoming more common, with techniques developed in Scandinavia and New Zealand. The Norwegian catheter is a 20- to 50-cm steel catheter with a 0.5- to 1-mm tip with a protecting nylon sheath, and is used with a 6- to 20-mL syringe. Transcervical catheterization is accomplished by passage of the Norwegian catheter through the vagina and blindly into the cervix by palpation and manipulation of the cervix through the abdominal wall. This technique requires training and expertise. Perforation of the uterus or vagina could occur, and introduction of vaginal flora into the abdomen is possible. Good success rates have been reported using this technique.

Transcervical insemination with fiberoptic visualization of the caudal cervical os permitting catheterization is optimal. After visualization, a polypropylene catheter is passed



FIG 54.23
Surgical insemination: injection of semen into the uterine horn.

through the channel of the scope, through the cervical os, and then into the uterine lumen (Figs. 54.24, 54.25, 54.26). Visualization of the cervix requires manipulation of vaginal folds and scope, and catheterization of the cervix takes expertise and requires practice. Sedation is usually unnecessary. This technique has a moderate learning curve. Once practiced enough to gain expertise, it is highly rewarding and often can be performed in a matter of minutes. Transcervical catheterization for intrauterine insemination is best accomplished with the estrual bitch standing on a nonskid surface under light restraint and with gentle support of the abdomen to inhibit sitting. The scopes were developed to be used in the standing bitch. The operator should work from a sitting position, with the arms raised to the level of the vulva to minimize muscle fatigue. An adjustable examination table and chair can facilitate operator comfort. Participation of the breeder client for restraint and observation is generally rewarding (Video 54.3). Concerns surrounding potential introduction of vaginal flora into the uterine lumen using transcervical insemination have not been realized thus far and are unlikely, given recent knowledge that normal vaginal flora can be found in the uterus during proestrus and estrus. Certainly vaginal flora is introduced into the uterine lumen with natural breedings; the uterus has an inherent ability to normalize its flora after estrus. Maintenance of the equipment is minimal; 10 minutes' soaking of the immersible parts in dilute (1:1000) chlorhexiderm solution and thorough rinsing with distilled water is optimal. Stronger disinfectants raise concerns because of their spermicidal potential. As with all reproductive procedures, the success is greatly influenced by the timing of ovulation in the bitch and the quality of the semen from the male. An increased number of inseminations (not limited by anesthesia and invasive surgery) may improve conception and is now feasible with this equipment and technique.

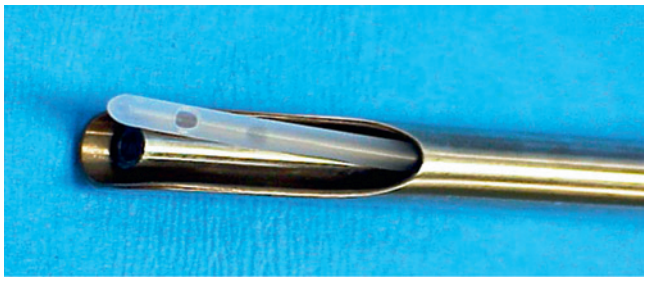


FIG 54.24
Working end of the vaginoscope, showing the catheter tip adjacent to the telescope.



FIG 54.25
Placement of the vaginoscope in the vaginal lumen to visualize the cervix.

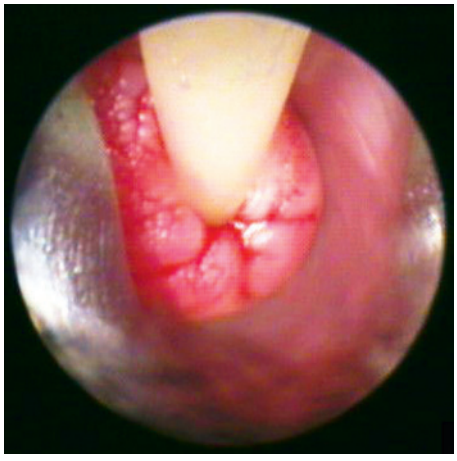


FIG 54.26
Transcervical insemination. Semen being transferred into the uterine lumen via a polypropylene catheter under endoscopic guidance.

ESTROUS CYCLE OF THE QUEEN

Puberty in the queen usually occurs at 9 to 10 months of age but may occur as early as 4 months or as late as 2 years. Because queens are seasonal breeders, the season in which the kitten was born influences the age at which puberty occurs. Cyclicity is dependent on the photoperiod, with queens requiring 12 hours or more of light to maintain normal cyclicity. Cyclicity and folliculogenesis stop abruptly in queens exposed to less than 8 hours of light but resume an average of 16 days after returning to a 14-hour photoperiod. Seasonality is more pronounced in queens exposed to natural lighting, especially at higher latitudes. Long-haired breeds tend to be more seasonal than short-haired breeds. The phases of the feline estrous cycle are proestrus, estrus, interestrus, diestrus or pseudopregnancy, and anestrus.

Proestrus precedes estrus and lasts 1 to 2 days but is recognized in fewer than 20% of queens. During proestrus, the female is attractive to but not willing to accept the male. The queen may rub against objects, vocalize, and assume a lordosis; she will place her front quarters on the ground, elevate her hindquarters, and lift her tail to one side. When the dorsal caudal area is stroked, she will tread with her hind legs.

Estrus is the period of sexual receptivity and lasts an average of 7 days (3-16) and then subsides for an average of 9 days (3-14). The external genitalia have no conspicuous changes in appearance, but behavioral changes are pronounced during estrus. Because of the relatively short length of proestrus, the ability to inadvertently induce ovulation by mechanical vaginal stimulation, and the less dramatic cellular changes observed in the queen, vaginal cytology is not used as commonly in the queen as it is in the bitch. Behavioral observations should dictate the best time to place the queen with the tom. Estrus duration is unaffected by breeding or ovulation. If vaginal cytology is desirable, flushing a small amount (<1.0 mL) of saline in and out of the vagina provides better results than using a swab. Interestrus is the period between successive estrus periods if ovulation does not occur. If the queen is not bred or otherwise stimulated to ovulate, estrus will occur every 2 to 3 weeks during the appropriate photoperiod. If the queen ovulates, corpora lutea are formed and secrete progesterone. If the queen is not pregnant, diestrus (pseudopregnancy) results and lasts 35 to 40 days. Anestrus is the seasonal period when the cat does not cycle; artificial lighting can alter its occurrence.

Queens are induced ovulators and ovulate in response to vaginal stimulation; however spontaneous ovulation can occur in the queen. Ovulation is most commonly triggered by copulation or mechanical stimulation of the vagina, which causes a reflex stimulation of the hypothalamus via pathways in the spinal cord. The hypothalamus releases GnRH, which then causes a release of LH from the anterior pituitary. LH then stimulates ovulation and the development of corpora lutea. Other forms of stimulation can occasionally be responsible for ovulation; active corpora lutea have been found in cats unexposed to males or artificial coital stimuli. Ovulation depends on adequate LH release, with both a peak concentration and duration of elevation being important. The LH release occurs within minutes of coitus and peaks about 1 to 2 hours later. Release of LH is partially dependent upon the duration of prior exposure to estrogen (time in estrus), so the LH response varies depending on the day of estrus at which coitus occurs. Multiple copulations result in higher concentrations of plasma LH and are more likely to result in ovulation than a single mating. The duration of elevated LH in plasma also determines whether ovulation occurs, with LH decreasing to baseline values within 12 to 24 hours after a single mating or after multiple matings at less than 2-hour intervals. However, LH remains elevated up to 38 hours after multiple mating intervals every 3 hours. To achieve sufficient LH release, repeated breeding at a reasonable interval should be encouraged. The LH response to a single mating can vary substantially, and neither single nor multiple copulations can ensure ovulation. To increase the likelihood of ovulation, breeders should try to maximize the number of matings and breed on successive days of estrus. Ovulation occurs 24 to 60 hours postcoitus and may vary depending on the mating pattern. Ideally, if the onset of estrus has been detected, breeding should occur on days 2 to 3.

Three alternatives following estrus are possible in the queen: (1) ovulation does not occur, and an average 9-day (4-22) interestrus occurs before the next proestrus; (2) ovulation occurs without fertilization, resulting in a 35- to 40-day pseudopregnancy and a 1- to 10-day interestrus; or (3) pregnancy. Pseudopregnancy occurs when ovulation and corpora lutea formation occur but not conception. The corpora lutea produce progesterone, with levels rising rapidly from basal concentrations to a peak of 16 to 17 ng/mL 18 to 25 days postovulation. After the peak, progesterone concentrations decline to basal at approximately 40 days postovulation. The normal pseudopregnancy duration lasts 35 to 40 days. The corpora lutea appear to have a preprogrammed finite life span in that they are not subject to regression from uterine sources of prostaglandins. Lactation (pseudogenetra) at the end of pseudopregnancy is less common in the queen. Induction of pseudopregnancy eliminates the so-called constant estrus seen in nonovulating queens; the duration of that estrus is not changed. After pseudopregnancy, the queen will go through a 2- to 4-week anestrus and either return to estrus if she is cycling or transition into a prolonged seasonal anestrus.

Gestation in the cat is 63 to 66 days when measured from a fertile mating. Because kittens born before 60 days of gestation have little chance of survival, it is important that gestation progress to 63 days for maximum kitten viability. Because queens are induced ovulators, clients should be counseled to recognize the signs of estrus and place queens with tomcats for the minimal time to accomplish a fertile mating (usually 2-3 days), making evaluation of the length of gestation more predictable. Unlike in the pseudopregnant queen, corpora lutea do not regress in the pregnant queen; despite placental progesterone production, the ovaries are needed to maintain pregnancy past day 50. As in the bitch, progesterone concentrations vary over time. Prolactin from the anterior pituitary also appears to be required for pregnancy maintenance.

OBSTETRICS

PREGNANCY DIAGNOSIS

Early pregnancy evaluation permits optimal obstetrics (Table 54.2). Pregnancy detection by abdominal palpation (best at



TABLE 54.2

Methods for Pregnancy Diagnosis

GESTATIONAL AGE (FROM LH SURGE)	METHOD
25+ days	Abdominal ultrasound, abdominal palpation
>20-31 days	Witness Relaxin (Pfizer/Zoetis)
>50 days	Radiography

approximately 30 gestational days) confirms the presence of an enlarged, presumably gravid uterus, but gives little other information. Produced by the placenta, the hormone relaxin is elevated in both canine and feline pregnancies. A serum relaxin assay (Witness Relaxin Assay [Synbiotics/Pfizer]) is available for pregnancy diagnosis after about 25 to 31 days of gestation, but it can be falsely negative with small litter size. Radiography (55+ days of gestation, the later the better) can confirm the presence of fetuses. Before fetal skeletal mineralization, other causes for uterine enlargement (hydrometra, mucometra, pyometra) cannot be ruled out radiographically. Radiography cannot be used to assess fetal viability in a timely fashion. Once profound postmortem changes have occurred, radiography can detect intrafetal gas accumulation or abnormal skeletal arrangement, suggesting fetal death. A single lateral projection is preferred; counting both fetal spines and fetal skulls most accurately provides litter size. A ventrodorsal projection should only be made if the litter size is difficult to determine on the lateral view, or if fetal positioning in relation to the pelvic canal needs evaluation at term. A fetal count radiograph carries little risk of teratogenic results in the fetuses (30-50 mrem).

Ultrasound is the optimal method to evaluate for conception, fetal health, and litter size and is best performed around 30 days after breeding (~35 days gestation). In later gestation (>50 days) the fetuses are so large the uterine horns overlap, making an accurate litter size evaluation difficult. Serial pregnancy ultrasound can identify resorption and early fetal death, as well as intrauterine pathology. Transabdominal pregnancy ultrasound is performed with the bitch or queen in comfortable, padded dorsal recumbency and does not require sedation or clipping. A variable frequency scanhead (6.0-8.0 MHz) typical of most small animal clinics is adequate. Doppler is not required. The normal uterus is best located by scanning transversely between the urinary bladder and the colon. The cervix and uterine body are seen as a continuous hypoechoic round structure dorsal to the anechoic urinary bladder and ventral to the hyperechoic crescent-shaped colon. A full urinary bladder acts as an acoustic window to improve uterine imaging. Once the uterine body has been identified, the uterine horns can be located by scanning in transverse toward each kidney. Definite ultrasonographic diagnosis of pregnancy in the queen based on the appearance of a "fetal pole" (the actual fetus) can be made at 15 to 17 days postcoitus, although gravid uterine enlargement (4-14 days) and the presence of a gestational sac (11-14 days) can be detected even earlier (Fig. 54.27). Ultrasonographic detection of the canine blastocyst (a 2-3 mm spherical hypoechoic structure surrounded by a hyperechoic rim within the uterus containing the fetus) occurs at 19 to 20 days post-LH surge (Fig. 54.28). Ultrasonography permits evaluation of early fetal cardiac motion (21-22 days post-LH surge), fetal movement (31-32 days post-LH surge), and the fetal heart rate, enabling assessment of viability. By 30 days' gestation pregnancy diagnosis with ultrasonography is straightforward.

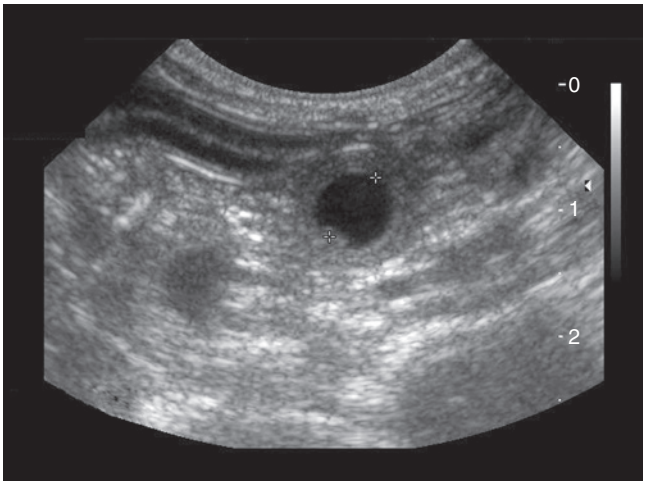


FIG 54.27
Early pregnancy ultrasound, feline; gestational age 18 days. Cursors mark the gestational sac diameter in centimeters. The fetal pole is evident at 7:00.

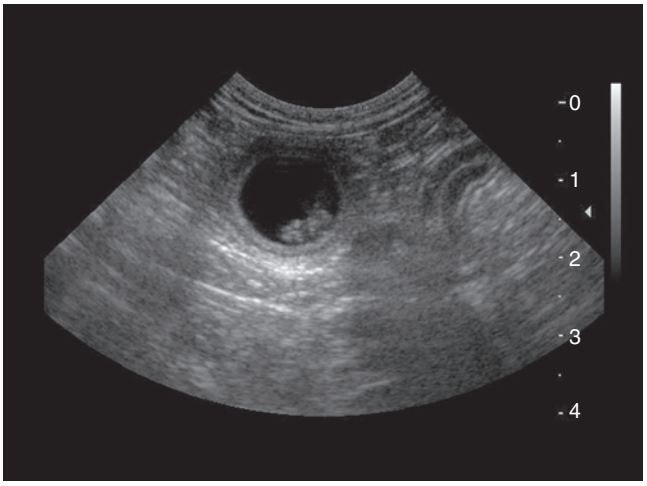


FIG 54.28
Pregnancy ultrasound canine; gestational age 20 days.

GESTATIONAL LENGTH AND FETAL AGE DETERMINATION

Determining gestational age can be of vital importance if an elective cesarean section is planned or prolonged gestation suspected. Accurate determination of gestational length can be difficult, especially if numerous copulations occurred and no ovulation timing was performed. Prolonged gestation is a form of dystocia. Gestation in the bitch is more challenging to calculate than in the cat, because bitches are spontaneous ovulators. Normal gestation in the bitch is 56 to 58 days from the first day of diestrus, 64 to 66 days from the initial rise in progesterone from baseline, or 64 to 66 days from the LH surge. Normal gestation can actually be 58 to 72 days from the first instance the bitch permitted breeding. Breed and litter size can influence gestational length. Predicting gestational length without prior ovulation timing is difficult because of the disparity between estrual behavior and the

actual time of conception in the bitch, and the length of time semen can remain viable in the bitch reproductive tract (often > 7 days). Breeding dates and conception dates do not correlate closely enough to permit very accurate prediction of whelping dates, and clinical signs of term pregnancy are not specific. Radiographic appearance of fetal skeletal mineralization varies at term, and fetal size varies with breed and litter size. Because the queen is an induced ovulator (ovulation follows coitus by 24-36 hours), gestational length can be predicted more accurately from breeding dates, assuming copulation provided adequate coital stimulation for the LH surge and subsequent ovulation, and a limited number of copulations were permitted. The gestational length of queens ranges from 52 to 74 days from the first to last breeding. The mean gestational length is 65 to 66 days. Because of the poor outcome with the delivery of premature puppies and kittens, elective intervention is best delayed until stage I labor has begun (see Chapter 55) or prolonged gestation is confirmed ultrasonographically.

Fetal age determination by ultrasonography is accomplished by either the first appearance of certain visible structures or by measuring certain parameters. Measurements such as the gestational sac diameter, fetal occipitosacral (crown-rump) length, and fetal head (biparietal) diameter can be obtained ultrasonographically, relate closely to fetal age, and permit estimation of gestational length and parturition dates, especially useful if ovulation timing was not performed (Figs. 54.27, 54.29, 54.30; Video 54.4). Variation in breed size (especially in the dog), brachycephalic canine and feline breed variation, and individual variation in measuring technique are sources of inaccuracy in predicting fetal age with ultrasound (Box 54.6).

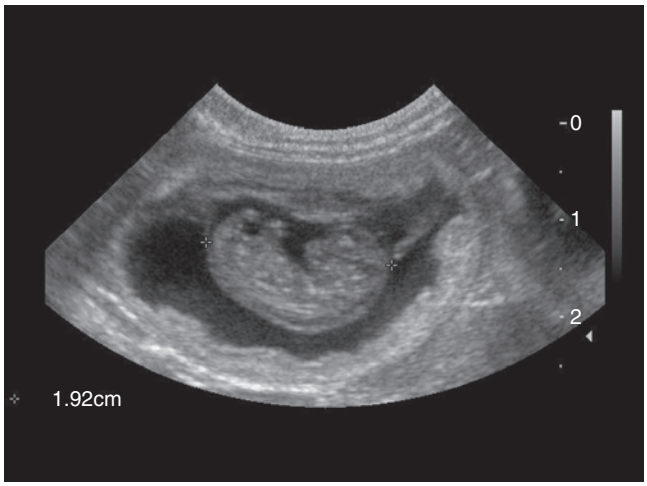


FIG 54.29
Pregnancy ultrasound feline; gestational age 30 days. Cursors mark the occipitosacral (crown-rump) length in centimeters.

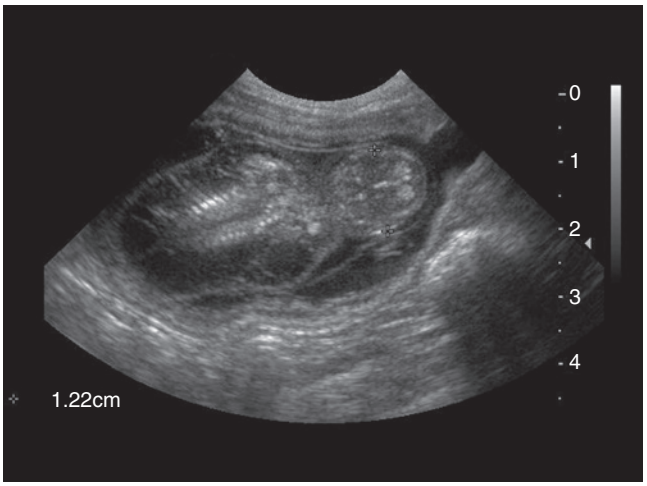


FIG 54.30
Pregnancy ultrasound canine; gestational age 39 days. Cursors mark the biparietal (head) diameter in centimeters.

BOX 54.6

Formulas to Predict Gestational Age and Days Before Parturition in the Dog and Cat

Gestational age (GA) is based on days post–luteinizing hormone (LH) surge in the dog and days postbreeding in the cat. Gestational sac diameter (GSD), crown-rump length (CRL), head diameter (HD), and body diameter (BD) measurements are in centimeters. Days before parturition (DBP) is based on 65 ± 1 days post-LH surge in the dog and 61 days postbreeding in the cat.

Gestational Age in the Dog (±3 Days)
Less than 40 days

GA = (6 × GSD) + 20
GA = (3 × CRL) + 27

Greater than 40 days

GA = (15 × HD) + 20
GA = (7 × BD) + 29
GA = (6 × HD) + (3 × BD) + 30

Days before parturition in the dog

DBP = 65 − GA

Gestational Age in the Cat (±2 Days)
Greater than 40 days

GA = 25 × HD + 3
GA = 11 × BD + 21

Days before parturition in the cat

DBP = 61 − GA

Novel feline gestational aging using crown-rump length

Y = 0.2423 × GA − 4.2165
Y is mean litter CRL (cm)
GA is the gestational age
(Solve for GA)

Data modified from Nyland et al: *Small animal diagnostic ultrasound*, ed 2, Philadelphia, 2002, Saunders.

Suggested Readings

Alwen S. Anthelmentics in pregnant and breeding dogs. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:1–10.

Bassu G. Evaluation of ovulation with ultrasound. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:529–535.

Beccaglia M. Ultrasonographic gestational aging in the bitch and queen. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:537–542.

Beccaglia M, et al. Comparison of the accuracy of two ultrasonographic measurements in predicting the parturition date in the bitch. *J Small Anim Pract*. 2006;47:670.

Beehan D, Lyle S. Vulvovaginal malformations. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:549–557.

Bones Larson J. Nutrition in pregnancy and lactation in the bitch and queen. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:389–394.

Cain J. An overview of canine reproductive services: getting started. Davidson AP, editor: Clinical theriogenology. *Vet Clin North Am Small Anim Pract*. 2001;31(2):209–219.

Cain J. Breeding management of the bitch and ovulation timing for optimal reproductive efficiency. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:23–32.

Casal ML. Breeding management of the queen: Pre-breeding examination and breeding husbandry. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:33–40.

Eilts B, et al. Factors affecting gestation duration in the bitch. *Theriogenology*. 2005;64:242.

England G, et al. Relationship between the fertile period and sperm transport in the bitch. *Theriogenology*. 2006;66:1410.

Fascetti AJ, Delaney SJ. Feeding the healthy dog and cat. In: Fascetti AJ, Delaney SL, eds. *Applied veterinary clinical nutrition*. Wiley Blackwell; 2016:75–94.

Goodman M. Ovulation timing: concepts and controversies. Davidson AP, editor: Clinical theriogenology. *Vet Clin North Am Small Anim Pract*. 2001;31(2):219–237.

Karmi N. Genetic disease counseling in the pre-breeding examination. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:147–152.

Kelley RL, et al. Impact of maternal dietary DHA and reproductive activity on DHA status in the canine. In: *Proceedings from 6th Congress of the International Society for the Study of Fatty Acids and Lipids*. Vol. 149. 2004.

Pukazhenthi BS, et al. The impact and potential etiology of teratospermia in the domestic cat and its wild relatives. *Theriogenology*. 2006;66(1):112–121. https://doi.org/10.1016/j.theriogenology.2006.03.020.

Rijsselaere T, et al. New techniques for the assessment of canine semen quality: a review. *Theriogenology*. 2005;64:706.

Silva T, et al. Sexual characteristics of domestic queens kept in a natural equatorial photoperiod. *Theriogenology*. 2006;66:1476.

Tsutsui T, et al. Relation between mating or ovulation and the duration of gestation in dogs. *Theriogenology*. 1706;66:2006.

Wilson MS. Transcervical insemination techniques in the bitch. *Vet Clin North Am*. 2001;31(291):291–304.

Zambelli D, et al. Ultrasonography for pregnancy diagnosis and evaluation in queens. *Theriogenology*. 2006;66:135.

Zambelli D, Cunto M. Semen collection in cats: techniques and analysis. *Theriogenology*. 2006;66(2):159–165.

Zambelli D, et al. Effects of ketamine or medetomidine administration on quality of electroejaculated sperm and on sperm flow in the domestic cat. *Theriogenology*. 2007;68(5):796–803.

CHAPTER 55

Clinical Conditions of the Bitch and Queen



NORMAL VARIATIONS OF THE ESTROUS CYCLE

LATER THAN TYPICAL PUBERTY

The onset of the first estrous cycle occurs after a bitch attains 70% of her adult height and body weight. Small breeds generally begin their first estrous cycle between 6 and 10 months of age; large breeds can begin as late as 18 to 24 months, which causes owner concerns. Family histories (dam and female siblings) can help predict the anticipated onset of reproductive cycling. Efforts at differentiating delayed puberty (as perceived by an owner) from an actual failure to have reproductive cycles should be postponed until a bitch is at least 2 to 2.5 years old. Bitches with delayed puberty generally have normal reproductive cycles once initiated. Housing such a bitch with another cycling bitch can promote her proestrus secondary to the pheromone-related "dormitory effect." Estrous induction protocols (later in this chapter) can be attempted if the bitch is mature (i.e., at least 24-30 months of age) and breeding is desired.

Puberty in the queen usually occurs at 9 to 10 months of age. Puberty can occur as early as 4 months or as late as 2 years; because cats are seasonal breeders, the season in which the kitten was born influences the age at which puberty occurs. Cyclicity is dependent on the photoperiod, with queens requiring 12 hours or more of light to maintain normal cycling.

SILENT HEAT CYCLES

The occurrence of a silent heat cycle must be ruled out during evaluation of a bitch suspected of failing to have estrous cycles. Fastidious bitches with minimal vulvar swelling, scant vulvar discharge, and few behavioral changes can have proestrus/estrus that escapes human detection ("silent"), especially in the absence of an intact male dog. Diestrus normally lacks clinical signs. Proestrus and estrus tend to become more apparent as the bitch ages. Performing weekly vaginal smears to detect cytologic proestrus, housing the bitch near an intact male, or using white bedding can aid in prospective detection of a silent heat, permitting proactive ovulation timing and breeding (see Chapter 54). Intact male dogs typically note pheromones produced days to weeks before the onset of proestrus and spend more time sniffing the bitch or her urine. Performing monthly progesterone assays permits retrospective identification of estrus but will not facilitate breeding in that cycle unless acquired before diestrus. Silent heat cycles must be differentiated from true primary anestrus. True primary anestrus in the bitch that fails to experience an estrous cycle is most likely due to a disorder of sexual development and is uncommon.

SPLIT HEAT CYCLES

Bitches with split heat cycles, in which proestrus and possibly early estrus occur without ovulation or progression to diestrus, can be thought to have abnormally short cycles, lack of sexual receptivity, or infertility if breedings were forced or artificial insemination performed without confirming ovulation. Waves of folliculogenesis with increased estrogen production but without ovulation occur in split heats. Follicular atresia follows, no luteal phase with progesterone production occurs, and normal sexual receptivity fails to develop. These cycles typically occur in young bitches and are characterized by periods of hemorrhagic vulvar discharge typical of proestrus, attractiveness to males, and usually no receptivity. In young bitches, split cycles are thought to be due to immaturity. These cycles can also occur in mature bitches with a history of normal past cycles, usually in association with stress. Increased endogenous cortisol levels associated with stress (travel, shipping, kenneling) may inhibit the luteinizing hormone (LH) surge and associated ovulation. Two to 10 weeks after a split cycle, another proestrus typically begins and could proceed to ovulation. Eventually most young bitches with split heats progress through a normal estrus to diestrus. The condition is not associated with reproductive pathology in the young or stressed bitch, and no treatment is recommended. Breeding a bitch in surroundings familiar to her is advised if stress might have altered a previous cycle. Delaying shipping of a bitch for breeding until after the LH surge (progesterone initial rise) has occurred is optimal. Using shipped semen (chilled,

extended) is a better alternative. Serial vaginal cytologies documenting the influence of estrogen on vaginal mucosa early in the cycle, and progesterone assays performed 1 to 2 weeks later documenting folliculogenesis without ovulation or luteinization (i.e., serum progesterone [<1.0 ng/mL]), confirm the diagnosis of a split heat. Occasionally split cycles occur on a regular basis in a mature bitch. This not only makes them difficult to breed but is likely associated with abnormalities of the hypothalamic-pituitary-ovarian axis.

ABNORMALITIES OF THE CANINE ESTROUS CYCLE

Abnormal estrous cycles result in either a prolongation or an abbreviation of a phase of the cycle, or an alteration in the normal sequence of events. An owner's interpretation of a bitch's behavior and physical characteristics may not equate with the actual physiologic events, necessitating prospective documentation of the cycle through vaginal cytologic evaluation, vaginoscopy, behavioral evaluation, and serum LH and progesterone levels as described (see Chapter 54).

PROLONGED PROESTRUS/ESTRUS

Prolonged proestrus or estrus occurs when a bitch displays vulvar bleeding for more than 30 to 35 consecutive days, accompanied by attractiveness to males. Greater than 80% to 90% superficial cells are present on vaginal cytology. Such bitches are variably receptive to breeding. Prolonged proestrus and/or estrus results from a persistent production of estrogens, with or without small elevations in progesterone. If present, progesterone enhances the presence of sexual receptivity. Endogenous sources of prolonged estrogen exposure in the bitch, with or without progesterone, include ovarian follicular cysts and secretory neoplasias. Secretory anovulatory follicular ovarian cysts tend to be solitary, lined with granulosa cells, and exceed normal preovulatory follicles in size when measured ultrasonographically, ranging from 1 to 5 cm in diameter. Bilateral follicular cysts may indicate a problem with the hypothalamic-pituitary-ovarian axis. Follicular cysts tend to occur in bitches younger than 3 years of age. Ovarian neoplasias capable of producing estrogen occur and include tumors of epithelial origin (cystadenomas and adenocarcinomas) as well as tumors of gonadal-stromal origin (granulosa-theca cell tumors). Ovarian neoplasia tends to occur in bitches older than 5 years of age. Ovarian tumors can occur unilaterally or, less commonly, bilaterally. Functional cystic ovarian pathology and ovarian neoplasia and can occur simultaneously. Cysts found in the contralateral ovary and endometrial hyperplasia accompanying a functional tumor occur most frequently with gonadal-stromal origin tumors.

Other than hyperestrogenism, there are few differential diagnoses for prolonged vulvar bleeding in the bitch. Vulvar bleeding secondary to infection, inflammation, or neoplasia of the genitourinary tract, a vaginal foreign body, or a coagulopathy should be differentiated from prolonged proestrus or estrus. Rare reports of vaginal vascular ectasia causing hemorrhage exist. Excessive exogenous administration of estrogen may be encountered when an ovariohysterectomized bitch is treated for urethral sphincter incompetence with estrogenic compounds or from attempts to prevent unwanted pregnancy using diethystilbesterol or estradiol cypionate in the intact bitch. Small dogs can acquire estrogen exposure iatrogenically from owners using transdermal or aerosolized topical hormone replacement therapy. Recognized sequelae to chronic estrogen exposure include bone marrow dyscrasias, predisposition to the cystic endometrial gland hyperplasia/pyometra complex, and development of ovarian cysts. After confirmation of endogenous hyperestrogenism is obtained through history and vaginal cytologies (which can be confirmed with serum estrogen measurement), abdominal ultrasonography is recommended to evaluate ovarian pathology (Fig. 55.1). Normal preovulatory follicles measure 4 to 9 mm in diameter, smaller than follicular cysts and most functional ovarian neoplasias. Analysis of the estrogen and progesterone levels in fluid from abnormal cystic ovarian structures obtained via ultrasound guidance can be contributory to the diagnosis but is not necessary if serum levels have been obtained. Histologic analysis of tissues obtained surgically confirms the diagnosis and is always indicated.

Because follicular cysts may spontaneously undergo atresia or luteinization, not all bitches experiencing prolonged proestrus or estrus require treatment. Progression of the follicular cyst to an atretic follicle or a corpora lutea can be monitored ultrasonographically, via vaginal cytologic analysis, and by serum estrogen and progesterone measurements. Therapy aimed at terminating prolonged proestrus or estrus becomes necessary if spontaneous regression fails to occur, vaginal bleeding is a continuing nuisance, estrus behavior and the attraction of males is unacceptable, or other complications develop (blood loss anemia, marrow dyscrasias, vaginal hyperplasia). Medical and surgical options exist for treatment of persistent pathologic follicular cysts. Medical

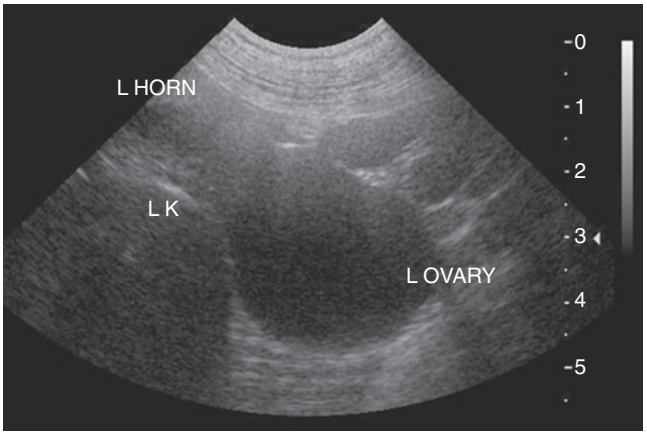


FIG 55.1
Follicular ovarian cyst *(L ovary). LK,* Left kidney, *L Horn,* left uterine horn.

therapies should not place the reproductive health of the bitch at risk. Progesterone treatment of bitches with functional follicular cysts puts the bitch at increased risk for development of cystic endometrial hyperplasia/pyometra and is not advised. Use of gonadotropin-releasing hormone (GnRH; 50-100 µg/bitch intramuscular [IM] q24-48h for up to 3 doses) or human chorionic gonadotropin (hCG; 500-1000 International Units [IU]/bitch IM) has been advocated as effective in inducing cyst regression or luteinization, but results are usually disappointing. GnRH does not appear to be antigenic in the bitch and may be the preferred treatment. Successful induction of cyst regression or luteinization is reflected by a reduction in vulvar discharge, change in vaginal cytology reflecting reduced estrogen effect, diminished attractiveness to males, and normalization of behavior. Serum estrogen concentrations fall and increased progesterone concentrations occur if luteinization results. Ultrasonographic monitoring of ovarian morphology shows regression of hypoechoic structures. Unfortunately, medical treatment of prolonged proestrus or estrus is usually unrewarding; surgical removal of the cyst is the most expedient means of managing the problem. Removal of the cyst alone is optimal, but resection of the associated ovary is usually necessary. Histologic evaluation of the removed tissue confirms the diagnosis and, importantly, permits evaluation for evidence of neoplasia that might warrant additional therapy and a different prognosis. Failure of medical therapies to resolve prolonged proestrus or estrus does not necessarily indicate that ovarian neoplasia is more likely than a follicular cyst. Effective therapy should not be delayed once the diagnosis is made, because prolonged hormonal stimulation of the endometrium contributes to subfertility.

PROLONGED INTERESTROUS INTERVALS

Bitches exhibiting prolonged interestrous intervals (interpreted as a failure to cycle) can have prolongation of either anestrus or diestrus; clinical differentiation is indicated.

PROLONGED ANESTRUS

Prolonged anestrus occurs when no ovarian activity is present for longer than 16 to 20 months in a bitch having previously experienced normal estrous cycles with 6 to 12 month intervals (secondary anestrus). An actual failure to continue to cycle must be differentiated from silent heats, which are normal but not apparent to owners. Bitches do not experience menopause. Underlying disease and iatrogenic causes for failure to cycle should be ruled out by a careful history, physical examination, and database including evaluation of thyroid function (see later). The mechanism by which anestrus is normally terminated in the bitch is not well understood. Dopamine inhibits prolactin secretion. Prolactin concentrations decrease from late diestrus to late anestrus. Both follicle-stimulating hormone (FSH) and LH have been reported as the hormone initiating proestrus folliculogenesis (Maenhoudt, 2012). The dopamine agonists bromocriptine (Parlodel [Novartis]) and cabergoline (Galastop [Vetem]) (5 µg/kg PO q 24h until proestrus is documented) can be used to shorten anestrus in both the normal bitch with inconveniently long interestrous intervals and those with secondary anestrus of unknown etiology; their success in the latter is less predictable. The mechanism by which dopamine agonists induce proestrus could be a direct reduction in prolactin concentration, or more likely a direct dopaminergic action on either the gonadotropic axis or on ovarian gonadotropin receptors. Medical estrous induction can be attempted; contributory pathology can reduce its effectiveness.

PROLONGED DIESTRUS

Prolonged diestrus occurs when progesterone levels remain elevated for longer than 9 to 10 weeks. The clinical behavior of the bitch cannot be differentiated from one experiencing prolonged anestrus. The value of vaginal cytologies, serial serum progesterone levels, and the ultrasonographic appearance of the ovaries and uterus becomes apparent in establishing a diagnosis. Prolonged diestrus occurs secondary to the presence of a luteinized (progesterone-secreting) ovarian cyst or neoplasia (luteoma). Progesterone provides negative feedback to the pituitary-hypothalamic axis, preventing the stimulation of normal ovarian activity. Luteinized cysts can be single or multiple, involving one or both ovaries. Abdominal ultrasonography can identify encapsulated hypoechoic structure(s) within the affected ovary(ies) (Fig. 55.2). Serum progesterone concentrations above 1.0 to 5.0 ng/mL confirm the diagnosis. Treatment with the natural prostaglandin $PGF_{2\alpha}$ (Lutalyse [Pharmacia]) or the synthetic analog cloprostenol (Estrumate [Schering-Plough]) usually causes only a transient decline in serum progesterone levels, indicating partial luteolysis. Surgical removal of the cyst(s) and histologic analysis is the recommended treatment (Fig. 55.3, *A*, 55.3, *B*). Separation of the cyst from the affected ovary is optimal but technically difficult; ovariectomy is usually indicated. Evaluating the presence and extent of accompanying cystic endometrial hyperplasia (CEH) is advisable and can provide valuable information to the owner concerning future fertility of the bitch, which is even more guarded than after

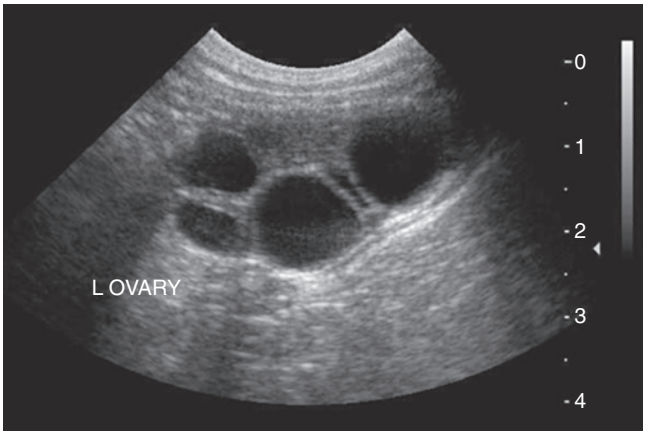


FIG 55.2
Multiple luteal ovarian cysts. *L ovary,* Left ovary.

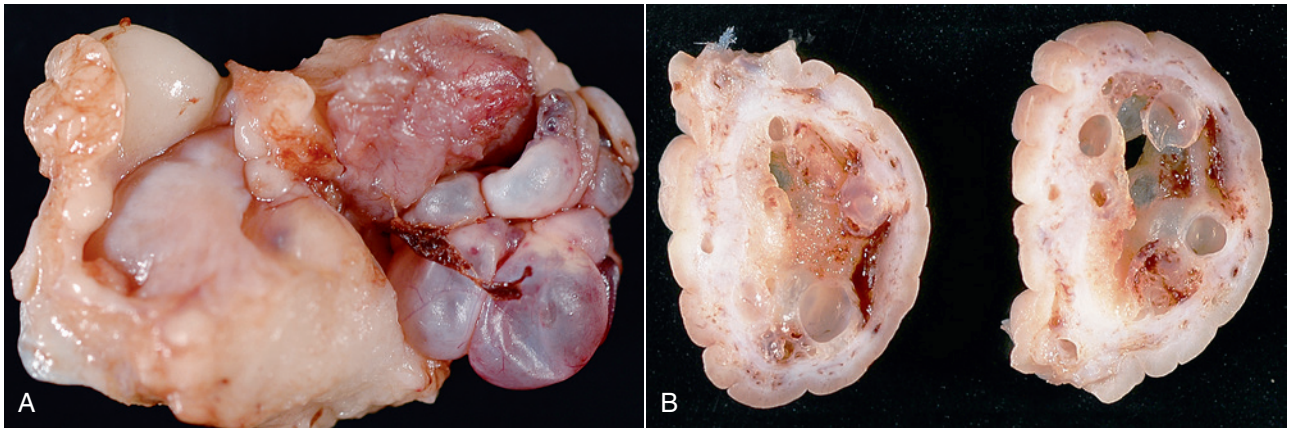


FIG 55.3
Gross specimen showing multiple luteal cysts found in one ovary of a bitch with prolonged diestrus and eventual pyometra. **(A)** Intact ovary. **(B)** Sectioned ovary.

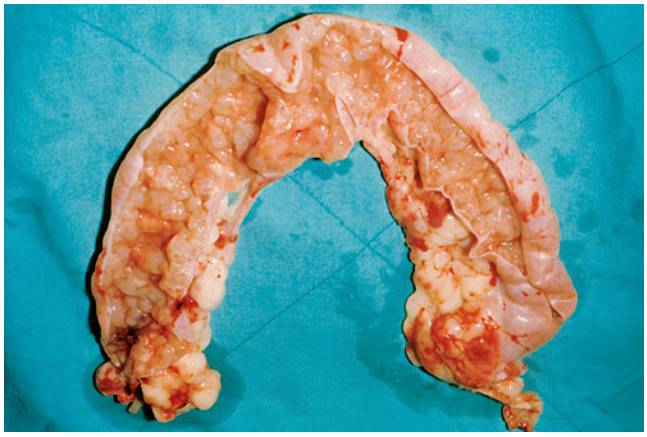


FIG 55.4
Gross specimen, same bitch, cystic endometrial hyperplasia.

resolution of follicular cysts. Cystic endometrial hyperplasia, if present, may resolve partially after elimination of the cyst but still contributes to subfertility (Fig. 55.4). Unfortunately, concern exists that uterine biopsy during diestrus could contribute to pyometra (Schlafer and Gifford, 2008).

Nonfunctional ovarian cysts may cause failure to cycle owing to their mass effect. Rete ovarii cysts and subsurface epithelial structure cysts are examples of nonfunctional ovarian cysts. Increases in plasma estrogen or progesterone concentrations will not be identified, although these cysts have the potential to produce a wide variety of other steroidal compounds without apparent systemic effect. This diagnosis, initially suspected using abdominal ultrasonography, is confirmed by histologic evaluation of surgically removed tissues.

Premature ovarian failure can result in permanent anestrus. Although the functional longevity of the ovaries of bitches is not known, on average the decline in function would not be expected before 7 to 10 years of age. Bitches can reproduce late in life. Prolonged anestrus due to premature ovarian failure could be supported by documenting markedly elevated FSH and LH concentrations, as would be seen after ovariohysterectomy. Such increases indicate a lack of negative feedback to the pituitary and hypothalamus, without any other identifiable cause for anestrus. Immune-mediated oophoritis, diagnosed by ovarian histopathology, could result in prolonged anestrus. A mononuclear infiltrate predominated by lymphocytes, plasma cells, and macrophages has been reported to occur in both ovaries in a bitch experiencing estrous cycle abnormalities. This is an extremely rare disorder.

Hypothyroidism is a potential cause for prolonged interestrous intervals or failure to cycle, but the diagnosis should be well supported by other clinical signs (lethargy, weight gain, bilaterally symmetric alopecia) and clinical pathologic data (hypercholesterolemia, nonregenerative anemia), as well as confirmation of subnormal serum thyroid (total T_4 and free T_4 by equilibrium dialysis) concentrations, ideally supported by elevated endogenous canine thyroid-stimulating hormone (cTSH) concentrations (see Chapter 48). Bitches with circulating antithyroid antibodies may have artificially elevated total T_4 concentrations due to cross-reactivity. Hypothyroid bitches placed on adequate replacement therapy should begin to cycle within 6 months of becoming euthyroid. The presence of immune-mediated thyroiditis is thought to have a genetic basis in some breeds and may occur with other immune-mediated endocrinopathies. Currently this is evaluated by periodic measurement of thyroglobulin autoantibodies (TGAA). The breeding soundness of such bitches should be addressed with clients. Glucocorticoids can feed back on pituitary gonadotropins FSH and LH, causing a failure to cycle, so administration of any steroid medication must be discontinued by taper in a bitch with prolonged anestrus.

SHORTENED INTERESTROUS INTERVALS

Bitches with short (<4.5 months) interestrous intervals can fail to conceive because of incomplete uterine involution and repair, precluding implantation. Classically, bitches

experiencing shortened interestrous intervals are normal in other respects. Ovulation and luteinization occur, and the secondary oocyte is fertilized but fails to implant successfully. Documentation of this disorder requires serial vaginal cytologic evaluations during estrus and diestrus, and serum progesterone concentrations during the luteal phase of at least two consecutive cycles. Currently, there is no reliable, commercially available, consistent preimplantation method of confirming fertilization in the dog. The occurrence of folliculogenesis without ovulation (split heat) and hypoluteiodism (premature luteal failure) should be ruled out. Both require evaluation of serum progesterone concentrations. In the former, ovulation has not occurred and progesterone remains at baseline (<1.0 ng/mL); and in the latter, progesterone concentrations are not maintained above 5.0 ng/mL for the normal length of diestrus (45+ days). True shortened interestrous intervals occur because anestrus is abbreviated. A defect in the hypothalamic-pituitary-ovarian axis could exist, causing interference with the normal maintenance of anestrus. An imbalance of dopamine versus prolactin concentrations have been theorized as contributing to this syndrome. One suggested therapy consists of prolonging anestrus through the use of progestational drugs during the first 3 days of the impending proestrus; this is undesirable because an increased risk of pyometra can occur. Similarly, the advocated use of anabolic compounds to prevent cycling has never been studied critically; the fertility of bitches previously treated with anabolics is not known, and side effects (epiphora, vaginitis, clitoral hypertrophy, hepatopathy, and aggression) do occur.

EXAGGERATED PSEUDOCYESIS (PSEUDOPREGNANCY)

Owners often interpret nonpregnant bitches showing overt signs of pseudocyesis as abnormal. Signs exhibited during overt pseudocyesis include weight gain, mammary gland development and lactation, mucoid vulvar discharge, inappetence, restlessness, nesting, and mothering of inanimate objects. Radiography (after 50+ days of diestrus) or ultrasonography can establish the presence or absence of fetuses. Alternatively, owners could be concerned about bitches showing overt signs of pseudocyesis because they find the behavior or physical symptoms objectionable in a bitch they know is not pregnant.

Pseudocyesis is a normal physiologic phenomenon experienced by any nonpregnant bitch completing the luteal portion of an estrous cycle. These signs are the result of progesterone concentrations declining and prolactin, a luteotroph, increasing. The clinical expression of pseudocyesis varies from indiscernible to (rarely) potentially serious. Clinical signs of pseudocyesis usually are reported from 6 to 12 weeks after estrus. Signs of pseudocyesis are often reported by owners when giving reproductive histories as if its occurrence indicates a reproductive disorder, when in fact pseudocyesis establishes that the bitch has a normal hypothalamic-pituitary-ovarian axis and estrous cycle. Bitches that exhibit signs consistent with a diagnosis of pseudocyesis are probably under the influence of prolactin. Similar concentrations can be demonstrated in bitches that have no clinical signs, suggesting that the former may have increased target organ concentrations or heightened peripheral sensitivity to the hormone. The condition is self-limiting, usually regressing in 1 to 3 weeks, and therapy is not recommended unless the signs are unusually prolonged or pronounced, such as causing mastitis. Unusually persistent cases of inappropriate lactation should be evaluated for hypothyroidism, in which elevated thyrotropin-releasing hormone (TRH) may cause increases in prolactin.

Therapy for pseudocyesis, when recommended, is usually directed at decreasing or eliminating lactation. Therapy is pursued to reduce the likelihood of mastitis occurring secondary to milk stasis, or to diminish lactation-induced household soiling. Minimal measures are recommended. Mammary stimulation via licking, mothering behavior, or warm or cold compressing should be discontinued. Dopamine antagonists, of which phenothiazines are a class, enhance prolactin secretion and should not be administered. Mild sedation with a nonphenothiazine tranquilizer may be helpful. A variety of hormonal and medical therapies have been employed to reduce or stop lactation in pseudopregnant bitches. Side effects, in most cases, outweigh the benefit of most of these medications. Therapy with gonadal hormones, progesterone, estrogen, or testosterone is not recommended owing to complications of repetitive cycles of pseudocyesis, symptoms of proestrus or estrus, and virilization behavior, respectively. Ergot alkaloids are potent prolactin inhibitors (dopaminergic) and can be used to abbreviate exaggerated pseudocyesis. Bromocriptine can be administered at 0.01 to 0.05 mg/kg/day in divided doses until lactation ceases. Vomiting, depression, and anorexia are commonly reported side effects, usually more problematic than the lactation. Cabergoline, administered at 5 µg/kg/day, given divided or once daily for 3 to 5 days effectively decreases prolactin concentrations and diminishes signs of pseudocyesis with fewer side effects but is expensive and must be compounded for use in all but giant breeds. Acupuncture has been suggested to reduce the signs of pseudocyesis. Fasting/water deprivation has no effect on pseudocyesis. Permanent resolution of clinical pseudocyesis requires ovariectomy.

VAGINAL HYPERPLASIA

Estrogen produced during folliculogenesis normally causes a generalized hyperplastic response of the vaginal mucosal epithelium and cornification of the vaginal epithelial cells in preparation for the copulatory lock. This estrogen response can induce a hyperplastic vaginal periurethral mass in some bitches that can prolapse through the vulvar cleft if large enough. The exposed vaginal tissue becomes traumatized and contaminated, and urethral obstruction at the level of the papilla can occur (Fig. 55.5, *A*). Follicular luteinization can be attempted to prematurely decrease estrogen production with GnRH (50-100 µg/bitch IM q 24-48h for up to 3 doses) or hCG (500-1000 IU/bitch IM q 24-48h for up to 3 days); this can compromise fertility if a breeding is

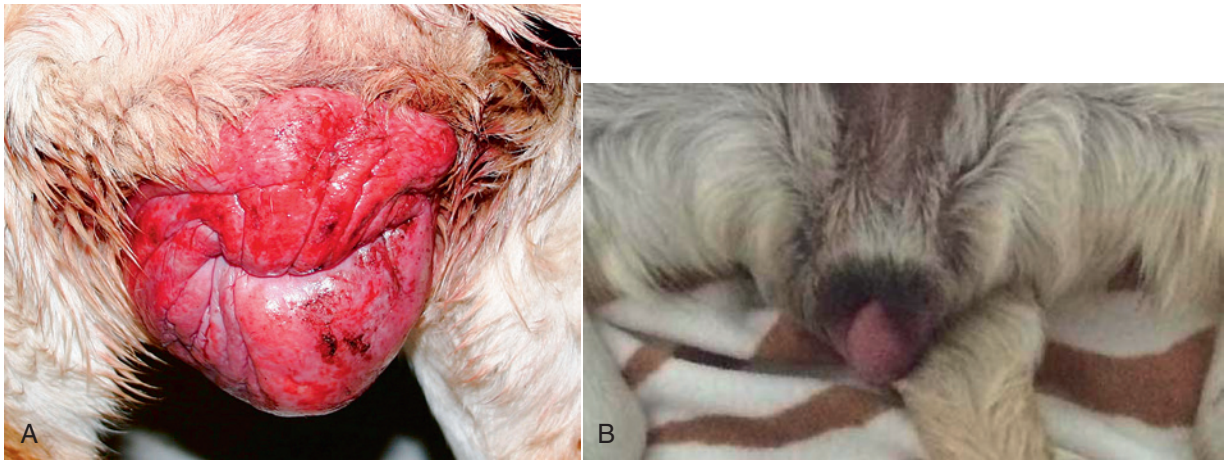


FIG 55.5
Vaginal hyperplasia. **(A)** Labrador Retriever bitch. Note mucosal hyperemia and abrasion secondary to prolapse of vaginal tissue. **(B)** Recurrence at parturition causing obstruction of the distal birth canal.

planned. It is doubtful that medical intervention is of benefit insofar as most bitches resolve this condition post ovulation when estrogen levels normally decline. Successful surgical methods of amputating the hyperplastic tissues have been reported. Prolonged (>1 month) vaginal hyperplasia/prolapse most commonly occurs with ovarian pathology (follicular ovarian cysts), requiring ovariectomy for resolution. Artificial insemination may be required because of vaginal hyperplasia, which can recur at term secondary to increased estrogen levels associated with parturition (Fig. 55.5, *B*). The heritability of this condition is not known.

MANIPULATION OF THE ESTROUS CYCLE

PREVENTION OF ESTROUS CYCLES

The best method to prevent estrous cycles in bitches and queens not intended for future breeding remains ovariectomy or ovariohysterectomy. Contraceptive vaccines generating antibodies to GnRH are under development and can be used in both male and female dogs and cats, but these are not yet commercially available. Temporary contraceptive measures for bitches and queens intended for future breeding are problematic; progestins and anabolic compounds have undesirable side effects and risks (e.g., endometrial hyperplasia/pyometra, diabetes mellitus, mammary hyperplasia; hepatopathy, behavioral changes, endometrial atrophy) and are not advised. GnRH agonists (leuprolide, lutrelin, deslorelin) have been shown to suppress gonadal activity in both male and female dogs, with few side effects. These agonists act by causing a downregulation of the GnRH receptors, often after an initial proestrus/estrus induction. Chronic suppression of LH and FSH concentrations and suppression of gonadal hormone secretion and gametogenesis eventually occurs (Trigg et al., 2006). The final result is a chemical castration of males and a protracted anestrus in females that is reversible. None of these products are universally available commercially in the United States. Depot forms of leuprolide acetate (Lupron [Tap Pharmaceutical]) are available on the human market but remain extremely expensive. Although these products are effective and safer than previous options, their lack of availability and high cost make them impractical.

ESTRUS INDUCTION

Many protocols exist in the veterinary literature for estrus induction in the bitch and queen. Most have disappointing clinical results or use agents that are no longer commercially available or are too cumbersome for clinical application. Estrus (behavior and attractiveness) induction is straightforward with estrogenic compounds, but estrus followed by ovulation of fertilizable oocytes that implant successfully is difficult in the bitch and queen.

Fertile estrus can be induced most reliably in the bitch using dopamine agonists. At least 90 days of anestrus (progesterone < 1.0 ng/mL) must be allowed for adequate uterine involution permitting implantation. Oral (PO) bromocryptine at 30-50 µg/kg per day in divided doses can induce a fertile proestrus in 17 to 49 days, but side effects (nausea and diarrhea) are common and usually unacceptable. Cabergoline at 5 µg/kg PO q24h can induce fertile proestrus in 4 to 34 days, with fewer side effects. The drug must be discontinued after 48 to 96 hours of proestrus (determined cytologically) to prevent downregulation of the hypothalamic-pituitary-ovarian axis. Fertile estrus induction has also been documented with GnRH analogs (lutrelin, deslorelin, leuprolide) that can also be administered as long-acting dosage forms via subcutaneous (SC) injections, mini pumps, inhalants, or implants. Both expense and side effects may limit use of these products. A synthetic sustained-release GnRH analog (deslorelin) was marketed for several years for equine patients and shown to be effective in canine patients, but it is currently not universally commercially available. Substitutions (Ovuplant [Fort Dodge]) are not U.S. Food and Drug Administration (FDA) approved and can have unreliable results. Side effects

have included premature luteal failure, shortened diestrus, and pregnancy loss. Long-term use is also associated with pituitary overstimulation, downregulation of GnRH receptors, suppression of LH, decreased progesterone secretion, and decreased luteal responsiveness to LH.

Feline estrus induction protocols exist in the literature but are affected by photoperiod, previous length of anestrus versus nonpregnant diestrus, and unpredictable maturity of postovulatory oocytes. Manipulation of photoperiod alone is difficult in the cattery setting and not very effective. Estrus induction in a cat colony is reportedly most successful if preceded with progestin administration to inhibit folliculogenesis, but this increases the risk of endometrial disease, diabetes, and mammary pathology, and cannot be advocated for pets. Estrus induction most commonly has been accomplished using equine chorionic gonadotropin (eCG) at 100 IU IM, followed in 80 to 84 hours with an injection of the LH-like hormone hCG (Follutein [Bristol-Meyers Squib]) at 75 to 100 IU IM. In the queen, administration of exogenous hormones such as GnRH (Cystorelin [Ceva]) or hCG can be used to increase the likelihood of ovulation but requires the presence of mature ovarian follicles (i.e., estrus). Both hormones stimulate ovulation by bypassing the vaginal-hypothalamic neural pathway. Administration of 25 µg of GnRH IM, or 75 to 100 IU hCG IM, in midestrus can induce ovulation in some queens (Pelican et al., 2006). GnRH or hCG administration may be useful when a tom has low libido, and a sufficient number of copulatory stimuli are not achieved (Wiebe and Howard, 2009).

PREGNANCY TERMINATION

Termination of pregnancy in the bitch is often requested by owners after unwanted mating, less commonly in queens. Because an estrual bitch has been found with a male, a successful mating is presumed to have occurred. Only one third of bitches become pregnant after a single unplanned mating. For this reason, therapy should be delayed until unwanted pregnancy is confirmed at about 30 days (see Chapter 54). Vaginal cytologic examination can be performed to document estrus by the presence of 90% to 100% cornified superficial cells. Further identification of sperm cells in a vaginal swab within 48 hours of mating can be used to confirm that mating has occurred but not necessarily conception. Unless there is a valid reason for keeping a reproductively intact animal, the veterinarian should highly recommend ovariohysterectomy/pregnancy termination once the female is in early diestrus. Ovariectomy during diestrus can induce acute decline in serum progesterone and growth hormone, and a reflex increase in prolactin, resulting in mild signs of pseudopregnancy that owners should be warned about.

Once pregnancy has been documented in a reproductively valuable bitch or queen, options for safe pregnancy termination can be discussed. Extensive counseling with the owner is required to establish which therapeutic option is best suited for the animal. Treatment options should be assessed by comparing safety, efficacy, cost, and compliance by the owner. Owners should understand that in all cases, the animal should be confined after treatment, and in future cycles to avoid further unwanted pregnancies. Medical pregnancy termination protocols are more effective during the second half of gestation (35-45 days gestation) when luteolysis occurs most readily. Later in gestation (>50 days), pregnancy termination protocols can cause abortion of live premature fetuses that die after parturition but could be distressing to owners or staff, necessitating their euthanasia. Lactation commonly occurs in dams after later gestational pregnancy termination and may necessitate antiprolactin therapy if discomfort or mastitis occur. All pregnancy termination protocols necessitate monitoring for completion with serial ultrasound (Fig. 55.6). Ultrasonography is important in defining the end point of any of the following protocols to confirm evacuation of all fetuses. Premature discontinuation of treatment could result in retention of nonviable fetuses or eventual whelping or queening of remaining fetuses.

Estrogens

In general, limited drugs are used to terminate pregnancy in bitches or queens during estrus. Estradiol cypionate (ECP [Pharmacia]), estradiol benzoate (Intervet), and diethylstilbestrol (DES) were used extensively for this purpose but are not currently commercially available from manufacturers. Use of estrogens during diestrus significantly increases the risk for the bitch or queen to develop a pyometra. Because of potential side effects (irreversible aplastic anemia, pyometra, prolonged estrus), lack of availability, and better alternatives, estrogens are no longer recommended for mismate injections. Estradiol cypionate is not considered safe in cats.

Antiestrogens

The antiestrogen tamoxifen citrate (Nolvadex [Zeneca]) has been evaluated as mismate drug but was associated with a high frequency of pathologic changes in the reproductive tract, including endometritis and ovarian cysts, and is not advised.

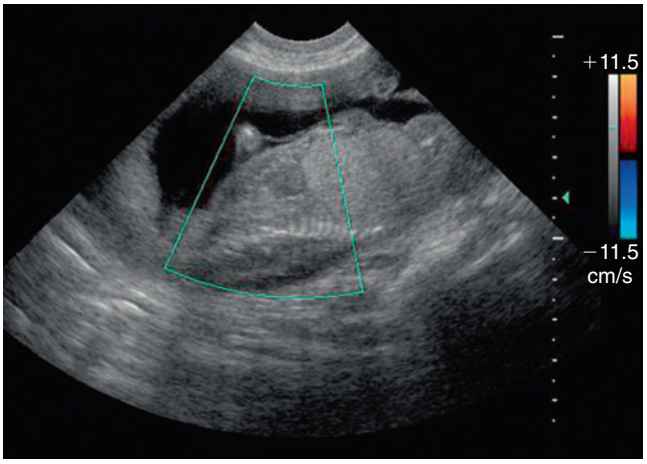


FIG 55.6
Fetal death before uterine evacuation. A lack of cardiac motion is evident; Doppler is useful but not essential for evaluation of fetal viability.

Prostaglandins

After confirmation of pregnancy, the natural prostaglandin $PGF_{2\alpha}$ (Lutalyse [Pharmacia]) has been administered to bitches and queens to lyse the corpora lutea and evacuate the uterus, causing pregnancy termination. Prostaglandins are associated with physical side effects that reflect the physiologic effects of endogenous prostaglandins and include emesis, salivation, tachypnea, diarrhea, urination, trembling, and nesting behavior. These reactions diminish in severity and duration as treatment progresses. The onset of vaginal discharge is often the first indicator that pregnancy termination has begun. Natural prostaglandins must be given for a significant length of time (often >7 days), adding to the overall cost of therapy. A dosage of 0.1 mg/kg SC q8h for 2 days, followed by 0.2 mg/kg SC q8h to effect, is recommended for induction of abortion in the bitch. Synthetic prostaglandins may have fewer side effects and require a shorter treatment period and are now preferred by this author to the natural prostaglandins. Cloprostenol (Estrumate [ICI, UK]), a synthetic prostaglandin, is dosed at 1-3 µg/kg SC q48h for 3+ doses and has been successful in terminating pregnancy in bitches and queens after 30 days' gestation. Although prostaglandins are not approved for use in domestic dogs or cats, they are recognized as a standard of care. Administration of prostaglandins in the clinic rather than by owners at home is advised because of their narrow therapeutic window, but pregnancy termination can be performed on an outpatient basis, especially with synthetic prostaglandins. Successful termination of pregnancy and evacuation of fetuses must be confirmed with ultrasound.

Combination prostaglandin therapy in the bitch with intravaginal misoprostol, prostaglandin E2 (Cytotec [Searle]), can reduce the mean time to abortion to under 5 days. Combination therapies appear to act synergistically: $PGF_{2\alpha}$ at 0.1 mg/kg to 0.2 mg/kg SC q8h in combination with intravaginal misoprostol at 1 to 3 µg/kg q24h (100 µg tablet dissolved in 5 mL water) shortened the treatment time to induce abortion in dogs by an average of 2 days over $PGF_{2\alpha}$ used alone. Misoprostol is thought to act as a cervical softening agent and has prolonged higher blood levels when administered intravaginally rather than orally. Side effects (nausea, cramping, diarrhea) are minimized with intravaginal administration as well.

The prognosis for resumption of estrous cycles and successful pregnancies after prostaglandin-induced abortion is good. Most bitches experience a return to proestrus 4 months (abbreviated diestrus) after prostaglandin-induced abortion. The onset of estrous cycles in the queen is more variable, reflecting the influence of length of daylight on a seasonally polyestrous species.

Dexamethasone

Dexamethasone has more recently been administered to terminate pregnancy in bitches. Dexamethasone is thought to have a direct antiprogesterone effect or to increase endometrial and placental prostaglandin synthesis and release. When used in pregnancies less than 40 days, only mild side effects are generally seen (mild vulvar bleeding, anorexia, panting, polydipsia, polyuria). Some bitches become markedly polydipsic and polyuric. Its efficacy, few and transient side effects, low cost, availability, and ease of administration have made dexamethasone the agent of choice when finances are limited. Oral doses of 0.2 mg/kg bid until fetal loss (confirmed ultrasonographically) occurs can be used. Abbreviated diestrus results. Because of the immunosuppressant effects of dexamethasone, postabortion metritis can occur; clients should be warned to monitor for its signs (malodorous discharge, lethargy, anorexia, fever).

Dopaminergic Compounds

Dopaminergic agents such as cabergoline (Dostinex, Pharmacia) are very effective if given later in pregnancy (>40 days gestation) but in small animals can be difficult to dose without compounding. Cabergoline is available in generic tablets that contain 0.5 mg (500 µg) of drug. Cabergoline inhibits prolactin, a potent luteotroph, and can result in 100% efficacy if given 40 days after the LH surge at 5 µg/kg PO q24h for 7 to 9+ days. The combination of a synthetic prostaglandin and a dopaminergic agent are most efficacious. Cloprostenol (1-3 µg/kg SC given on days 1 and 3) and cabergoline (5 µg/kg PO q24h) for 2 to 10 days to effect is the author's preferred protocol for canine pregnancy termination; in the queen $PGF_{2\alpha}$ at 2.5 mg/cat SC q 24h and cabergoline 50 µg/cat PO q 24h is highly effective within 3-6 days.

Antiprogestational Agents

Antiprogestational agents, mifepristone (RU486, Mifeprex [Danco]) and aglepristone (Alizine [Virbac]), are noted to be very effective (85%-100%) in pregnancy termination and lack the severe side effects noted with some other agents. Aglepristone blocks uterine progesterone receptors; serum progesterone levels remain unchanged. These products do not appear to affect long-term fertility, are rapid in onset, and can be given as an outpatient medication. Unfortunately they are not readily available in the United States and remain very expensive. As these agents become more cost-effective and availability improves, antiprogestational agents may eventually become the treatment of choice in the United States. Aglepristone has the best efficacy used early in gestation (21-45 days). In the bitch, aglepristone is dosed at 10 mg/kg SC, given twice, 24 hours apart. No more than 5 mL of the 30 mg/mL solution should be given in one SC site, owing to tissue irritation. In the queen, aglepristone is dosed at 15 mg/kg SC given twice, 24 hours apart; the higher dose is due to poorer bioavailability and faster metabolic clearance in the feline. After 45 days gestation, combination therapy with cloprostenol and cabergoline is advised.

PREPARTUM DISORDERS

DRUG THERAPY DURING PREGNANCY

The pharmacologic armament for treating reproductive disorders is not large, especially if limited to those drugs

for which sound studies provide support. Breeder clients often request therapies they have heard about through the grapevine or on the Internet, usually anecdotal and often without clinical data supporting their use. The consequences of mistreating pregnant or nursing bitches or neonates should limit the clinician to prescribing therapies with sound scientific rationale in most cases. During the first month of pregnancy, organogenesis takes place, and the impact of potentially teratogenic drugs is most critical. At therapeutic levels, most drugs in the maternal bloodstream are capable of crossing the placenta to reach fetal circulation. Even before implantation, drugs in maternal circulation reach embryos. Any drug that reaches the fetal circulation must be metabolized and excreted by the immature fetal kidney and/or through subfunctional hepatic metabolism. Clinicians should evaluate the package insert on any drug before prescribing its use in pregnant bitches. Cautions for use in pregnant or lactating individuals will be outlined as "safe, untested/unknown, or problematic." Extrapolation across species may not be reliable (i.e., tested in laboratory mice). Dose reduction of many drugs is advised, but guidelines are lacking (Wiebe and Howard, 2009).

VACCINATION DURING PREGNANCY

Shelter personnel may be faced with the dilemma of vaccinating a pregnant bitch or queen upon admission to a facility. Bitch and queen owners commonly request booster vaccinations before breeding. Historically, vaccination in pregnancy has been advised against in small animal medicine, because of the paucity of data concerning vaccine safety and efficacy during gestation, and because it is accepted that no substance should be administered unnecessarily during pregnancy. However, when the immunity of the dog or cat is unknown, the risk of maternal, fetal, and neonatal infection must be weighed against that of vaccination. The U.S. Centers for Disease Control and Prevention states that risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical, that no evidence exists of risk from vaccinating pregnant women with inactivated viral or bacterial vaccine or toxoids, and that the benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high. Further research in vaccination of pregnant dogs and cats is needed; extrapolating from the human field is advised at this time. The shelter environment provides an example of likely disease exposure in the face of unknown vaccination history, warranting vaccination of pregnant dogs upon admission with canine distemper virus, parvovirus, and bordetella bronchiseptica (intranasal/oral), and cats with feline viral rhinotracheitis, calicivirus, and panleukopenia. Inactivated, subunit, recombinant, polysaccharide conjugate vaccines should be selected for use in the pregnant dog/cat if available. Client-owned bitches should not be boosted during pregnancy if they have been vaccinated within the previous 3 years, queens (recombinant) if within 1 year.

SEMEN PERITONITIS

The differential diagnoses for a sexually intact bitch with acute onset of signs of abdominal pain include pyometra, uterine rupture, and uterine torsion. Acute peritonitis secondary to deposition of semen into the abdominal cavity should also be considered in the estrual bitch with acute signs of abdominal pain and a history of possible exposure to an intact male dog, or with a recent history of artificial insemination. Semen is forced into the uterus during the copulatory lock because of the large amount of prostatic fluid in the final fraction of the canine ejaculate. Normally the semen should not enter the peritoneal cavity of bitches after mating, but in the case of mates mismatched in size or a diseased uterus, semen could be forced into the peritoneal cavity through a tear in the uterus or vagina or through the fallopian tubes. Intraperitoneal deposition of semen results in peritonitis because prostatic fluid contains a large amount of foreign antigens. Severe suppurative peritonitis and the systemic inflammatory response syndrome are likely sequelae (Fig. 55.7, *A*, 55.7, *B*). Stabilization followed by exploratory

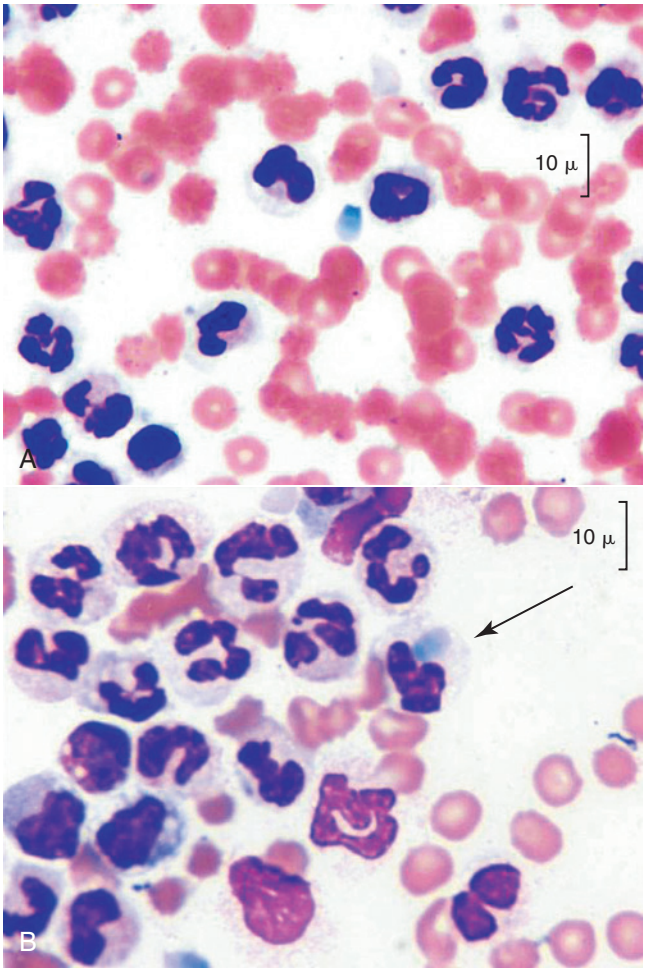


FIG 55.7
Semen peritonitis. **(A)** Cytology of peritoneal fluid showing toxic neutrophils, red blood cells, and a spermatozoon head are present. **(B)** Phagocytosis of a spermatozoon head *(arrow)*.

laparotomy and lavage of the abdomen are indicated. Inspection of the vagina (endoscopically) and uterus (grossly) for perforation should be carefully performed. This syndrome has high morbidity and mortality for the bitch.

PREGNANCY LOSS

The prepartum period is defined as 9 weeks before term. Pregnancy loss most commonly occurs with idiopathic premature labor, infectious causes, or significant maternal disease or trauma.

IDIOPATHIC PRETERM LABOR

Late-term gestational loss attributed to preterm or premature labor occurs in both bitches and queens. Both hypoluteoidism (inadequate production of progesterone to maintain pregnancy) and inappropriate uterine activity (myometrial irritability) accompanied by cervical changes (softening) have been implicated in the pathophysiology of preterm birth in veterinary medicine, but the syndrome is not well understood or adequately researched. Premature labor is defined as uterine activity and cervical changes leading to the loss of pregnancy via resorption or abortion before term for which no metabolic, infectious, congenital, traumatic, or toxic cause is identified. Progesterone levels can be normal for pregnancy (5-90 ng/mL) when increased myometrial contractility is first detected. Premature deliveries occur when progesterone levels are less than 2.0 ng/mL. Premature labor is often a retrospective diagnosis achieved after thorough evaluation of the dam and stillborn fetuses has been performed. This evaluation should include metabolic screening of the dam for systemic disease, infectious disease (brucellosis) evaluation, histopathology and microbiologic evaluation of expelled fetuses and placentae, and review of kennel/cattery husbandry, including nutrition, medications, and environmental factors. All results are normal or negative. Dams experiencing premature myometrial activity in one pregnancy might or might not exhibit it during subsequent pregnancies, but the syndrome can be a chronic cause of failure to successfully reproduce. In human medicine, preterm birth complicates 10% to 12% of human pregnancies, but it accounts for 80% of fetal morbidity and mortality (Dyson et al., 1998). Women with histories of preterm deliveries appear to be at risk for the same in subsequent pregnancies.

Tocolytic therapy inhibits myometrial contractility and is indicated in the management of premature labor when no contributory pathology is identified. Contraindications to tocolytic therapy in women include severe preeclampsia, placental abruption, intrauterine infection, lethal congenital or chromosomal abnormalities, advanced cervical dilation, and evidence of fetal compromise or placental insufficiency. Tocolytic agents inhibit myometrial contractions and include beta mimetics (terbutaline, ritodrine), magnesium sulfate, calcium channel blockers, and prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac). Contraindications to beta mimetics in women include maternal cardiac arrhythmias, poorly controlled diabetes mellitus, and hyperthyroidism—unlikely conditions in breeding bitches or queens. The main contraindication to tocolytic therapy in veterinary medicine is undetected uterine, fetal, or placental pathology, making forced maintenance of the pregnancy problematic for the dam.

Dams with historical late-term loss of pregnancy with no apparent pathology should be prospectively evaluated for premature myometrial activity midgestation, using uterine monitoring, for example, tocodynamometry (Healthdyne) (Fig. 55.8, *A*, 55.8, *B*). Elaboration of prostaglandins from the endometrium and placenta associated with premature myometrial activity can result secondarily in luteolysis. Premature uterine activity endangering fetal survival can be identified before significant luteolysis occurs, and intervention is indicated if the pregnancy is otherwise normal. Pharmacologic intervention to decrease myometrial activity is indicated with tocolytic agents. Terbutaline (Brethine [Ciba Geigy]) at 0.03 mg/kg PO q8h has been used to suppress uterine contractility in bitches and queens with historical preterm loss of otherwise normal pregnancies (Figs. 55.9, *A*, 55.9, *B*, 55.10). The dose is ideally titrated to effect using tocodynamometry. Diltiazem (Cardizem [Bioval Laboratories]) at 0.5 mg/kg PO q8h (canine) and 1.5-2.5 mg/kg PO q8h (feline) can be used if response to terbutaline is inadequate. Therapy is discontinued 24 to 48 hours before term to allow labor to proceed. In the author's experience, poor quality labor requiring cesarean section is common posttocolytic therapy. An elective cesarean section should be discussed with clients.

Canine and feline pregnancy maintenance requires serum progesterone levels of greater than 2.0 ng/mL. Serum progesterone levels during pregnancy normally range widely from 5-15 to 90 ng/mL, declining gradually during the latter half of gestation and falling abruptly at term to <2.0 ng/mL (usually the day before or the day of parturition). Progesterone promotes development of endometrial glandular tissue, inhibits myometrial contractility (causes relaxation of myometrial smooth muscle), blocks the action of oxytocin, inhibits formation of gap junctions, and inhibits leukocyte function in the uterus. In several species, local changes in progesterone level or the ratio of progesterone to estrogen in the placenta, decidua, or fetal membranes is important in the initiation of labor. Progesterone antagonists administered at term can result in an increased rate of spontaneous abortion. In the bitch, the corpora lutea are the sole source of progesterone, whereas in the queen, placental progesterone production occurs in the latter half of gestation. Canine luteal function is autonomous early in pregnancy but supported by luteotrophic hormones (LH and prolactin) after the second week of gestation. Hypoluteiodism, primary luteal failure occurring before term gestation, is a potential but not yet documented cause of late-term abortion in otherwise normal bitches and queens. It has been documented that the induction of abortion in a normal but undesired pregnancy requires a reduction of plasma progesterone levels to less than 2.0 ng/mL. The diagnosis of gestational loss caused by premature luteolysis/luteal insufficiency



FIG 55.8
Tocodynamometry. **(A)** *Left to right,* Fetal Doppler, uterine sensor, modem, and recorder. **(B)** Tocodynamometry session with a pregnant Chihuahua (**A** Courtesy CooperSurgical and **B** Courtesy Micropath, Inc.).

is difficult, requiring documentation of inadequate plasma progesterone levels before abortion for which no other cause is found. Progesterone levels diminish in response to myometrial activity and fetal death, so documentation of a low progesterone level after an abortion does not establish the diagnosis of hypoluteiodism as the primary cause for reproductive failure. Administration of progesterone to maintain pregnancy in dams with primary fetal abnormalities, placentitis, or intrauterine infection can cause continued fetal growth with the possibility of dystocia and sepsis. Administration of excessive progesterone to maintain pregnancy in a dam not actually requiring therapy can delay parturition and diminish lactation, endangering the life of the bitch and her fetuses, and can masculinize female fetuses (see Chapter 56, Fig. 56.35). Historically, premature pregnancy loss has been treated by administering injectable natural progesterone or oral synthetic progestagens. In women, prevention of preterm delivery or recurrent miscarriage appears to be based on the use of only the natural metabolite of progesterone, 17α-hydroxyprogesterone caproate (17P). Total serum concentrations of progesterone can be monitored only when supplemented with the natural product. Progesterone in oil is given intramuscularly at 2 mg/kg q72h. Altrenogest (Regumate [Hoechst-Roussel]), a synthetic progestagen manufactured for use in the mare, is dosed orally at 0.088 mg/kg q24h. Both forms of supplementation must be discontinued in a timely fashion so as not to interfere with normal parturition, within 24 hours of the due date with the oral synthetic product, and within 72 hours with the natural injectable depot form. This requires accurate identification of gestational length via prior ovulation timing (see Chapter 54). Less accurate identification of gestational length can be made from breeding dates, radiography, or ultrasound (see Chapter 54). The unfavorable side effects of exogenous progesterone supplementation must be outlined to clients and make its use in premature labor unattractive. Studies have shown that early tocolytic therapy prevents luteolysis and precludes the use of progestational compounds in preterm labor (Davidson, 2015).

PREGNANCY LOSS ASSOCIATED WITH INFECTIOUS DISEASE

CANINE BRUCELLOSIS

Brucellosis is the primary contagious infectious venereal disease of concern in canine reproduction. Canine brucellosis is caused by *Brucella canis,* a small, gram-negative, non–spore-forming aerobic coccobacilli. *B. canis* was first isolated by Leland Carmichael in 1966. *Brucella abortus, Brucella melitensis,* and *Brucella suis* have occasionally caused canine infections but are comparatively rare. *B. canis* causes reproductive failure in both the male and female dog. Screening for *B. canis* infection is an important part of the prebreeding evaluation of any dog and should be included in the initial diagnostics in any case of canine abortion, orchitis, epididymitis, and apparent infertility in bitches or dogs. Because the incidence of canine brucellosis is low in many geographic locations, breeder compliance with regular screening can wane, making continued veterinary vigilance important. Notably, neutered and maiden or virgin dogs can also be infected. *B. canis* can also occasionally cause systemic disease

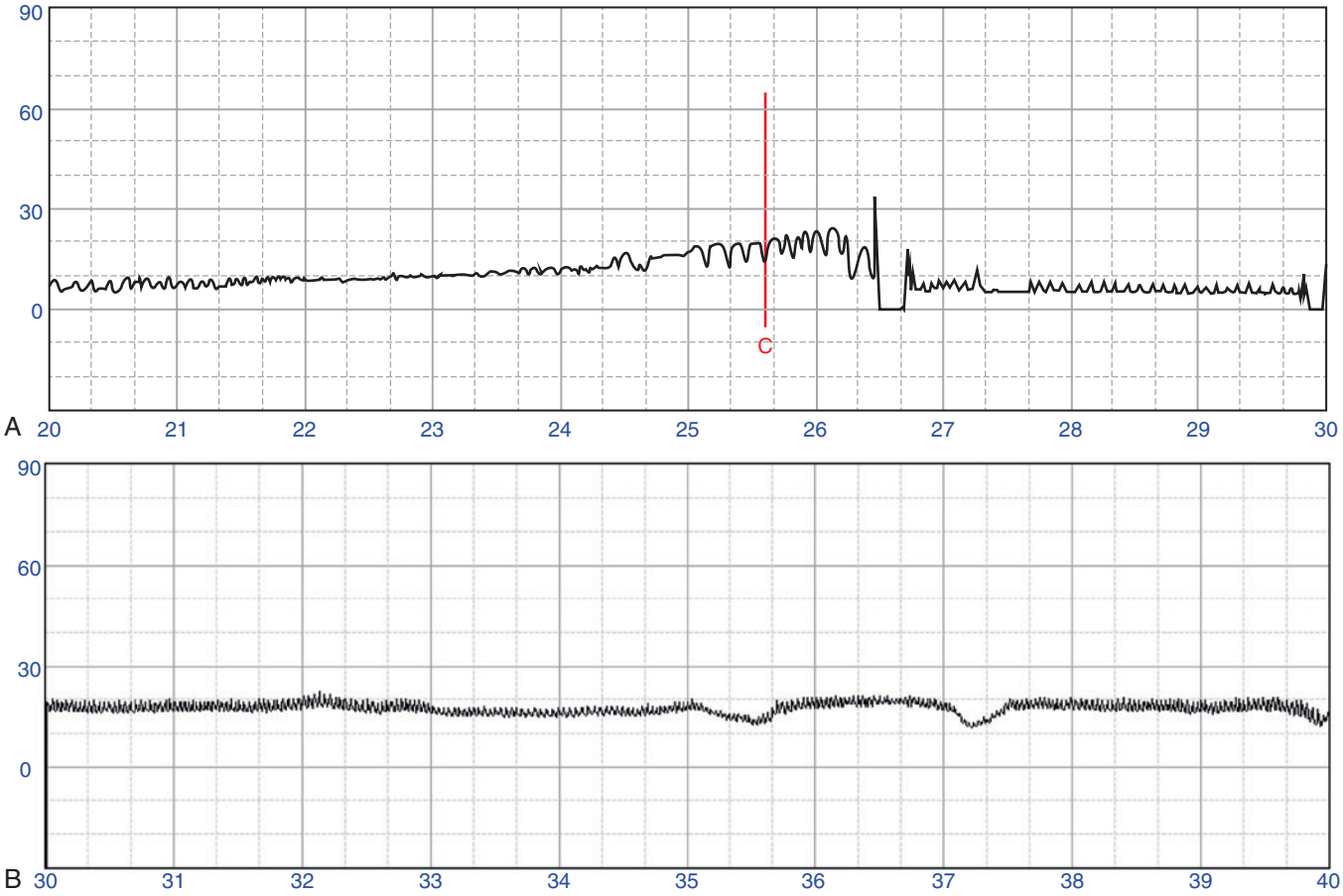


FIG 55.9
Tocodynamometry recordings. **(A)** Premature uterine contraction *(C)* in a bitch at midgestation. X axis is mm Hg; y axis is time in minutes. **(B)** Uterine irritability. X axis is mm Hg; y axis is time in minutes.

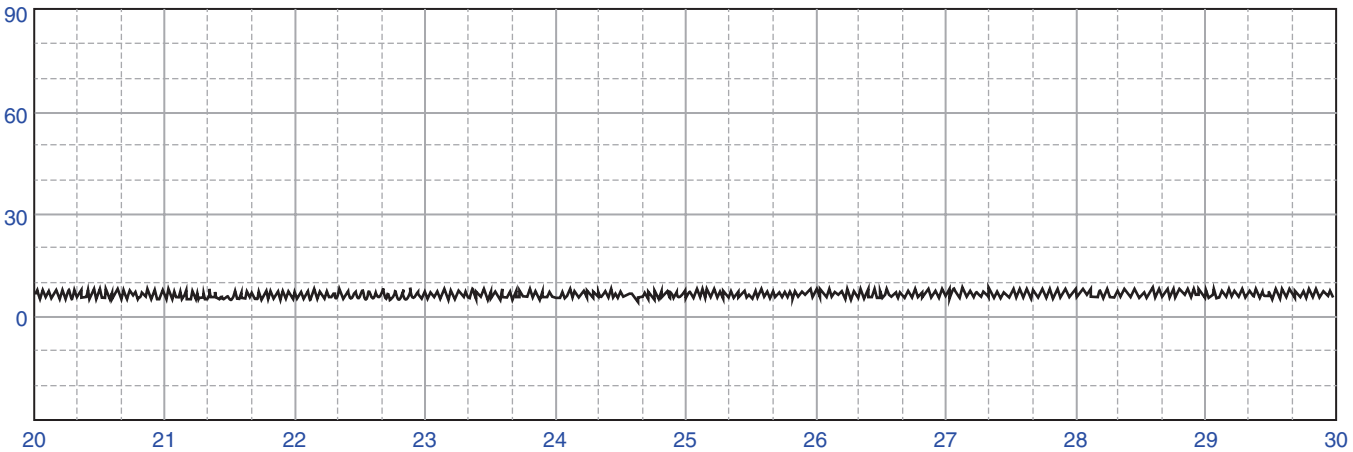


FIG 55.10
Tocodynamometry recording: normal quiescent myometrium. X axis is mm Hg; y axis is time in minutes.

(e.g., discospondylitis) in dogs not used for reproduction. Transmission occurs through direct exposure to bodily fluids containing an infectious dose of organism (semen, lochia, aborted fetuses/placentas, milk, and urine). Transmission is primarily oral, nasal, conjunctival, and secondarily venereal (i.e., through mucous membranes), the former associated with ingestion or aerosolization of infectious materials. The aerosol route is especially important if kennel conditions are crowded. Transplacental transmission and direct cutaneous inoculation can occur.

Canine brucellosis has high morbidity but low mortality in the adult dog. The clinical systemic signs are often subtle (suboptimal athletic performance, lumbar pain, lameness, weight loss, lethargy). The primary clinical sign of canine brucellosis in the breeding bitch is pregnancy loss, which can occur early (day 20) in gestation and result in fetal resorption, or more commonly later in gestation (generally 45-59 days), resulting in abortion. Bitches with pregnancy loss early in gestation can appear to be infertile (failed to conceive) unless early ultrasonographic pregnancy evaluation is performed. Nongravid bitches can be asymptomatic or show regional lymphadenomegaly (pharyngeal if orally acquired, inguinal and pelvic if venereally acquired).

The diagnosis of canine brucellosis is based on suggestive clinical signs and the results of serology studies; culture of blood, urine, or tissues; and histopathology and/or polymerase chain reaction (PCR) assays. Because no single antemortem test has 100% sensitivity and serologic assays lack specificity, a combination of diagnostic assays is often required to make a diagnosis. Antibodies to *Brucella* do not become detectable until 2 to 12 weeks after infection, so a window of time exists in which an infected dog can elude diagnosis with any serologic assay used. Assays used for screening purposes are usually rapid and inexpensive but can suffer from low specificity (high rate of false-positive test results) due to strong cross-reactivity between surface LPS antigens of *B. canis* and those of other nonpathogenic infectious agents. Up to 50% to 60% of dogs may have false-positive test results because of cross-reacting antibodies to other microorganisms such as *Bordetella, Pseudomonas, Escherichia coli,* and *Moraxella* spp. Examples of screening assays include the rapid slide agglutination test (RSAT), the semiquantitative 2-mercaptoethanol modified RSAT (ME-RSAT), and the semiquantitative tube agglutination test (TAT). If the test result is positive, a confirmatory assay should be performed. This could include tests such as the specific cytoplasmic agar gel immunodiffusion (AGID) assay, blood culture, or a reliable PCR assay.

Brucellosis is a zoonotic disease and may be a reportable disease in either the dog or human in certain jurisdictions. Infected dogs and bitches should be removed from breeding programs and quarantined. Eradication of the disease in kennel situations has not been successful without removal (culling) of all infected (current or historically) dogs. Because of the zoonotic potential of the disease and difficulty in actually eradicating the infection, euthanasia of affected dogs has been advised. Infection in household or small hobby kennel dogs often results in client requests for alternatives to euthanasia. Neutering decreases the amount of organism shed in semen and uterine discharge but does not eradicate the infection. Urine shedding can persist, and the organism can be found in internal organs and the bloodstream. Antibiotic therapy has not been historically rewarding, likely because the organism is intracellular and bacteremia periodic. Antibiotic therapy may reduce antibody titers without clearing the infection. Relapses are common. Combination therapy with tetracyclines (doxycycline or minocycline 25 mg/kg bid PO for 4 weeks) and dihydrostreptomycin (10-20 mg/kg bid IM or SC for 2 weeks, given during weeks 1 and 4) or an aminoglycoside (gentamicin 2.5 mg/kg bid IM or SC for 2 weeks, given during weeks 1 and 4) has been advocated as being the most successful, but unavailability, nephrotoxicity, parenteral therapy requirements, and expense remain problematic. Recently one study reported a slightly encouraging outcome of therapy with enrofloxacin (Enrofloxacin [Bayer], 5 mg/kg bid PO for 4 weeks, often for multiple courses) in a small group of infected dogs and bitches. Enrofloxacin was not completely efficacious in eliminating *B. canis,* but it maintained fertility and avoided the recurrence of abortions, transmission of the disease to subsequently whelped puppies, and dissemination of microorganisms during parturition (Wanke et al., 2006). Ultimately, however, most treated dogs remained culture positive. Combinations of enrofloxacin and doxycycline may be a more effective alternative for dogs unable to tolerate aminoglycoside, but studies are lacking. A combination of doxycycline and rifampin has been used successfully to treat human brucellosis but may not be well tolerated by dogs because of gastrointestinal adverse effects.

Private breeders should require screening testing of all bitches presented for breeding and confirmatory negative testing if positive results occur during screening before accepting a bitch into their kennel. Stud dogs should be screened appropriately at least annually. Because of the potential for nonvenereal transmission, screening of maiden dogs and bitches before breeding is also recommended.

ABORTION ASSOCIATED WITH OTHER BACTERIA

Opportunistic intrauterine aerobic and anaerobic bacteria, usually of vaginal origin, can cause septic abortion in the bitch and queen. *Escherichia coli* is the most common organism found in the bitch with septic abortion. Controversies exist about the role of mycoplasmas and ureaplasmas. The most common intrauterine bacterial-associated causes of abortion in the queen include *Streptococcus sp., Escherichia coli, Campylobacter spp,* and *Salmonella spp.* Bacterial abortion is associated with placentitis and fetal death, commonly in a progressive manner; the prognosis for fetal survival is guarded. Pregnancy termination and medical uterine evacuation along with appropriate antibiotic therapy can salvage the bitch or queen for future breeding.

PROTOZOAL DISEASE

Toxoplasmosis/Neosporosis/ Cryptosporidiosis

Toxoplasma gondii and *Neospora caninum* have been associated with abortion (toxoplasmosis) and resorption (neosporosis) in the bitch; *T. gondii* causes feline abortion. Transplacental transmission with placental vasculitis and necrosis occurs. Loss of pregnancy results; in rare cases neonates survive but are weak, with neurologic (ocular),

gastrointestinal, and respiratory disorders. Toxoplasmosis can be spread venereally. The diagnosis is based on serology and PCR. *Cryptosporidia canis* and *C. felis* develop in the microvillus border of epithelial cells in the digestive, respiratory, and genitourinary tracts and can cause abortion. The diagnosis is made with the direct immunofluorescent antibody (IFA) test or PCR.

CANINE VIRAL-ASSOCIATED PREGNANCY LOSS

Herpes Virus

Adequate exposure of a non-immune bitch to canine herpesvirus (CHV-1) during the last 3 weeks of gestation can result in infection of the dam and subsequently her neonates. Venereal transmission is believed to be rare and community (respiratory) transmission more common. Signs in the bitch are usually limited to a mild, clear upper respiratory discharge and transient sneezing; however, reports of a more severe respiratory form of CHV-1 exist in adult dogs, often with other viral coinfections (Piewbang et al., 2017). Infection in the naïve pregnant bitch commonly results in late term abortion or neonatal death within the first few weeks of life. The recently infected bitch has inadequate time to form protective maternal antibodies and allow passive immunity (transplacental or transmammary) to be acquired by the neonates. Incompletely developed immune systems and inadequate thermoregulation during the first weeks of life make neonates vulnerable to systemic viral infection. Adequate ingestion of colostrum must occur promptly postpartum for puppies to acquire passive immunity. The transmission of protective immunity (placental or colostral antibodies) between a bitch and her puppies depends upon the prior existence of adequate serum maternal antibodies. CHV-1 can evade the immune system and become latent in the nervous system; immunosuppression during pregnancy can promote viral reactivation, but if this occurs it will likely boost the immune response and increase the level of colostral antibodies available to neonates.

Transmission of herpesvirus from an infected, viremic dam to neonates occurs subsequent to contact with infectious vaginal fluids or oronasal secretions. Signs in the neonate are progressive and severe, and include anorexia (poor weight gain), dyspnea, abdominal pain, incoordination, diarrhea, serous to hemorrhagic nasal discharge, and petechiation of the mucous membranes. The mortality rate in untreated litters infected in utero or during birth is commonly 100%, with deaths occurring during the first few days to 3 weeks of life. Infection in neonates born to a non-immune bitch may also result from contact with CHV-1 from another dog shedding the organism in the vicinity. Older naive (>3-4 weeks of age) puppies exposed to herpesvirus may have an inapparent infection; some authors have reported concerns with later central nervous signs including blindness and deafness. Subsequent litters of the bitch infected during a previous pregnancy are usually resistant to infection, having acquired adequate circulating maternal antibodies via colostrum. Bitches can be screened before breeding for CHV-1 titers; negative serology should prompt strict hygiene and isolation during the last 3 weeks of pregnancy and the first month postpartum. Vaccine development is hampered by the poor immunogenicity of the herpesvirus, as evidenced by other herpesviral vaccines developed for different species, such as feline and bovine rhinotracheitis. A commercial CHV vaccine is currently available in Europe; it has not been subjected to nonproprietary critical evaluation.

Minute Virus

Canine Minute Virus (canine parvovirus type 1) causes resorption and abortion after transplacental transmission. Any fetuses surviving to term can have anasarca and myocarditis, with poor neonatal survival. The diagnosis is based on virus isolation, immunofluorescence, or PCR.

FELINE VIRAL-ASSOCIATED PREGNANCY LOSS

Leukemia Virus (FeLV), Panleukopenia Virus (FPV), Herpes Virus (FHV), Infectious Peritonitis (FIP), and Feline Immunodeficiency Virus (FIV)

Viral-associated pregnancy loss is in the queen is more common than bacterial; reproductive failure can be associated with feline leukemia virus (FeLV), feline panleukopenia virus (FPV), feline herpes virus (FHV), feline infectious peritonitis (FIP), and feline immunodeficiency virus (FIV). Viral transmission can occur transplacentally, via oronasal contact, and in some cases can be transmammary. Infection can result in resorption, mummification, or abortion of fetuses, as well as neonatal death. Abortion PCR and culture panels are commercially available. The queen and tom cat should be FIV antibody- and FeLV antigen-screened and appropriately vaccinated. The most effective management system to prevent infectious causes of pregnancy loss in the queen include rigorous health maintenance of both the queen and tom, routine annual screening for underlying health problems, retrovirus status, and excellent nutrition. Queens should be maintained in a closed colony environment and new additions to the colony quarantined.

Vector Borne Disease

Babesiosis and leishmaniasis have both been implicated in canine abortion.

METABOLIC DISORDERS

HYPEREMESIS GRAVIDARUM

Bitches can experience a transient loss of appetite and sometimes have periodic vomiting during the second and third weeks of gestation. This usually resolves spontaneously, but sometimes marked anorexia hinders adequate nutrition during gestation. Antiemetic therapy can be helpful with

metoclopramide at 0.1 to 0.2 mg/kg PO or SC bid. Alternative antiemetic drugs may not be safe or recommended for pregnancy; clinicians must evaluate risk versus benefit. In uncommon cases, force-feeding must be undertaken. Hyperemesis gravidarum in women is believed to occur secondary to an acute elevation of human chorionic gonadotropin; no pregnancy gonadotropin has been identified in the bitch.

GESTATIONAL DIABETES

Gestational diabetes occurs infrequently in the bitch and is attributed to the antiinsulin effect of progesterone (mediated by increased levels of growth hormone) during the luteal phase. Polydipsia, polyuria, and polyphagia with weight loss occur. High-fiber diets promote euglycemia in the bitch, but the diet must remain balanced for pregnancy and lactation. Insulin may be indicated. Oversized fetuses can result from their increased production of insulin in response to maternal hyperglycemia and may cause dystocia due to fetal-maternal mismatch (Fig. 55.11). Gestational diabetes can resolve postpartum when progesterone levels decline; if not, it is reclassified as type I diabetes. Ovariohysterectomy is indicated postweaning as recurrence with diestrus is likely.

PREGNANCY TOXEMIA

Pregnancy toxemia in the bitch is due to altered carbohydrate metabolism in late gestation, resulting in ketonuria without glycosuria or hyperglycemia. The most common cause is poor nutrition or anorexia during the last half of gestation. Hepatic lipidosis can occur. An improved plan of nutrition can resolve the condition in most cases, but termination of the pregnancy may be indicated in severe cases.

VASCULITIDES

Pregnancy Thrombosis

Pregnancy is a recognized hypercoagulable state that becomes problematic in women with genetic prothrombosis. Hypercoagulability has also been recognized in pregnant dogs. Affected bitches have an increased tendency for thrombosis, as evidenced by an elevated D-dimer level, with variable clinical appearances. Ultrasound can be used to document thrombosis, which occurs commonly in the caudal vena cava, resulting in venous congestion in the pelvic limbs (Fig. 55.12). Antithrombotic therapy with low molecular weight heparin is well documented in women but undocumented in the bitch and can easily result in congenital defects (aspirin-induced cleft palates) or loss of pregnancy due to placental or fetal hemorrhage. Warfarin is contraindicated in pregnancy because it crosses the placenta. The condition is believed to be inherited in women; affected bitches should be removed from the breeding pool.

Pregnancy Edema

Marked edema of the distal pelvic limbs, caudal mammary glands, and perineum has been observed, usually in large-breed bitches with large litter size (Figs. 55.13, 55.14). These bitches are not hypoalbuminemic. Venous thrombosis should be ruled out with Doppler ultrasonography. Vaginal hyperplasia can occur at term and be mistaken for pregnancy edema. Mild elevation of estradiol at the end of gestation in the bitch can induce reformation of vaginal hyperplasia, seen more commonly during estrus, and can cause compromise of the birth canal. Elective cesarean section is then indicated. Vaginal hyperplasia can be confirmed by digital examination of the vagina, finding a mass originating cranial to the urethral papilla. If pregnancy edema is confirmed, mild exercise (walking or swimming) can be helpful. Diuretics are contraindicated; furosemide can cause a decrease in placental intervillous blood flow and spironolactone is a pregnancy category D (positive evidence of fetal risk) drug in humans. Mild sodium restriction can help. Severe edema of the perineum can cause dystocia (Fig. 55.15).

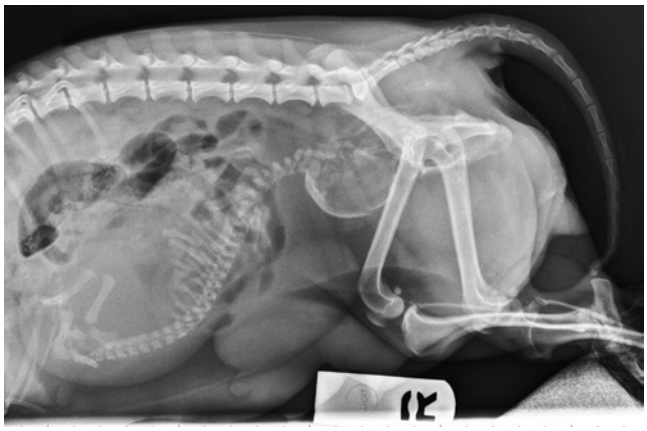


FIG 55.11
Oversized singleton fetus in a Chihuahua bitch with gestational diabetes. Dystocia and fetal death occurred.



FIG 55.12
Venous distention noted in a Labrador Retriever bitch during the eighth week of gestation. A caudal vena caval thrombus was diagnosed ultrasonographically.



FIG 55.13
Distal pelvic limb pitting edema in a pregnant Labrador Retriever.



FIG 55.14
Mammary edema in a Labrador Retriever bitch in the eighth week of gestation.

PARTURITION AND PARTURIENT DISORDERS

Although many bitches and queens deliver in the home or kennel/cattery setting without difficulty, requests for veterinary obstetric assistance are becoming more common. The increased financial and emotional value of stud dogs, brood bitches, toms, queens, and their offspring to the pet fancier makes preventable loss of even one neonate undesirable. Breeding colonies in academic, scientific, and industrial facilities have to maximize neonatal survival for financial and ethical reasons. Veterinary involvement in canine and feline obstetrics has several goals: to increase live births (minimizing stillbirths due to difficulties in the birth process), minimize morbidity and mortality in the dam, and promote increased survival of neonates during the first week of life.



FIG 55.15
Marked vulvar and perineal edema in a Boxer bitch at term gestation. Cesarean section was performed.

Neonatal survival is directly related to the quality of labor. Optimal management of whelping/queening requires an understanding of normal labor and delivery in the bitch and queen, as well as the clinical ability to detect abnormalities in the birthing process.

EUTOCIA

Bitches typically enter stage I labor within 24 hours of a decline in serum progesterone to below 2.0 to 5.0 ng/mL, which occurs in conjunction with elevated circulating prostaglandins and is commonly (~60% detection) associated with a transient drop in body temperature, usually to below 100° F (33.7° C). Queens typically enter stage I labor 24 hours after serum progesterone falls to less than 2.0 ng/mL. Monitoring serial progesterone concentrations for impending labor is problematic because in-house canine kits enabling rapid results are inherently less accurate between 2.0 and 5.0 ng/mL, and a rapid decline in progesterone levels can occur over a period of a few hours. Commercial laboratories offering quantitative progesterone by chemiluminescence typically have a 12- to 24-hour turnaround time, which is not rapid enough to enable decisions about an immediate indication for obstetrical intervention. If progesterone is <2 ng/mL, labor is imminent.

Stage I labor in the bitch normally lasts from 12 to 24 hours, during which time the uterus has myometrial contractions of increasing frequency and strength, associated with cervical dilation. No abdominal effort (visible external contractions) is evident during stage I labor. Bitches and queens can exhibit changes in disposition and behavior during stage I labor, becoming reclusive, restless, and nesting intermittently, often refusing to eat and sometimes vomiting. Panting and trembling can occur. Vaginal discharge is clear and watery, sometimes voluminous.

Stage II labor in the bitch is defined to begin when external abdominal efforts can be seen, accompanying myometrial contractions to culminate in the delivery of a neonate. Presentation of the fetus at the cervix triggers the Ferguson reflex, promoting the release of endogenous oxytocin from the hypothalamus. Typically these efforts should not last longer than 1 or 2 hours between puppies, although great variation exists. The entire delivery can take from 1 to more than 24 hours, but normal labor is associated with shorter total delivery time and shorter intervals between neonatal births. Vaginal discharge can be clear, serous to hemorrhagic, or green (uteroverdin). Typically bitches continue to nest between deliveries and may nurse and groom neonates intermittently. Anorexia, panting, and trembling are common.

Stage III labor is defined as delivery of the placenta. Bitches and queens typically vacillate between stages II and III of labor until the delivery is complete. During normal labor, all fetuses and placentae are delivered vaginally, although they are not be delivered together in every instance.

The stages of labor in the queen can be similarly defined. Stage I labor in the queen is reported to last 4 to 24 hours and stages II and III from 2 to 72 hours, although completion of delivery of neonates within 24 hours is expected with normal queening.

DYSTOCIA

Dystocia is difficulty with normal vaginal delivery of a neonate from the uterus and must be diagnosed in a timely fashion for medical or surgical intervention to improve outcome. Dystocia results from maternal factors (uterine inertia, pelvic canal anomalies, intrapartum compromise), fetal factors (oversize, malposition, malposture, anatomic anomalies), or a combination of both. For effective management, prompt recognition of dystocia and correct identification of etiologic factors are essential to making the best therapeutic decisions (Fig. 55.16).

Uterine inertia is the most common cause of dystocia. Primary uterine inertia results in the failure of delivery of any neonates at term and is thought to be multifactorial, including metabolic defects at the cellular level. Intrinsic failure to establish a functional, progressive level of myometrial contractility occurs. A genetic component could be present. Secondary uterine inertia results in cessation of labor once initiated and consequential failure to deliver the entire litter. Secondary inertia can be due to metabolic or anatomic (obstructive) causes and is also thought to have a genetic component when no contributory cause can be identified.

Birth canal abnormalities such as vaginal strictures, stenosis from previous pelvic trauma or particular breed conformation, and intravaginal or intrauterine masses can cause obstructive dystocia. In most cases, canal abnormalities can be detected in the prebreeding examination and resolved or avoided by elective cesarean section (see Chapter 54).

Causes of intrapartum compromise rendering the dam unable to complete delivery include metabolic abnormalities such as hypocalcemia and hypoglycemia, systemic inflammatory reaction, sepsis, and hypotension (due to hemorrhage or shock).

Fetal factors contributing to dystocia most commonly involve mismatch of fetal and maternal size, fetal anomalies, and fetal malposition and/or malposture. Prolonged gestation with small litter size can cause dystocia due to an oversized fetus(es). In one study, induction of parturition was successfully performed at gestational day 59 using aglepristone (15 mg/kg SC bid [Alzine, Virbac]); this could be used in bitches with small litters and anticipated delayed parturition (Baan et al., 2005). Fetal anomalies such as twinning, hydrocephalus, and anasarca similarly can cause dystocia (Figs. 55.17, 55.18). Fetal malposition (ventrum of fetus proximal to the dam's dorsum) and fetal malposture (flexed neck and scapulohumeral joints most commonly) promote dystocia because the fetus cannot transverse the birth canal smoothly.

An efficient diagnosis of dystocia is dependent upon taking an accurate history and performing a thorough physical examination in a timely manner. The clinician must quickly obtain a careful reproductive history detailing breeding dates, any ovulation timing performed, historical and recent labor, as well as a general medical history. The physical examination should address the general status of the patient and include a digital and/or vaginoscopic pelvic examination for patency of the birth canal, evaluation of litter and fetal size (radiography most useful), assessment of fetal viability (Doppler or real-time ultrasound, ideally), and uterine activity (tocodynamometry most useful).

TOCODYNAMOMETRY

The canine and feline uterus each have characteristic patterns of contractility, varying in frequency and strength before and during different stages of labor. Serial tocodynamometry in the bitch and queen permits evaluation of the progression of labor (Fig. 55.19). During late term, the uterus may contract once or twice an hour before actual stage I labor is initiated. During stage I and II labor, uterine contractions vary in frequency from 0 to 12 per hour, and in strength from 15 to 40 mm Hg, with spikes up to 60 mm Hg. Contractions during active labor can last 2 to 5 minutes. Recognizable patterns exist during prelabor and active (stages I-III) labor. Aberrations in uterine contractility can be detected during monitoring. Abnormal, dysfunctional labor patterns are often associated with maternal morbidity and fetal distress (Figs. 55.20, *A*, 55.20, *B*, 55.21, *A*, 55.21, *B*). Completion of labor (or lack thereof) can be evaluated via tocodynamometry. Fetal viability is evaluated best by external doppler fetal heart rate monitoring or ultrasonography; 180 to 220 beats/min are normal, persistent deceleration (<180 beats/min) reflects stress (Fig. 55.22).

Medical Therapy

Medical therapy for dystocia, based on administration of oxytocin and calcium gluconate, can be guided and tailored by maternal and fetal monitoring. Oxytocin generally increases the frequency of uterine contractions, whereas

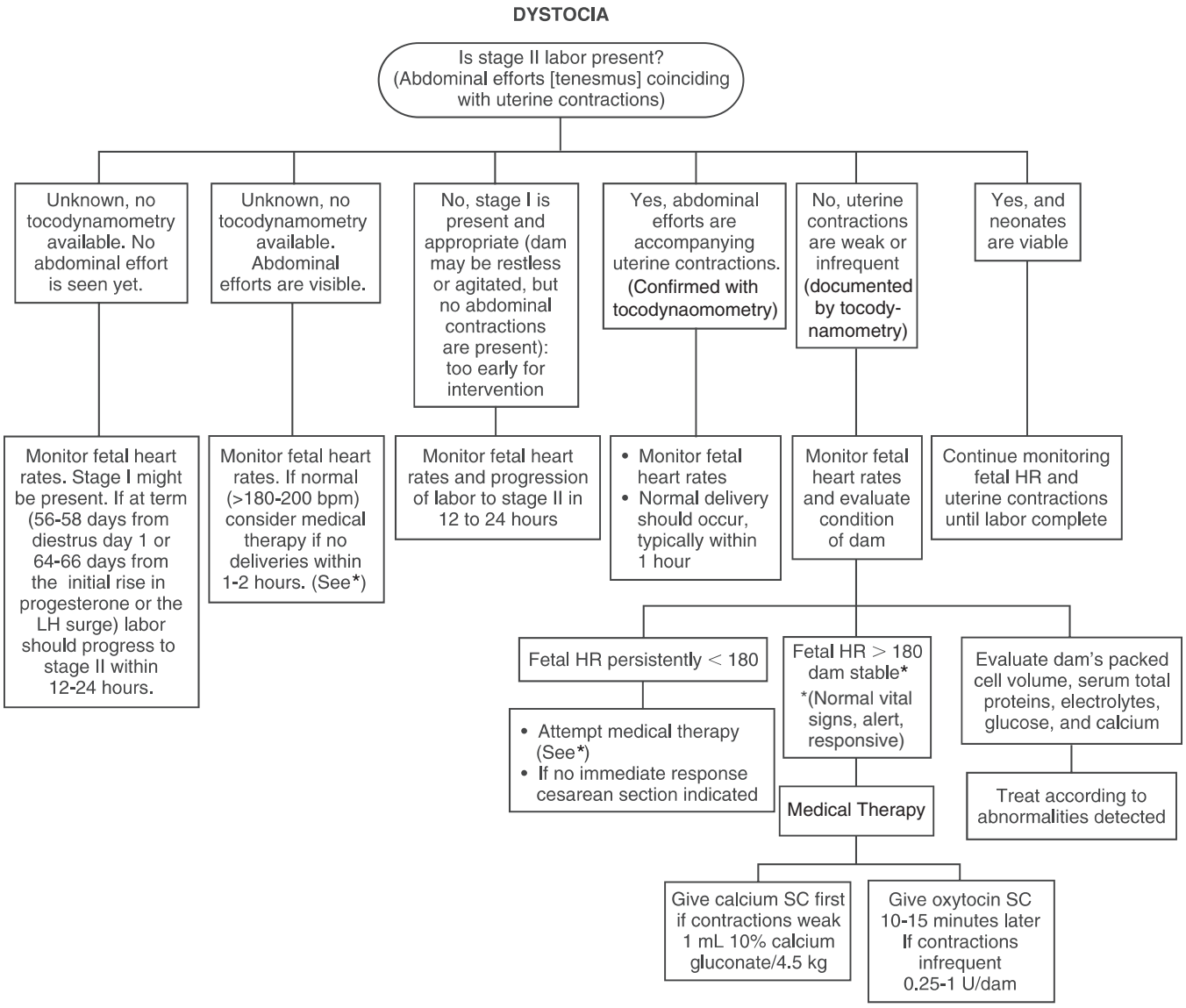


FIG 55.16
Flowchart showing recognition, categorization, and management of dystocia.



FIG 55.17
Canine twins, a rare condition. Malpresentation resulted in dystocia and fetal death.

calcium increases their strength. Calcium gluconate 10% solution with 0.465 mEq Ca^{++}/mL (see Fujisawa) is given SC at 1 mL/5.5 kg body weight as indicated by the strength of uterine contractions (best measured with tocodynamometry), but generally no more frequently than every 4 to 6 hours. Oxytocin, 10 USP units/mL (American Pharmaceutical Partners), is effective at minidoses, starting with 0.25 units SC or IM per bitch or queen regardless of weight, to a maximum dose of 5 units. The dose can be gradually increased to effect (delivery) or until fetal distress is detected; generally no more than 2 units is necessary. Higher doses of oxytocin or intravenous (IV) boluses can cause tetanic, ineffective uterine contractions that can further compromise fetal oxygen supply by placental compression. The frequency of oxytocin administration is dictated by the labor pattern, and it is generally not given more frequently than every 30 to 60 minutes. Calcium is given before oxytocin in most cases, improving contraction strength before increasing



FIG 55.18
Hydrops fetalis (water puppy) in a Labrador Retriever. Fetal oversize caused an obstructive dystocia.



FIG 55.19
Tocodynamometry session with a pregnant queen.

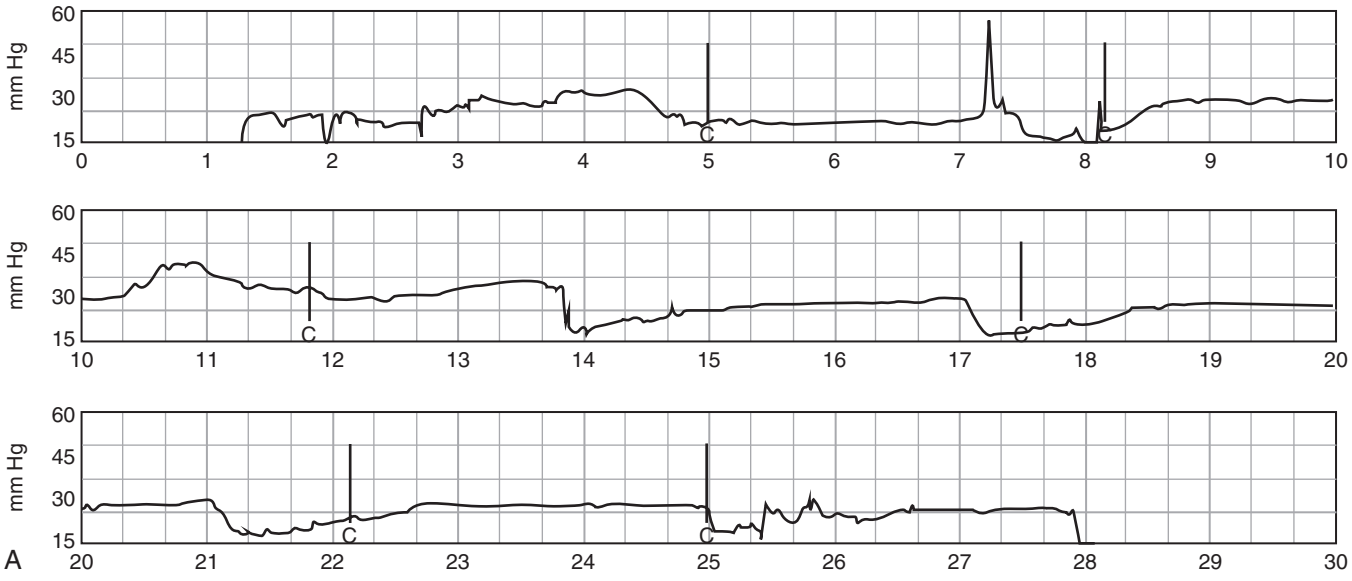




FIG 55.20
Tocodynamometry. **(A)** Abnormal tocodynamometry recording. X axis is mm Hg; y axis is time in minutes. **(B)** Rupture of a uterine horn *(arrow)* in the bitch with this abnormal tocodynamometry.



FIG 55.21
Tocodynamometry. **(A)** Abnormal tocodynamometry recording. X axis is mm Hg; y axis is time in minutes. **(B)** Uterine torsion with loss of fetus in the bitch with this abnormal tocodynamometry.

contraction frequency. The action of oxytocin appears to be improved when given 10 to 15 minutes after giving calcium. Most bitches/queens are eucalcemic, suggesting that the benefit of calcium administration is at a cellular or subcellular level.

Cesarean Section

Surgical intervention (cesarean section) is indicated if a bitch or queen fails to respond to medical management, or if fetal distress is evidenced despite adequate to increased uterine contractility (suggesting mismatch of maternal birth canal to



FIG 55.22
Fetal heart rate (HR) monitoring in an Airedale bitch during the eighth week of gestation. Normal fetal HR should be over 180 beats/min.

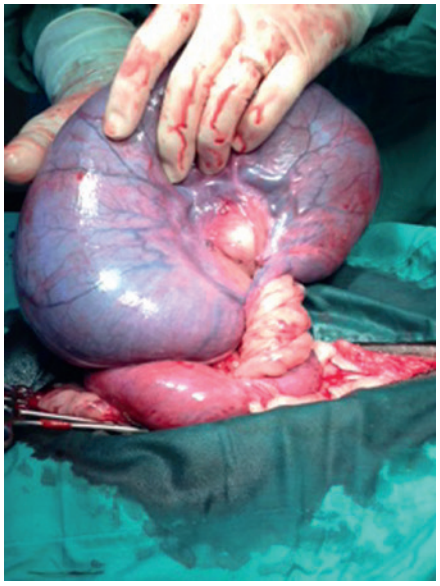


FIG 55.23
Uterine torsion diagnosed preoperatively with tocodynamometry. Immediate cesarean section resulted in preservation of the uterus and survival of all fetuses.

fetal size, or fetal malposition or malposture incompatible with vaginal delivery), or if aberrant contractile patterns are noted by uterine monitoring (Fig. 55.23). If fetal heart rates decline in response to administration of calcium or oxytocin, further medical management is contraindicated. Well-orchestrated cesarean sections result when anesthetic and neonatal resuscitative protocols are established and coordinated, and the preoperative preparation of the dam optimized. The dam can be debilitated and require careful anesthetic management, there often is be little time for routine preanesthetic preparation, and the dam might have been fed recently. Minimally, the hematocrit, total solids, serum calcium, and glucose concentrations should be evaluated preoperatively. IV fluid support at an operative rate is indicated (5-10 mL/kg/h).

Preoxygenation by mask (5-10 minutes) is always indicated. Initial preparation of the abdomen (clipping and first scrubbing) can be undertaken during this time. Atropine is undesirable as a premedication anticholinergic because it crosses the placenta (can exacerbate fetal myocardial hypoxemia) and causes relaxation of the lower esophageal sphincter making maternal aspiration more likely. However, an anticholinergic is indicated for the dam because of the anticipated vagal stimulation during manipulation of the gravid uterus. Glycopyrrolate (Robinul [AH Robins] at 0.01-0.02 mg/kg SC) does not cross the placenta and is preferred. Most dams are tractable or exhausted and do not need preanesthetic tranquilization, which has a depressant effect on the fetuses. Phenothiazine tranquilizers are transported rapidly across the placenta and are depressants. α_2-adrenoceptor agonists such as dexmedetomidine and xylazine are contraindicated because of their severe cardiorespiratory depressant effects. Similarly, the respiratory depressant effect of opioids makes them unpopular before removal of the fetuses. If tranquilization is necessary with an intractable dam, narcotic sedatives are preferable because their effects can be reversed (IV or IM naloxone, 1-10 µg/kg) during neonatal resuscitation. Metoclopramide (0.1-0.2 mg/kg) can be administered subcutaneously or intramuscularly to the dam before induction of anesthesia to reduce the risk of vomiting during the procedure. Dissociative induction agents such as ketamine and the barbiturates are best avoided because they produce profound depression of the fetuses. Propofol (Rapinovet [Bayer Animal Health] at 6 mg/kg IV to effect) appears to be the most useful induction agent; because of its rapid redistribution it has a limited effect upon the neonates. Alfaxalone (Alfaxan [Jurox]) at 2 mg/kg IV (canine) and 5 mg/kg IV (feline) is an alternative. Mask induction actually produces *more* maternal and fetal hypoxemia than IV propofol induction. For maintenance of anesthesia, volatile agents are preferable, especially those with low partition coefficients, such as isoflurane and sevoflurane. These agents show rapid uptake and elimination by the animal and may have a better cardiovascular margin of safety than the more soluble agents (e.g., halothane). Nitrous oxide may be used to reduce the dose of other anesthetic agents. It is transferred rapidly across the placenta, and although it has minimal effects upon the fetus in utero, it may result in a significant diffusion hypoxia after delivery. Using a local anesthetic (bupivacaine 1-2 mg/kg, lidocaine (canine only) up to 2 mg/kg diluted to necessary volume) line block in the skin and SC tissues before incising permits more rapid entry into the abdomen while the dam is making the transition from propofol induction to inhalant maintenance, and helps with postoperative discomfort. Care must be taken not to inadvertently administer bupivacaine or lidocaine into a mammary vessel. Local (epidural) anesthetic techniques require expertise and monitoring for severe hypotension. Sedatives could still be required to enable positioning for surgery. Epidural lidocaine is preferable (bupivacaine has too long a duration of action and is a more potent negative inotrope) at 2 to 3 mg/kg, not to exceed a maximum volume of 6 mL; adding epinephrine 5 µg/mL intensifies and prolongs the block achieved. Inadvertent penetration of the dura mater can occur.

Ovariohysterectomy at the time of cesarean section is an option for the surgeon and owner but results in longer

anesthetic time for the dam, delayed nursing for the neonates, and increased loss of blood in the dam, and should be postponed unless indicated (devitalized uterus, uncontrollable hemorrhage). Postoperative hemorrhage due to surgical error is more common if ovariohysterectomy has been performed. There is evidence that estrogen acts in a permissive fashion for prolactin receptors in the mammary glands, making ovary removal at cesarean section undesirable. If uterine viability is questionable, however, an ovariohysterectomy should be performed. In the normal dam the uterus will begin to involute shortly after removal of the fetuses, but if this is not the case oxytocin may be administered (0.25-1 unit per dam) to facilitate involution and arrest any hemorrhage; this also promotes milk letdown.

Postsurgical discomfort should be addressed in the dam. Once the fetuses are removed, narcotic analgesia can be administered parenterally to the dam. Postoperatively, nonsteroidal antiinflammatory drugs (NSAIDs) are not advisable because of their uncertain metabolism by the nursing neonates with immature renal and hepatic metabolism. Narcotic analgesia is preferable. Oral narcotics such as tramadol (Ultram [Janssen Pharmaceuticals]) at 10 mg/kg/day in divided doses provide fair to good postoperative analgesia for nursing bitches, with minimal effect in the neonates. In all cases, clients should be advised to closely monitor bitches postoperatively until normal maternal behavior emerges. After cesarean section, bitches can be clumsy and inattentive to the neonates and can even become aggressive, because the normal mechanisms of maternal bonding have been bypassed. The neonates should be allowed to nurse colostrum as soon as possible under close supervision (Fig. 55.24, see Chapter 57).

POSTPARTUM DISORDERS

Normally, dams stay very close to their offspring during the first 2 weeks postpartum, leaving the whelping/queening box briefly if at all to eat and eliminate. They are alert and content to remain with their offspring. Some protective dams may show aggression to housemate animals or even people with whom they are normally tolerant; such behavior tends to dissipate after 1 or 2 weeks of lactation. Lactation typically presents the greatest nutritional and caloric demand of the female's life. Weight loss and dehydration may occur and impact lactation if food and water are not made readily available. Sometimes this entails leaving both in the nest box with a nervous dam. Partial anorexia can be exhibited during the last weeks of gestation and in the immediate postpartum period, but the appetite should return and increase as lactation progresses. Poor appetite during the last weeks of gestation can be due to displacement of the gastrointestinal tract by the gravid uterus. Partial anorexia early in the postpartum period can occur secondary to digestive upset after the consumption of numerous placentae. Diarrhea can occur secondary to increased rations and rich food (bacterial overgrowth secondary to carbohydrate malassimilation).



FIG 55.24
Golden Retriever neonates nursing during the postoperative period after cesarean section. Close monitoring is indicated during this period. Nursing enables acquisition of colostrum.

Marked postpartum effluvium is normal in the bitch, usually occurring at 4 to 6 weeks after whelping and sparing only the head. This is usually more marked than that which occurs in conjunction with the typical estrous cycle, and can cause owner concern, especially in conjunction with the weight loss typically associated with peak lactation.

The body temperature of the dam may be mildly elevated (<39.44° C, 103° F) in the immediate postpartum period, reflecting normal inflammation associated with parturition, but should return to normal levels within 24 to 48 hours. If a cesarean section took place, differentiating normal postsurgical inflammation from fever associated with pathology may be difficult. The physical examination and a complete hemogram help the clinician differentiate between the two. Normal postpartum lochia is brick red in color and nonodorous, and diminishes over several days to weeks (Fig. 55.25, *A*). The mammary glands should not be painful; rather they are symmetric and moderately firm without heat, erythema, or palpable firm masses. If expressed, normal colostrum is yellow to white; milk is gray to white in color and of more watery consistency.

INAPPROPRIATE MATERNAL BEHAVIOR

Appropriate maternal behavior is critical to neonatal survival and includes attentiveness, facilitation of nursing, retrieving neonates, grooming, and protecting neonates. Although maternal behavior is instinctual, it can be negatively influenced by anesthetic drugs, pain, stress, and excessive human interference. Maternal bonding is a pheromone-mediated event initiated at parturition. Whelping and queening should take place in quiet familial surroundings, with minimal human interference yet adequate supervision. Dams with good maternal instincts exhibit caution when entering or moving about the nest box so as not to traumatize neonates by stepping or lying on them. A guardrail along the inside of the whelping box prevents inadvertent smothering of canine neonates (Fig. 55.25, *B*). The neuroendocrine reflex regulating mammary gland myoepithelial cell contraction and subsequent milk ejection is mediated by oxytocin and activated by neonatal suckling. During stress, epinephrine

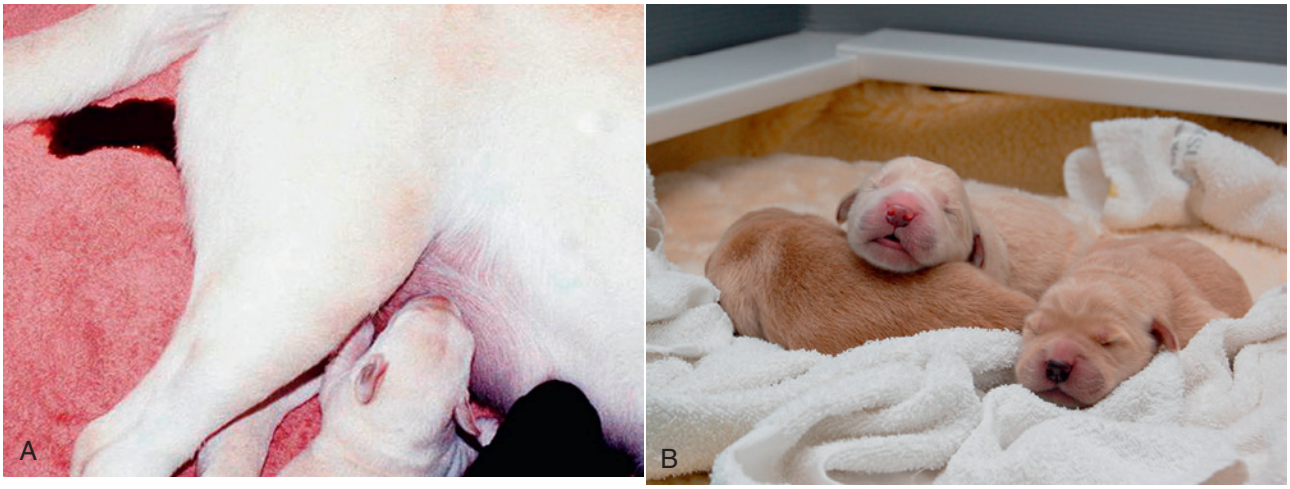


FIG 55.25
(A) Normal lochia, red-brown in color and not malodorous. **(B)** Placement of a guard rail along the inner perimeter of the whelping box helps prevent the dam from lying on puppies.

induces vasoconstriction, blocking the entry of oxytocin into the mammary gland and preventing milk ejection. A nervous, agitated dam will likely have poor milk availability. Dopamine antagonist tranquilizers with minimal prolactin interference (acepromazine 0.01-0.02 mg/kg), administered at the lowest effective dose to minimize neonatal sedation, can improve maternal behavior and milk ejection in nervous dams.

Piling of neonates near their dam facilitates maintenance of their body temperature (neonates cannot thermoregulate/shiver for up to 4 weeks of age) and makes nursing readily available. Normal maternal behavior includes gentle retrieval of neonates who have become dispersed and isolated across the nest box. Grooming of the neonates immediately after parturition stimulates their cardiovascular and pulmonary function and removes amniotic fluids. Dams demonstrating little interest in resuscitating neonates can have poor maternal behavior throughout the postnatal period. Later, maternal grooming stimulates reflex neonatal urination and defecation and maintains the neonatal coat in a clean, dry state. Occasionally, excessive protective behavior or fear-induced maternal aggression can occur. Mild tranquilization of the dam with an antianxiety agent can help, but neonatal drug administration via the milk can be problematic. Benzodiazepines (diazepam 0.55-2.2 mg/kg), γ-aminobutyric acid (GABA) synergists, are reportedly superior to phenothiazines for fear-induced aggression. The role of newer antianxiety pharmaceuticals in maternal aggression has not been described in a controlled setting.

METABOLIC DISORDERS

Eclampsia

Puerperal tetany or eclampsia occurs most commonly during the first 4 weeks postpartum but can occur in the last few weeks of gestation. The condition occurs in bitches more frequently than queens. Puerperal tetany can be life-threatening, and is caused by a depletion of ionized calcium in the extracellular compartment. Predisposing factors include improper perinatal nutrition, inappropriate calcium supplementation, and heavy lactational demands. Small dams with large litters are at increased risk. Excessive prenatal calcium supplementation can lead to development of puerperal tetany by promoting parathyroid gland atrophy and inhibiting parathyroid hormone release, thus interfering with the normal physiologic mechanisms to mobilize adequate calcium stores and utilize dietary calcium sources. Thyrocalcitonin secretion is stimulated. Use of a balanced growth (puppy/kitten) formula commercial feed without additional vitamin or mineral supplementation is optimal during the second half of gestation and throughout lactation. Supplementation with cottage cheese should also be avoided because it disrupts normal calcium-phosphorus-magnesium balance in the diet.

Metabolic conditions favoring protein binding of serum calcium (e.g., alkalosis due to prolonged hyperpnea during labor or dystocia) can promote or exacerbate hypocalcemia. Hypoglycemia and hyperthermia can occur concurrently. Therapeutic intervention should be initiated immediately upon recognition of the clinical signs of tetany without waiting for biochemical confirmation. Signs preceding the development of tetany, tonic-clonic muscle contractions include behavioral changes, salivation, facial pruritus, stiffness/limb pain, ataxia, hyperthermia, and tachycardia. Immediate therapeutic intervention should be instituted with a slow IV infusion of 10% calcium gluconate (1-20 mL) given to effect. Cardiac monitoring for bradycardia and arrhythmias should accompany administration; their occurrence warrants temporary discontinuation of the infusion and a slower subsequent rate. Actual seizures should not occur from hypocalcemia; hypoglycemia should be investigated. Corticosteroids are undesirable because they promote

calciuria, decrease intestinal calcium absorption, and impair osteoclasia. Hypoglycemia should be corrected if present, and exogenous treatment for hyperthermia given if necessary.

Once the immediate neurologic signs are controlled, a SC injection of the equal volume of calcium gluconate, diluted 50% with saline is given and repeated q6-8h until the dam is stable and able to take oral supplementation. Calcium gluconate or carbonate (10-30 mg/kg q8h) should be instituted. Each 500-mg calcium carbonate tablet (Tums) supplies 200 mg calcium. Efforts to diminish lactational demands on the dam and improve her plane of nutrition are indicated. If response to therapy has been prompt, nursing can be gradually reinstituted until the neonates can be safely weaned, usually at a slightly early age (3 weeks), and concurrent supplementation with commercial bitch/queen milk replacement is encouraged. Bottle feeding should precede nursing, and nursing limited to 10 min q4-6h rather than continuously. Giving calcium throughout lactation (but not prepartum) may be attempted in dams with a history of recurrent eclampsia (calcium carbonate 500-4000 mg/dam/day, divided).

UTERINE DISORDERS

Uterine Trauma

Complete or partial prolapse of the uterus is an uncommon postpartum condition in the bitch, occurring rarely in the queen experiencing dystocia. The diagnosis is based on palpation of a firm, tubular mass protruding from the vulva postpartum, and inability to identify the uterus with abdominal ultrasonography. The prolapsed uterine tissues are at risk for maceration and infection from exposure and contamination (Fig. 55.26). The size of most bitches and queens precludes manual replacement; laparotomy and ovariohysterectomy are usually indicated. Vaginal hyperplasia and prolapse, secondary to a hypersensitivity of focal (periurethral) vaginal mucosa to estrogen, can recur near parturition and can be differentiated by physical examination or vaginoscopy (see Fig. 55.5, *B*).

Rupture of the uterus occurs most commonly with very large litters causing marked stretching and thinning of the uterine wall, especially in multiparous dams with dystocia. Immediate laparotomy for retrieval of fetuses and repair or removal of the uterus, as well as culture and lavage of the abdominal cavity, is indicated. The uterus should be carefully examined at any cesarean section for any areas with or prone to rupture. Peritonitis or hemoabdomen can result from an undetected uterine tear. A unilateral hysterectomy can be considered if the damaged area is limited and the dam valuable to a breeding program; these females can be prone to uterine torsion as a consequence.

Subinvolution of Placental Sites

The persistence of serosanguineous to hemorrhagic vaginal discharge beyond 16 weeks postpartum can indicate subinvolution of the placental sites of attachment (SIPS) in the bitch. Histologically, fetal trophoblastic cells have persisted in the myometrium instead of degenerating, endometrial vessel thrombosis is lacking, and normal involution of the uterus is prevented. Normal interplacental regions exist. Eosinophilic masses of collagen and dilated endometrial glands protrude into the uterine lumen, oozing blood (Fig. 55.27). The cause is unknown, blood loss is usually minimal, intrauterine infection not present, and fertility is unaffected. Treatment is generally not necessary; recovery is spontaneous and symptoms mild. In the uncommon situation where vaginal bleeding from SIPS is copious enough to cause serious anemia, coagulopathies (likely defects in the intrinsic pathway or thrombocytopenia/thrombocytopathies), uterine trauma, neoplasia of the genitourinary tract, severe metritis, and excessive hemorrhage from prematurely separated placental sites should be ruled out. Cytology of vulvar discharge (trophoblast cells can be evident), vaginoscopy to localize



FIG 55.26
Uterine prolapse postdystocia in a queen. Devitalized tissue necessitated ovariohysterectomy.

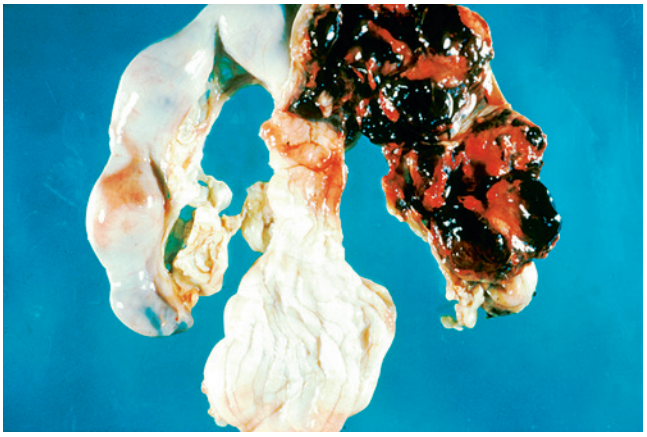


FIG 55.27
Gross specimen, subinvolution of placental sites. The right horn has been incised to illustrate hematoma formation at placental sites.

the source of hemorrhage, coagulation testing, and abdominal ultrasound assist in the diagnosis. Therapy with prostaglandins has not been substantiated. The preventive value of oxytocin given in the immediate postpartum period is also unproven but not likely harmful. Laparotomy and ovariohysterectomy are curative. Histologic examination of the uterus is indicated to confirm the diagnosis.

Postpartum Endometritis

Acute infection of the postpartum endometrium should be suspected if lethargy, anorexia, decreased lactation, and poor mothering are reported and are accompanied by fever and malodorous vulvar discharge (Fig. 55.28). Endometritis is serious and sometimes preceded by dystocia, contaminated obstetrical manipulations, or retained fetuses and/or placentae. Hematologic and biochemical changes often suggest septicemia, systemic inflammation reaction, and endotoxemia. Cytology of vulvar discharge is hemorrhagic to purulent (Fig. 55.29). Ultrasound of the abdomen allows evaluation of intrauterine contents and the uterine wall; endometritis is characterized by thickened, corrugated endometrium with echogenic fluid in the lumen (Fig. 55.30). Postpartum metritis is best differentiated from the normal postpartum uterine enlargement by a failure of normal progressive decrease in uterine lumen contents and horn width. The canine uterus involutes and repairs for up to 16 weeks, making the normal postpartum ultrasonographic appearance challenging; serial evaluations (q24-48h) are helpful. Retained fetuses and placentae can also be identified with ultrasound.

A guarded cranial vaginal culture is likely representative of intrauterine flora and should be submitted immediately for both aerobic and anaerobic culture and sensitivities; this permits retrospective assessment of empirically selected antibiotic therapy. Bacterial ascension from the lower genitourinary tract is more common than hematogenous spread, and *E. coli* is the most common causative organism in both bitches and queens. Empirical selection of a broad-spectrum bactericidal antimicrobial (potentiated amoxicillin such as ticarcillin, 15-25 mg/kg IV q8h, or cefazolin, 22 mg/kg IV q8-12h) must take into consideration that nurslings will be treated as well. Additional therapy consists of IV fluid and electrolyte support as indicated and pharmacologic uterine evacuation, either with synthetic prostaglandins (cloprostenol at 1-3 µg/kg q12-24h) or natural $PGF_{2\alpha}$ (0.1-0.2 mg/kg q 12-24h) for 3 to 5 days to effect. Oxytocin is unlikely to promote effective uterine evacuation when administered more than 24 hours postpartum. Nurslings should be hand-reared if the dam is seriously sick or requires antibiotics contraindicated for neonates. An ovariohysterectomy may be indicated if the bitch's condition

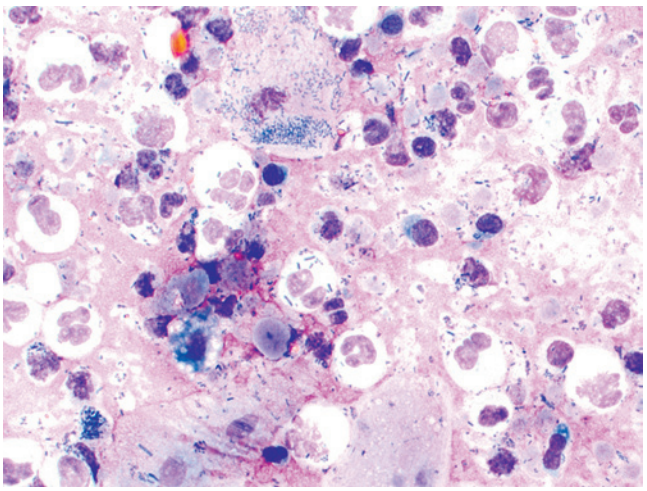


FIG 55.29
Cytology of vulvar discharge in postpartum endometritis: numerous free and phagocytized bacteria, toxic neutrophils, and macrophages.



FIG 55.28
Malodorous purulent to hemorrhagic vulvar discharge in postpartum endometritis.

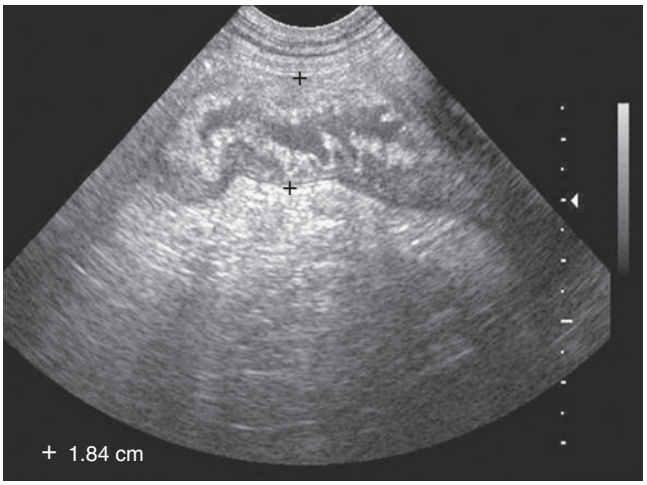


FIG 55.30
Ultrasonographic appearance of postpartum endometritis. Note the irregular hyperechoic endometrium and echogenic fluid content.

permits and she is poorly responsive to medical management; however, this is uncommon. Therapy of postpartum metritis is best monitored by serial evaluations of uterine luminal contents with ultrasound along with hematology, biochemistry, and clinical parameters (appetite, fever, vulvar discharge). Metritis can become chronic and cause infertility. Mild cases, when the bitch is eating, able to take oral antibiotics (Clavamox [14 mg/kg q12h] or cephalexin [10-20 mg/kg q8-12h]), and is still providing good maternal care, can be successfully managed on an outpatient basis, preserving home care of the litter. Bitches with metritis should be evaluated clinically for mastitis as well, owing to the potential for bacteremic contamination of the lactating mammary glands.

MAMMARY DISORDERS

Agalactia

Agalactia is defined as a failure to provide milk to neonates. Primary agalactia, a lack of mammary development during gestation, results from a failure of milk production and is uncommon. A defect in the pituitary-ovarian-mammary gland axis is suspected. Administering progesterone compounds late in gestation can interfere with normal development of the mammary glands, precluding lactation. Secondary agalactia, a lack of milk availability due to a failure of letdown and ejection, is more common. Mammary development is marked, but milk cannot be readily expressed through the teat sphincter. The normally scant production of colostrum in the immediate postpartum period should not be confused with agalactia. Agalactia can occur secondary to premature parturition, severe stress, malnutrition, debility, metritis, or mastitis. Treatment includes providing supplementation to the neonates while encouraging suckling to promote milk letdown, providing optimal levels of nutrition and adequate hydration to the dam and resolution of any underlying disease. Pain management after cesarean section is indicated. If detected early, milk letdown can often be induced pharmacologically. Minidose oxytocin, 0.25-1 unit per injection, is given subcutaneously every 2 hours. Neonates are removed for 30 minutes preinjection and then encouraged to suckle, or gentle stripping of the glands is performed postinjection. Metoclopramide, 0.1-0.2 mg/kg SC, is given q12h to promote prolactin release and mild production. Therapy is usually rewarding within 24 hours. Some authors advise a much higher dose of metoclopramide, risking neurologic side effects; the author has not found this necessary. The use of domperidone (Motilium [Janssen Pharmaceuticals]) at 2.2 mg/kg PO q12h PO from 6 days prepartum to 7 days postpartum resulted in normal lactation in a queen previously agalactic.

Galactostasis

Galactostasis causes engorgement and edema of the mammary gland, with associated discomfort making further nursing unlikely, and can become self-perpetuating. Galactostasis occurs secondary to inverted or imperforate teats, failure to rotate nurslings, litter loss, an unusually small litter, ineffective nursing, and rarely with pseudocyesis (Fig. 55.31). Warm compresses, cleansing/lubricating the nipple, gentle expression of the affected gland, and rotating neonates is advised. With the loss of a litter, antiprolactin therapy with cabergoline (1.5-5 μg/kg/day, divided bid) can be helpful. Galactostasis likely increases the potential for mastitis to develop.



FIG 55.31
Inverted nipple with associated pyoderma, Old English Sheepdog bitch.

Mastitis

Mastitis, septic inflammation of the mammary gland, can be acute and fulminate or chronic and low grade, involving a single or multiple mammary glands. Coliforms, staphylococci, and streptococci are most commonly isolated in both bitches and queens. The source of bacteria is cutaneous, exogenous, or hematogenous. Mastitis can be comorbid with metritis. Mild mammary discomfort and heat, galactostasis, cutaneous inflammation, and the presence of an intramammary mass effect are the earliest signs. Milk is commonly discolored red or brown due to the presence of red and white blood cells. The dam exhibits pain, reluctance to nurse or lie down, anorexia, and lethargy. Fever can be marked and may precede other clinical signs. Advanced cases can present in septic shock, with abscessed or necrotic glands. The diagnosis is based upon physical examination. Milk cell counts in bitches are not predictive of mastitis.

Culture and sensitivity of milk collected aseptically from affected glands allows retrospective evaluation of empirical antibiotic selection. Therapy should begin immediately and consists of broad-spectrum bactericidal antimicrobials and gentle physical therapy. Analgesics may be indicated; neonates tolerate opioid analgesia in the dam. First-generation cephalosporins (cephalexin, 10-20 mg/kg q8-12h) and β-lactamase-resistant penicillins (Clavamox 14 mg/kg q12h) are advised and safe for neonates. Antibiotic therapy may be warranted until weaning and can preclude further nursing if

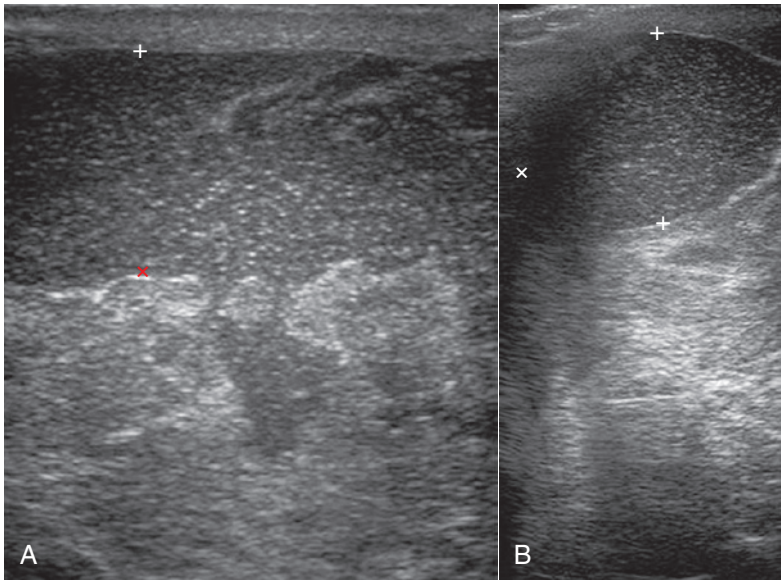


FIG 55.32
Ultrasonographic evaluation of mastitis (cursors). **(A)** Cellulitis. **(B)** Abscessation, surgery is indicated.

sensitivities force the choice of a drug potentially toxic to neonates. Warm compresses or whirlpool therapy of the affected gland, with gentle stripping of milk, can potentially avert abscessation and rupture of the gland. Serial ultrasonography can help identify abscessation (Fig. 55.32, *A*, 55.32, *B*). Severe necrosis warrants debridement or mastectomy when the dam is stabilized, as well as more aggressive wound management. Antiprolactin therapy (cabergoline, 1.5-5 µg/kg/day, divided bid) may be indicated in severe cases to reduce lactation. There is no evidence that nursing from affected glands is problematic for neonates; they tend to avoid glands that are difficult to obtain milk from and are already exposed to flora in the box. The affected gland should be protected from trauma from nest box edges and neonatal claws. Mastitis can recur in subsequent lactations regardless of preventive measures. Early detection and treatment is optimal, rather than prophylactic, antibiotics, which tend to favor development of resistant organisms rather than preventing mastitis.



FIG 55.33
Feline mammary hyperplasia of 6 weeks' duration in a 5-month-old queen. (Image courtesy Dr. Cheri Johnson.)

Feline Mammary Fibroadenomatous Hyperplasia

Feline mammary fibroadenomatous hyperplasia is a non-neoplastic progesterone-mediated condition usually found in pregnant or pseudopregnant queens or in neutered male or female cats given exogenous progestins, most commonly methylprednisolone acetate (Depo-Medrol [Upjohn]). Progestins are most commonly used for behavioral or antiinflammatory therapy in cats. Cats present with mammary enlargement involving one or more glands; the enlargement is due to rapid proliferation of mammary duct epithelium and stroma (Fig. 55.33). Hyperplastic mammary tissue may undergo spontaneous regression or progress to mastitis with abscessation and gangrene. Mammary hyperplasia must be distinguished from mammary neoplasia, by cytology or biopsy. Ovariohysterectomy (if intact) prevents recurrence. NSAID (licensed for use in felines) and antimicrobial therapy, as well as antiprolactin therapy (cabergoline 1.5-5 µg/kg PO q24h for 5-7 days), can be helpful. Mastectomy can be indicated in severe cases. Progestin therapy should be discontinued in neutered cats. More recently, the progesterone antagonist aglepristone (Alizine [Virbac]) has been used successfully to treat fibroadenomatous hyperplasia (10-15 mg/kg SC on days 1, 2, and 8) but is not yet available in the United States.

DISORDERS OF THE REPRODUCTIVE TRACT IN OVARIOHYSTERECTOMIZED BITCHES AND QUEENS

Despite the majority of client-owned pets in the United States being neutered, veterinarians are commonly confronted with disorders of the (residual) genitourinary tract.

CHRONIC VESTIBULOVAGINITIS IN THE OVARIOHYSTERECTOMIZED OR OVARIECTOMIZED BITCH

These bitches present with variable vulvar discharge that is mucoid to hemorrhagic or purulent, and usually accompanied by signs of discomfort (licking, scooting, pollakiuria). Perivulvar and vulvar dermatitis are also frequently present. The condition is invariably seen in ovariectomized bitches of any age, and at variable times from the spay procedure. The history usually includes multiple therapeutic efforts without resolution, although transient improvement can occur. The duration is generally chronic, from weeks to months, sometimes lasting years.

The etiology of chronic vestibulovaginitis is usually multifactorial, and the primary cause is often masked and exacerbated by previous therapies, including long-term antimicrobial use, self-mutilation, and topical irrigations. The vaginal mucosa is erythemic and nodular showing lymphoid follicles; biopsy frequently shows nonspecific lymphoplasmacytic inflammation, but sometimes suppurative (neutrophilic) or eosinophilic inflammation is predominant (Fig. 55.34). Vaginal cultures can show overgrowth of an atypical bacterial species (pure gram-negative cultures, resistant organisms, *Pseudomonas* spp.) or pure culture of *Mycoplasma* spp. if antibiotics have been used extensively. Occasionally a yeast overgrowth is identified. Primary bacterial vaginitis is rare.

The most common documented etiologies of chronic vestibulovaginitis include:

1. Extensive perivulvar dermatitis associated with redundant dorsal and lateral vulvar folds
2. Granulomatous uterine stump (rule out stump pyometra)
3. Vaginal foreign bodies (foxtails, bone fragments)
4. Chronic urinary tract infection with urethritis/vestibulitis/vulvitis
5. Cystic, urethral, vaginal, or vestibular neoplasia

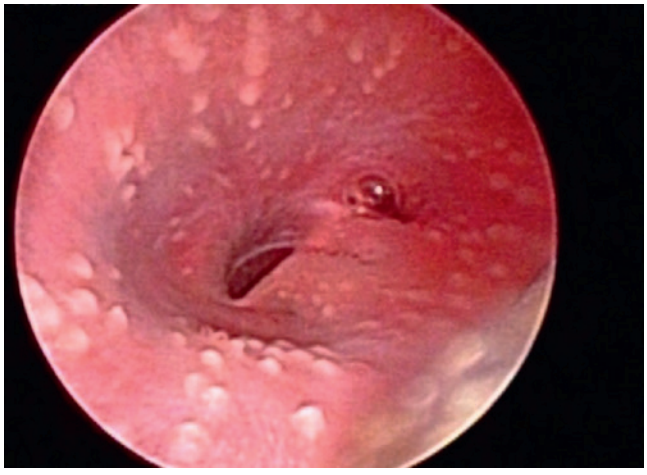


FIG 55.34
Vaginoscopic image of lymphoid follicles in the cranial vagina in an ovariohysterectomized bitch with chronic vestibulovaginitis.

Vaginal strictures are commonly identified and implicated but are rarely causal in this author's opinion. Most are cranial to the urethral papilla, and the pathology caudal. A minimum database should be performed on these chronically affected bitches, involving a complete blood count (CBC) and serum chemistries, including a urinalysis (preferably acquired by cystocentesis), and culture or culture "if indicated." A careful vulvovaginal examination under adequate (heavy) sedation or anesthesia, with endoscopic equipment allowing evaluation of the entire vaginal vault, should be performed. This usually means a rigid cystourethroscope with saline insufflation is a necessity. Otoscopes and vaginal speculums do not permit adequate evaluation of the entire vaginal vault. Pediatric proctoscopes lack the sensitive optics of cystourethroscopes. It is important to observe the undisturbed perivulvar anatomy and then retract surrounding skin to expose the perivulvar region to evaluate for significant dermatitis (Fig. 55.35, *A*, 55.35, *B*). Vaginoscopy permits localization of pathology and identification of foreign bodies, masses, or anatomic anomalies. Contrast radiography (vaginogram, urethrogram, cystogram, IV pyelogram) and/or ultrasound of the entire genitourinary tract can be helpful in localizing the problem and eliminating differential diagnoses. Ultrasound is preferable because it does not require anesthesia and is the best method to noninvasively evaluate the uterine stump, bladder, and urethra (Fig. 55.36, *A*, 55.36, *B*). Ideally ultrasound should be performed before vaginoscopy; saline insufflation can iatrogenically introduce fluid into the uterine stump, making its appearance suspect.

Vaginal cytology, cytologic evaluation of vulvar discharge, guarded vaginal swabs for aerobic bacterial and *Mycoplasma* cultures, and pinch biopsy of affected vaginal mucosa may be helpful in better defining the problem. If estrogen influence is detected with vaginal cytology (superficial cells), evaluation for an ovarian remnant is indicated (see later). If vulvar discharge is purulent and the ultrasonographic appearance of the uterine stump suggests abscessation, evaluation for stump pyometra with serum progesterone and close inspection for ovarian structures with abdominal ultrasound is indicated (see later). Identification of any contributory anatomic abnormalities is important (e.g., significant caudal vaginal strictures causing urine pooling or accumulation of secretions, masses, redundant dorsal or lateral vulvar folds, anomalous ureteral anatomy). It is helpful to evaluate the bitch in a normal standing position to accurately assess external anatomy, followed by another examination after she has urinated, and again after recumbency for urine pooling and scalding. The presence of urine pooling in the vaginal vault, noted only when the bitch is under anesthesia, can be misleading. The presence of redundant vulvar folds is also difficult to ascertain when the bitch is anesthetized and positioned for vaginoscopy, but the presence of perivulvar dermatitis implicates external anatomic contribution to chronic vestibulovaginitis.

General therapeutic guidelines apply to most cases. Discontinuation of topical irrigations, prevention of self-mutilation

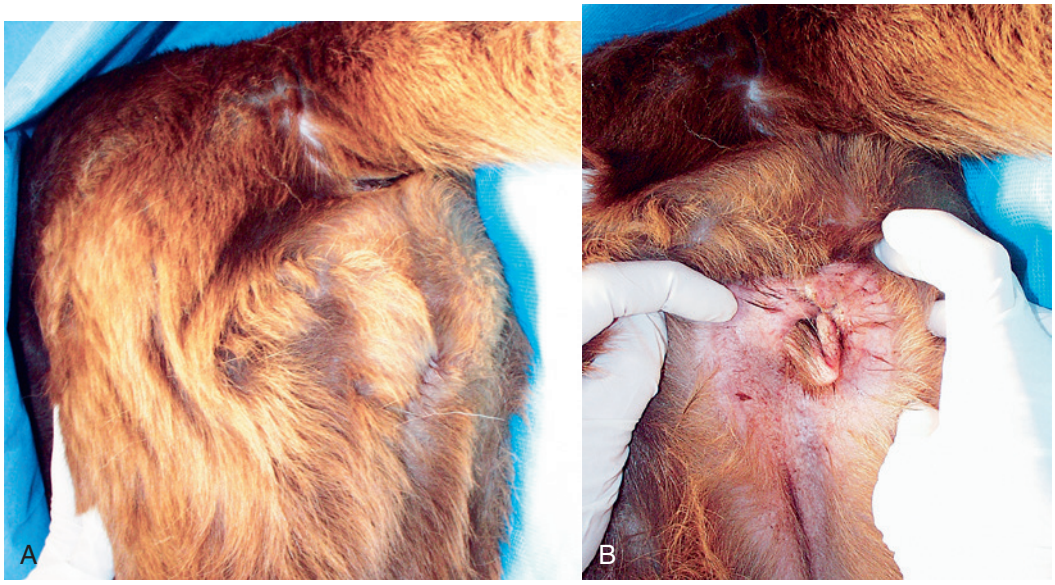


FIG 55.35
Perivulvar anatomy. **(A)** Perivulvar anatomy (hooded vulva) in an ovariohysterectomized mixed breed bitch with chronic vulvar discomfort. **(B)** Marked perivulvar dermatitis in the same bitch.

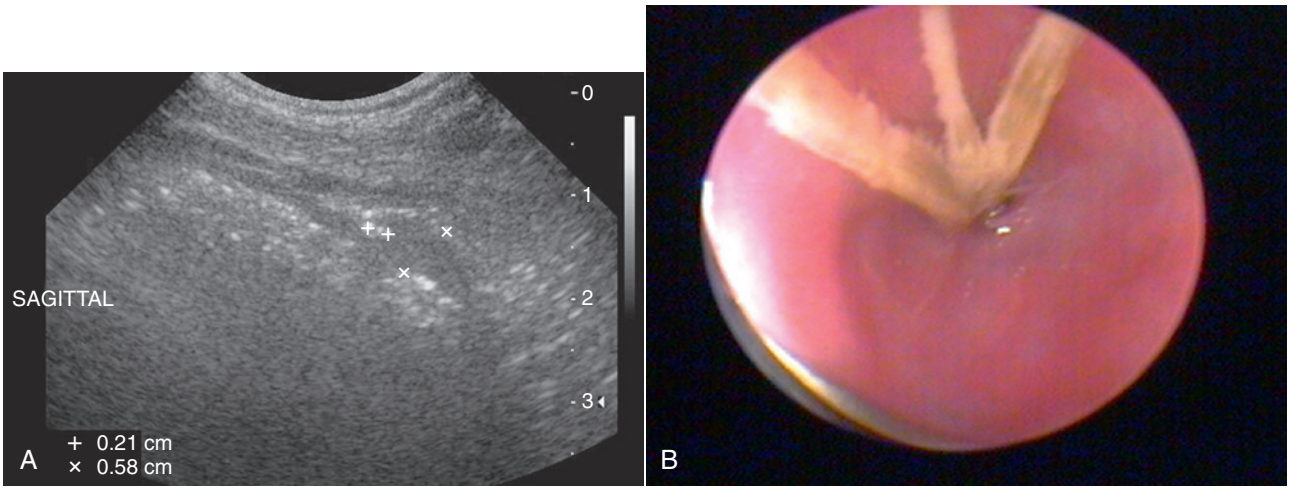


FIG 55.36
(A) Sagittal image of an ovariohysterectomized bitch with chronic vulvar discharge. Cursors (x) note cervical height and (+) a focal hyperechoic structure. **(B)** Grass awn removed vaginoscopically from caudal cervical os.

with Elizabethan collars, and initiation of antimicrobial therapy only when indicated by proper interpretation of culture and sensitivity testing should be undertaken. Antimicrobial therapy should be limited to those cases where pathogens have been identified as displacing normal flora. Analgesia and antiinflammatory therapies are indicated in most cases. A short antiinflammatory course of corticosteroids can be useful in diminishing vaginal inflammation, but the subsequent propensity for urinary tract infection must be kept in mind, and problems with long-term use limit usefulness. NSAIDs such as carprofen (Rimadyl [Pfizer]), meloxicam (Metacam [Boehringer Ingelheim]), firocoxib (Previcox [Merial]) or grapiprant (Galliprant® Aratana) are preferred. Narcotics (tramadol) or gabapentin may be necessary short term for adequate analgesia. If a specific cause is identified, resolution is more straightforward. Surgical correction with careful postoperative control of self-mutilation is indicated if anatomic abnormalities (redundant dorsal and lateral vulvar folds, significant vaginal stricture, granulomatous uterine stump, clitoral hyperplasia) have contributed to or caused the condition (Fig. 55.37). The identification and removal of foreign bodies should cure chronic vestibulovaginitis. Appropriate management of chronic urinary tract infection (if identified) should resolve associated vaginitis.



FIG 55.37
Postoperative image of corrected redundant dorsal vulvar hooding (Fig. 55.35).

Therapy of urogenital neoplasia can include surgery, chemotherapy, or both.

If no anatomic, foreign body, infectious, granulomatous, or neoplastic cause can be discerned, oral estrogen replacement therapy is often helpful in establishing normal mucosal integrity and eventual normalization of the vaginal vault. The condition is similar to atrophic vaginitis in women. The prevalence of atrophic vaginitis is particularly high among postmenopausal women who experience decreased ovarian estrogen production. This common menopausal condition is caused by estrogen-related changes to the vaginal epithelium and can adversely affect quality of life. Women improve with vaginal estrogen application, difficult in the dog. Oral diethylstilbestrol (compounded DES) or an FDA-approved estriol (Incurin [Merck]; off label) is advised in bitches. The dose is empirical and usually the same as used for urinary incontinence due to sphincter incompetence (DES 0.035 mg/kg PO every 3-4 days; Incurin 1-2 mg PO q24h, taper as possible). Several weeks of therapy may be required before improvement is recognized. Side effects are uncommon; mild overdosage results in signs of proestrus (attraction to male dogs, vulvar swelling); myelosuppression is highly unlikely if the dosage is conservative as suggested.

OVARIAN REMNANT SYNDROME/ HYPERESTROGENISM

Ovarian remnant syndrome (ORS) causes behavioral and/or physical signs of estrus in a bitch or queen having previously undergone ovariohysterectomy. It is caused by the presence of functional residual ovarian tissue and is reported to be responsible for 17% of all postovariohysterectomy complications. It is more common in cats. No breed predisposition or geographic distribution has been reported. The signs of estrus usually occur months to years after ovariohysterectomy but can begin within days after surgery. In bitches, signs reported include attraction of male dogs, swelling of the vulva, mucoid to sanguineous vulvar discharge, passive interaction with male dogs, and flagging; some even allow copulation. Of note, the signs are usually cyclical or periodic (i.e., every 6 months) rather than constant as occurs with chronic vestibulovaginitis or exogenous estrogen exposure. In queens, signs reported include vocalization, lordosis, restlessness, head rubbing, rolling, tail deviation, and treading the hind limbs; the queen may allow copulation. Queens demonstrate typical behavioral signs of estrus in a cyclical (seasonally polyestrous) fashion.

The most common cause is a previous failure to remove both ovaries completely. There is no correlation with age at ovariohysterectomy, difficulty of surgery, obesity of patient, or experience of the surgeon. The presence of anatomically abnormal ovarian tissue (fragmentation into the broad ligament) is possible but uncommon, and a supernumerary ovary is very rare. Experimentally, functionality returns to ovarian tissue removed from its vascular supply and replaced into or onto the lateral abdominal wall. The clinician needs to consider multiple differentials, including inflammation or infection of the genitourinary tract, vaginal hemorrhage due to foreign body, trauma, a uterine stump granuloma or pyometra, neoplasia of the genitourinary tract, vascular anomalies of the genitourinary tract, a coagulopathy, exogenous estrogen administration, and an endogenous extraovarian source of estrogen associated with adrenal pathology (rare). Exposure to exogenous estrogen is not uncommon in small dogs whose owners use transdermal hormone replacement therapy, usually on their forearms. In this case, the signs of hyperestrogenism would be more constant than the cyclical nature of an ovarian remnant. Ovarian remnants can undergo neoplastic transformation; external signs of hormonal influence then become chronic rather than episodic (Fig. 55.38, *A*, 55.38, *B*).

A minimum database should be performed: CBC and serum chemistries, including a urinalysis (preferably acquired by cystocentesis), and culture or culture "if indicated" of the urine is advised. Pancytopenia is possible from estrogen toxicity. Critical observation of behavioral and physical signs of estrus together with vaginal cytologic analysis and/or measurement of serum progesterone or estradiol concentrations can confirm the presence of functional ovarian tissue. Vaginal cytology will identify estrogen effect: vaginal mucosal cornification is a bioassay for elevated plasma estradiol concentrations (see Chapter 54). Note that peak estradiol concentrations triggering behavioral estrus range from 20 to more than 70 pg/mL; however, vaginal cytology findings closely correlate with serum estradiol, and this study is much less expensive to perform. A serum progesterone level >2.0 ng/mL (measured 1-3 weeks after behavioral estrus) is consistent with functional luteal tissue. GnRH (50 µg IM bitch, 25 µg IM queen) or hCG (500-1000 IU IM) can be used to attempt to induce ovulation or luteinization for diagnostic purposes or to end estrus. Serum progesterone is measured 2 to 3 weeks later; this is

often unrewarding because of the refractory nature of the ovarian remnant. In the queen, if ovulation or luteinization is stimulated during behavioral estrus, serum progesterone levels >2.0 ng/mL are consistent with adequate coital stimulation and functional luteal tissue. Serum LH is elevated in ovariectomized females; it is only elevated in intact females during the 12 to 24 h surge. Serum Anti-Müllerian Hormone (AMH) assays are now commercially available, have excellent correlation with ORS in postpubertal females, and will differentiate exogenous estrogen exposure from ORS (Themmen et al., 2010).

Ultrasound should be used to support a diagnosis of ORS based on history, clinical signs, vaginal cytology, and serum hormone tests; ultrasound also gives the surgeon guidance (Video 55.1). Imaging should begin in a sagittal plane slightly caudolateral to the kidneys (where remnant ovarian tissue is expected). Remnant ovarian tissue may be visible only during the follicular phase (anechoic cystic structures) or the luteal phase (hypoechoic or isoechoic cystic structures) (Fig. 55.38, *C*). Ectopic ovarian tissue can be difficult to locate and image using ultrasonography and often requires operator expertise. The adrenal glands should be evaluated at the same time for normal size and shape.

Exploratory laparotomy with the goal of removal of residual ovarian tissue confirms and resolves the problem. The identification of residual ovarian tissue is facilitated by the presence of active follicles or resultant corpora lutea. The clinician should schedule the surgical procedure during estrus of when progesterone is elevated. All visible ovarian tissue should be removed and evaluated by histopathology. If no visible ovarian tissue is identified, all residual tissue at the ovarian pedicles should be resected and submitted for histopathology. Removal of functional luteal tissue may induce transient signs of pseudopregnancy in dogs and cats postoperatively. If profound, antiprolactin therapy (cabergoline 5 µg/kg q24h to effect) can be offered. Successful removal of remnant ovarian tissue should result in cessation of clinical signs of estrus.

Medical therapy is often requested by clients not eager to permit another surgical procedure. Progestational or androgenic compounds used to suppress follicular ovarian activity are not recommended because of undesirable side effects (mammary neoplasia, diabetes mellitus, undesirable behavior). Immunocontraception or GnRH agonist administration will offer a viable alternative to laparotomy when perfected and commercially available in the United States.

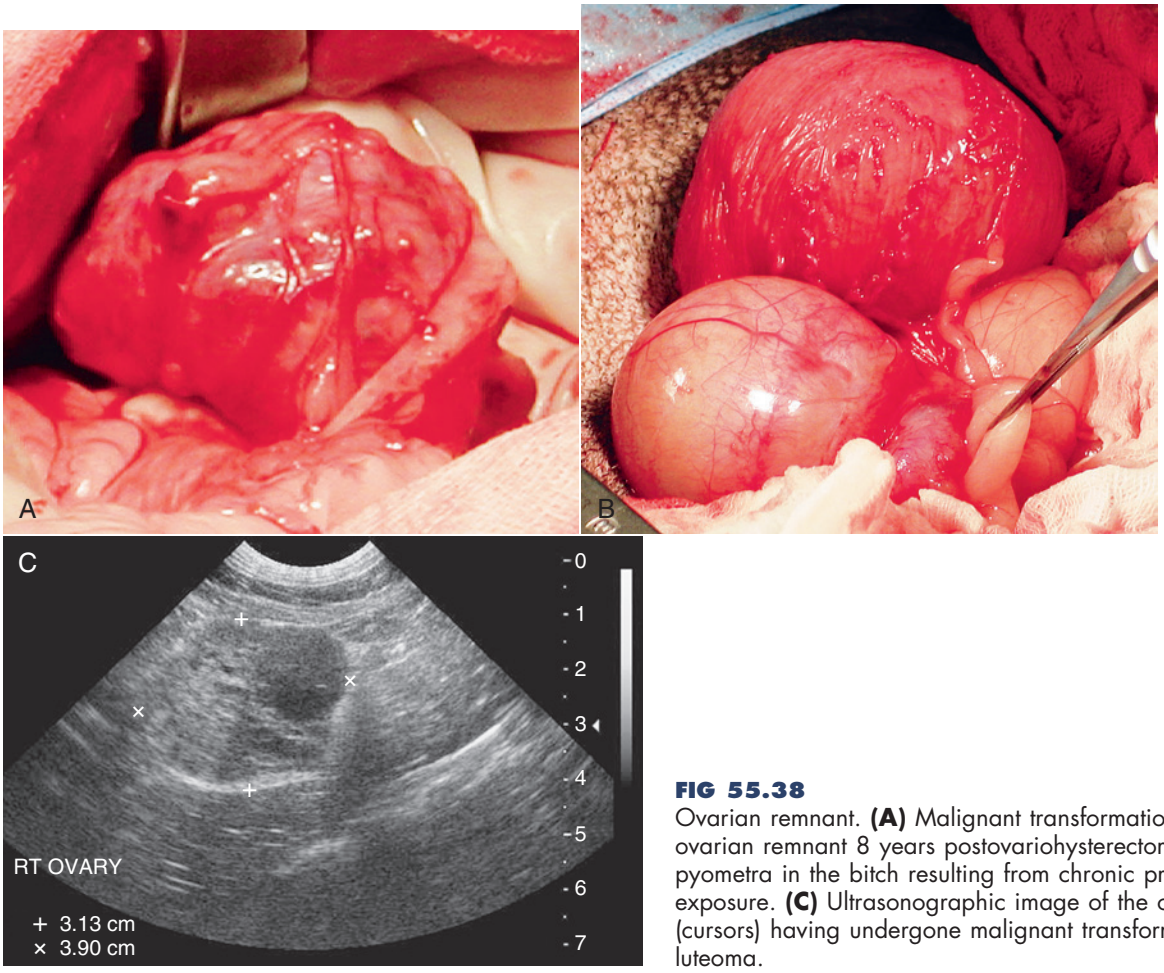


FIG 55.38
Ovarian remnant. **(A)** Malignant transformation (luteoma) of an ovarian remnant 8 years postovariohysterectomy. **(B)** Stump pyometra in the bitch resulting from chronic progesterone exposure. **(C)** Ultrasonographic image of the ovarian remnant (cursors) having undergone malignant transformation into a luteoma.

INFERTILITY/SUBFERTILITY IN THE BITCH AND QUEEN

Infertility of the bitch or queen refers to the inability to conceive and produce viable offspring; subfertility refers to small litter size. With the exception of developmental abnormalities (see Chapter 56), the majority of bitches brought to a veterinarian for reproductive evaluation for infertility are actually healthy and fertile. Perceived infertility in the bitch is most commonly due to inappropriate breeding management, poor husbandry, or stud dog problems rather than inability of the bitch to conceive. Queens presented for infertility are more likely to actually be infertile; appropriate husbandry and good breeding management have usually taken place using a fertile male. A complete history should be obtained so that problem areas with breeding management or husbandry can be identified and corrected (Box 55.1). Recent fertility of the male(s) used should be verified (litters produced within the last 4 months, not just semen evaluation). The bitch's breeding and general health history including her environment, other animals, housing arrangements, routine prophylactic therapy (vaccinations, heartworm prevention, deworming regimen), current medications, all supplements, diet, and any travel history should be obtained. Of particular interest are age, date(s) of onset of previous cycles (if any), method of ovulation timing used in the past (if any), results of ovulation timing and dates of breeding/insemination based on those results, methods of breeding/insemination, previous pregnancy (if any), method of pregnancy diagnosis or exclusion, date of any pregnancy loss (if known), number of prior litters, litter size, and the reproductive history of the bitch or queen's dam and female siblings. Unless adequate breeding management with a proven currently fertile male, good husbandry, and a documented failure to conceive can be shown, the female should then be managed and monitored (including ovulation timing) through her next cycle before infertility is diagnosed. A sire producing normal litter size for the breed should be used. If failure to conceive persists despite correction of identified problems with husbandry and the male, and incorporation of ovulation timing, then acquired infertility in the bitch and queen usually implicates endometrial pathology rather than pituitary-gonadal or ovarian disorders.

BOX 55.1

Female Fertility Evaluation History Form

DOB
WEIGHT/BODY CONDITION
DIET (BRAND)
HOUSING
(K9)BRUCELLA TESTED?
(Feline) VIRAL TESTED?
MEDICATIONS (LIST ALL)
  CURRENT
  HISTORICAL (WHEN)
SUPPLEMENTS (LIST ANY)
PREVIOUS BREEDING(S)
  DATE
  OUTCOME?
  LITTER SIZE
  SURVIVAL TO WEANING?
MOST RECENT BREEDING
  DATE(S)
  METHOD(S)
  OVULATION TIMING? (ATTACH RESULTS)
PROVEN STUD?
  DATE OF MOST RECENT LITTER
  SEMEN EVALUATION IF NOT PROVEN?
  (K9) BRUCELLA TESTED?
  (Feline) VIRAL TESTED?
METHOD OF PREGNANCY EVALUATION?
KNOWN FERTILITY OF YOUR DAM?
SIBLINGS?

MICROBIOLOGY AND FEMALE FERTILITY

Breeders commonly express concern that infertility or subfertility is related to vaginal and uterine flora, requesting pre-breeding vaginal cultures and antimicrobial therapy based on the results. Stud dog owners specifically fear that a bitch will expose their male to pathologic bacteria and damage his fertility. It has been shown that normal flora is exchanged during natural breedings, without any detriment to either the bitch or the stud dog or to their fertility or fecundity. The normal female reproductive tract harbors a variety of aerobic bacterial (including *Mycoplasma*) populations in the vaginal vault and uterus (Box 55.2). Mixed vaginal cultures can be present in healthy fertile bitches; the most common isolates include *Pasteurella multocida,* β-hemolytic streptococci, *Escherichia coli,* and *Mycoplasma* spp. The only bacterial species proven to be a specific cause of infertility in the bitch is *Brucella canis*. Recent development of transcervical uterine cannulation has enabled intrauterine cultures and biopsies to be collected noninvasively and can provide more accurate evaluation of actual infectious problems in the uterus than cranial vaginal cultures acquired with guarded swabs; however, problems with interpretation persist. During normal canine estrus, bacteria ascend the reproductive tract and are present within the uterus, subsequently regressing spontaneously. Vaginal and intrauterine cultures must both be interpreted with caution because many bacterial populations represent normal bacterial flora and do not indicate disease or explain infertility. Indiscriminant use of antibiotics before and during pregnancy is counterproductive and associated with development of resistant organisms; it is not contributory to improved fertility or fecundity. It is unjustified to treat all positive vaginal cultures with antimicrobials or to assume that all positive vaginal or uterine bacterial cultures are associated with infertility. As a general rule, growth of bacteria from the vagina or uterus in conjunction with clinical signs

BOX 55.2

Normal Bacterial Florae of the Canine Vagina

Aerobic Bacteria
Pasteurella multocida
β-hemolytic *Streptococci*
Escherichia coli
Unclassified gram - rods
Unclassified gram + rods
Mycoplasma
α and nonhemolytic *Streptococci*
Proteus
Bacillus
Corynebacterium
Coagulase-positive and coagulase-negative *Staphylococci*
Pseudomonas
Klebsiella
Neisseria
Micrococcus
Haemophilus
Moraxella
Acinetobacter
Flavobacterium
Lactobacillus
Enterobacter
Anaerobic Bacteria
Bacteroides melaninogenicus
Corynebacterium
Haemophilus aphrophilus
Bacteroides
Enterococcus
Peptostreptococcus (hemolytic and nonhemolytic)
Ureaplasma

of excessive malodorous or abnormal vaginal discharge, vaginal mucosal inflammation, peripheral leukocytosis, and systemic illness is significant and warrants treatment with antimicrobial agents. If possible, a uterine cytologic specimen or biopsy should be examined for evidence of inflammation or infection.

CYSTIC ENDOMETRIAL HYPERPLASIA/ PYOMETRA COMPLEX

Uterine pathology (e.g., CEH) must be considered as a cause of infertility in bitches and queens once all other possibilities have been excluded. CEH is a hormonally dependent, predictable condition in the bitch that results from repeated cycles of progesterone stimulation inducing endometrial glandular proliferation and secretion. Glandular changes may be focal or diffuse and may interfere with implantation and placentation. Definitive diagnosis of CEH requires biopsy at an affected site or can be confirmed by histopathology post ovariohysterectomy. The CEH-pyometra complex is a progesterone-mediated uterine disorder of both bitches and queens. During the luteal phase of the estrous cycle, progesterone suppresses the leukocyte response to infectious stimuli in the uterus, decreases myometrial contractility, and stimulates endometrial gland development and activity. During diestrus, the nongravid uterus is flaccid and contains endometrial gland secretions that are a growth medium for bacteria. Bacteria reach the uterus via ascension from the distal portion of the genitourinary tract, or less commonly by hematogenous spread. Failure to clear transient bacterial inhabitants from the uterus after estrus can result in pyometra, a septic inflammatory condition of the uterus. *E. coli* is most commonly isolated from both bitches and queens with pyometra (Hagman and Greko, 2005; Chen et al., 2003). Strong correlation exists between the onset of clinical signs of pyometra and recent heat in both species; because queens are induced ovulators, their incidence may be lower.

Pyometra can occur with or without purulent vulvar discharge, depending on the patency of the cervix. Closed-cervix pyometra is more serious because of the potential for leakage of purulent fluid through the fallopian tube(s) or uterine rupture and resultant septic peritonitis. The classic clinical signs of pyometra include variably copious vulvar discharge, partial to complete anorexia, vomiting, lethargy, weight loss, an unkempt appearance, and polydipsia/polyuria. Most pets are considered ill (lethargic, anorexic) by their owners at the time of examination. Abnormalities detected most frequently by physical examination include a mucopurulent to hemorrhagic vulvar discharge, a palpably enlarged uterus, and pyrexia. Some bitches and queens have no physical signs of disease other than abnormal vulvar discharge. Clinicopathologic evaluation most commonly demonstrates neutrophilic leukocytosis, hyperfibrinogenemia, and hyperglobulinemia. Azotemia and low urinary specific gravity can reflect nephrogenic diabetes insipidus secondary to endotoxin elaboration by *E. coli*. Urine should *not* be obtained by cystocentesis if pyometra is suspected. Cytologic examination of the vulvar discharge shows septic inflammation (Fig. 55.39). Plasma progesterone is typically 5.0 ng/mL or higher, typical of diestrus, although pyometra can also be initially diagnosed in early anestrus as well. Abdominal radiography can identify a large, tubular, soft tissue density compatible with uterine enlargement. Ultrasonography is indicated to differentiate the enlarged fluid-filled uterus of pyometra from early pregnancy. Ultrasonographic evaluation of the uterus provides important information concerning uterine wall thickness and composition (presence of cystic structures), lumen size and content, and overall organ symmetry and position. CEH is characterized by endometrial thickening with focal anechoic structures noted in the uterine wall, representing dilated cystic glands and tortuous glandular ducts (Fig. 55.40). With advanced disease, these changes do not disappear ultrasonographically during anestrus. Fluid accumulation in the uterine lumen may represent hydrometra, mucometra, or developing pyometra and can be very difficult to differentiate (echogenicity may suggest cellularity) (Figs. 55.41, *A*, 55.41, *B*, 55.42). Because of the potential for peritonitis, centesis of the uterus is not advocated. One study found that measurement of the circulating

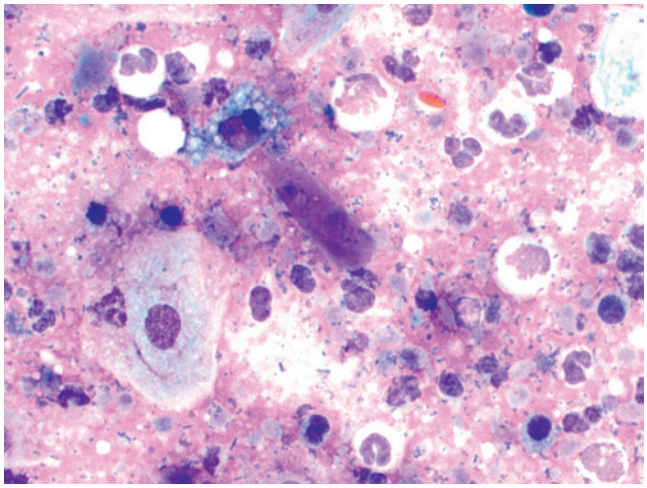


FIG 55.39
Cytology of vulvar discharge associated with open pyometra. Numerous intra- and extracellular bacteria, degenerative neutrophils, macrophages, proteinaceous debris and epithelial cells are present.

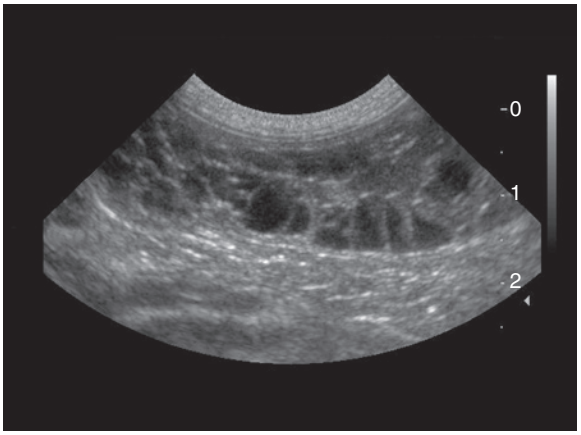


FIG 55.40
Cystic endometrial hyperplasia. Ultrasonographic image showing multiple anechoic endometrial cystic glands and dilated ducts.

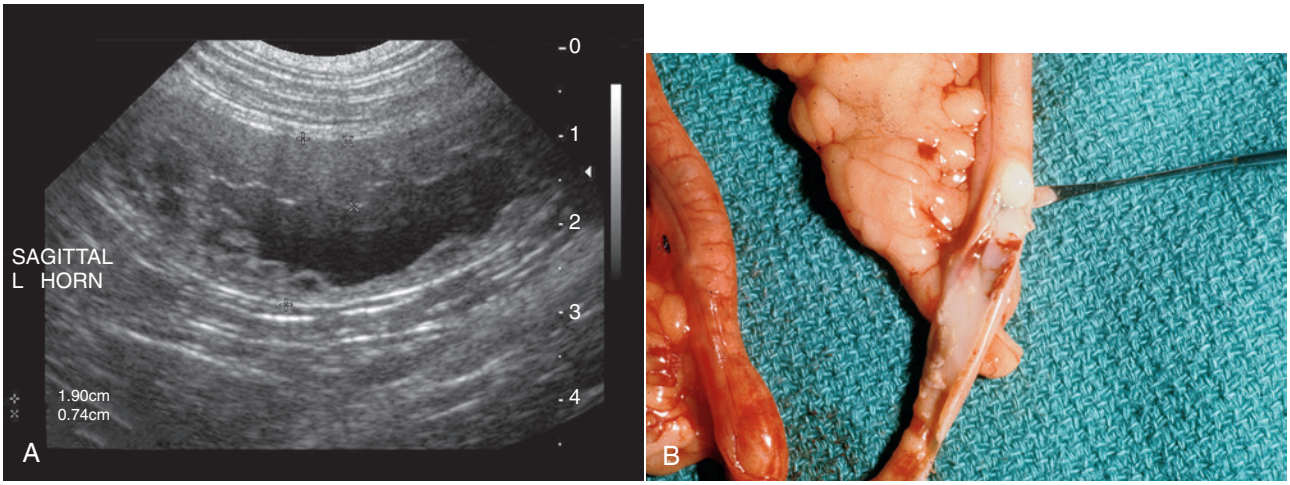


FIG 55.41
Mucometra. **(A)** Ultrasound image of the sagittal left uterine horn. Cursors measuring the full thickness (+; 1.90 cm) and wall thickness (x; 0.74 cm). **(B)** Gross specimen; endometrial cysts and mucoid luminal content (Courtesy Dr. P. Olson).

$PGF_{2\alpha}$ metabolite (15-keto-13,14-dihydro-$PGF_{2\alpha}$) differentiated between CEH and pyometra when clinical signs were absent (Hagman et al., 2006). Uterine enlargement with pyometra is variable. Pyometra can occur in one uterine horn, with a viable pregnancy in the other.

The treatment of choice for pyometra, after stabilization of the patient with IV fluids and antibiotics, is ovariohysterectomy, a challenging surgery and an undesirable option for valuable breeding bitches or queens (Fig. 55.43). Medical treatment of open-cervix pyometra, identified clinically by the presence of vulvar discharge, can be offered in the case of young, valuable breeding females who are stable (Table 55.1). Systemic antibiotic treatment alone is ineffective in resolving clinical signs. Medical management of open-cervix pyometra with prostaglandins (natural prostaglandin $PGF_{2\alpha}$ or the synthetic prostaglandin cloprostenol) has been successfully employed in both the bitch and queen. Successful treatment of pyometra using prostaglandins results from their effect on the uterine myometrium, cervix, and corpora lutea. These agents stimulate uterine motility in dogs and cats, and this myotonic effect increases intrauterine pressure. Administration of prostaglandins should cause movement of uterine contents toward the cervix because of the distribution of prostaglandin receptors within the myometrium. Restricting the use of prostaglandins to treatment of open-cervix pyometra should reduce the potential for complications

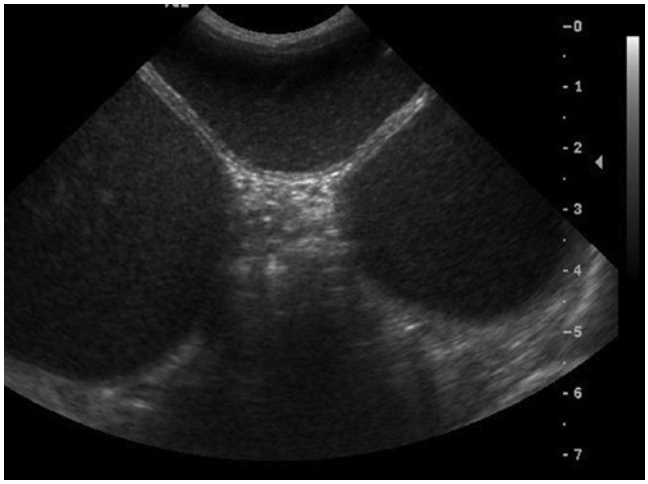


FIG 55.42
Ultrasound image of closed pyometra; multiple distended loops of uterine horns filled with echogenic fluid.



FIG 55.43
Pyometra; 5.5-kg uterus removed from a Black Russian Terrier with open cervix pyometra.

(peritonitis) attributable to myometrial contraction of a fluid-filled uterus against a closed cervix. Prostaglandins induce luteolysis or decreased luteal steroidogenesis. The presence of live fetuses should be ruled out by use of ultrasound before prostaglandin administration because of the drug's abortifacient potential. The prognosis for concurrent pyometra and pregnancy is guarded to poor. Management is limited medically to antibiotics, and intrauterine fetal death and premature labor are common. Adverse reactions observed after $PGF_{2\alpha}$ administration reflect the physiologic effects of endogenous prostaglandins. Endogenous prostaglandins are derived from arachidonic acid by the action of cyclooxygenase and mediate many normal physiologic processes, including vasodilation, hemostasis, pulmonary

TABLE 55.1

Medical Therapy of Open Cervix Pyometra

DRUG	DOSAGE	SIDE EFFECTS
$PGF_{2\alpha}$	0.1-0.2 mg/kg SC q12-24h to effect	Cat: Vocalization, panting, drooling, vomiting, defecation Dog: Panting, nesting, drooling, vomiting, defecation
Cloprostenol	1-3 mcg/kg SC q12-24h to effect	Diminished, vomiting most common

vasoconstriction and bronchodilation, gastrointestinal tract secretion, renal blood flow and glomerular filtration rate, inflammation, hyperalgesia, and fever. The contractile effect of prostaglandins on the myometrial, gastrointestinal, tracheobronchial, and bladder smooth musculature accounts for the clinical responses observed. Predictable physical reactions occur after SC injection of prostaglandins and include restlessness, panting, salivation, emesis, tenesmus, diarrhea, urination, and mydriasis (both bitch and queen), and grooming, lordosis, and kneading (queen). These reactions resolve within 1 hour after prostaglandin injection. Walking bitches for 10 or 15 minutes after prostaglandin administration seems to help minimize the severity of reactions. After each subsequent prostaglandin administration, reactions diminish in severity and duration; they are rarely considered severe enough to warrant discontinuation of the drug. Anticholinergic or other antiemetic premedication can reduce the severity of side effects. Candidates for prostaglandin treatment should be young (<5 years) and otherwise healthy, with evidence of a patent cervix (i.e., vulvar discharge). Potential contraindications to the use of prostaglandins include coexisting viable pregnancy, sepsis, peritonitis, significant organic disease, and the presence of mummified fetal remains. During prostaglandin treatment, bitches and queens may need to be hospitalized (as warranted by their clinical condition) to enable administration of adjunct supportive care (e.g., IV administration of fluids and antibiotics) and monitoring of adverse effects and treatment outcome. Concurrent administration of broad-spectrum bactericidal antimicrobials (potentiated amoxicillin, combination fluoroquinolone, amoxicillin, or cephalosporin) is advised. Anaerobic and aerobic culture of vaginal discharge should be submitted before antibiotic use to better guide antimicrobial selection if response to therapy is not optimal. Response to therapy depends on the degree of underlying uterine pathology rather than the dosage of prostaglandins.

The lower dosage of $PGF_{2\alpha}$ (Lutalyse [Pharmacia]) at 0.1-0.2 mg/kg q12-24h) is recommended, although the

minimal effective dose of $PGF_{2\alpha}$ has not been established. This dosage should *only* be used for natural $PGF_{2\alpha}$. Cloprostenol, a synthetic prostaglandin, is more potent in its actions than is natural $PGF_{2\alpha}$, and use of synthetic prostaglandins at the dosage recommended for natural $PGF_{2\alpha}$ may result in a fatal outcome. Synthetic prostaglandins have more uterine-specific smooth muscle stimulation and cause fewer systemic side effects, and currently are the author's choice. Administer cloprostenol (Estrumate [ICI, UK]) at 1-3 μg/kg SC q12-24h. If cervical patency is questionable (closed cervix pyometra), misoprostol (prostaglandin E2) can be administered intravaginally (Cytotec, [Searle] 100 μg tablet dissolved in 5 mL water; at 1-3 μg /kg q24h) in an attempt to relax the cervix before ecbolic therapy is instituted. Transcervical endoscopic catheterization technique is advocated by some authors to lavage viscous fluid from the uterus using LRS or 0.9% saline, or acetylcysteine 1:5 parts 0.9% saline. Great care must be taken not to overdistend or perforate the uterus. Surgical lavage is also an option but rarely used due to the success of medical therapy. Prostaglandins are not approved for use in domestic dogs and cats but are commonly used and are an acceptable form of medical therapy. Successful clinical response to medical therapy is best monitored by serial evaluations of uterine luminal contents with ultrasound, along with hematology, biochemistry, and clinical parameters (appetite, fever, vulvar discharge). Successful short-term outcome of medical therapy, defined as resolution of the signs of pyometra, should be evident at the completion of prostaglandin treatment.

At the time of release from the hospital, bitches and queens should have an improved appetite, normal rectal temperature, and diminished or no vulvar discharge. Initial reexamination should be scheduled within 2 weeks of the last prostaglandin administration, finding no clinical signs of illness. Abdominal ultrasonography should be used to evaluate for an overall reduction in uterine size and lack of fluid in the uterine horn lumens, compared with that of previous examinations. Persistence of clinical signs warrants retreatment; sequential treatment of recurrent pyometra can be successful and could be considered if the bitch's or queen's condition permits. Reported resolution of the immediate clinical signs of open cervix pyometra after therapy varies from 82% to 100%. Successful long-term response is defined as a return to normal estrous cycles and, if bred, conception and carrying a litter to term. Breeding at the next estrus is recommended to avoid the potential complications after progesterone's effects on a nongravid uterus. Prostaglandins do not resolve underlying cystic endometrial hyperplasia. The more clinically benign hydrometra and mucometra commonly precede the development of pyometra, giving a guarded to poor prognosis for fertility. The onset of proestrus in the bitch after $PGF_{2\alpha}$ therapy is variable; bitches will experience proestrus 1 or 2 months earlier than anticipated because diestrus was abbreviated by prostaglandin use. The onset of proestrus after prostaglandin treatment varies from 0.5 to 12 months in queens, due to the influence of day length on this seasonally polyestrous species. The overall recurrence rate of pyometra in bitches can be 20% to 80%, and in queens 14%, higher in older individuals. Clients should always be forewarned that successful resolution of pyometra can be followed by chronic infertility due to underlying CEH.

Suggested Readings

Baan M, et al. Induction of parturition in the bitch with the progesterone-receptor blocker aglepristone. *Theriogenology*. 2005;63(7):1958–1972.

Bassu G. Mammary gland disorders: agalactia, galactostasis and mastitis. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:325–336.

Bergstrom A. Cesarean section, elective and emergency. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:45–51.

Burdick S, et al. Endoscopic-guided laser ablation of vestibulovaginal septal remnants in dogs: 36 cases (2007-2011). *J Am Vet Med Assoc*. 2014;244(8):944–949.

Chen YM, et al. Uropathogenic virulence factors in isolates of *Escherichia coli* from clinical cases of canine pyometra and feces of healthy bitches. *Vet Microbiol*. 2003;94:57–69.

Copley K. Uterine inertia. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:521–528.

Corrada Y, et al. Combination dopamine agonist and prostaglandin agonist treatment of cystic endometrial hyperplasia-pyometra complex in the bitch. *Theriogenology*. 2006;66:1557–1559.

Davidson AP, Baker TW. Reproductive ultrasound of the bitch and queen. *Top Companion Anim Med*. 2009;24(2):55–63.

Davidson AP, Cain J, Goodman M. Pregnancy edema in the bitch. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:427–432.

Davidson AP, Cain J. Antibiotic stewardship in small animal reproduction. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:11–16.

Davidson AP. Tocodynamometry detects preterm labor in the bitch before luteolysis. *Top Companion Anim Med*. 2015;30(1):2–4.

Drobatz K, et al. Eclampsia in dogs: 31 cases (1995-1998). *J Am Vet Med Assoc*. 2000;217:216.

Dyson DC, et al. Monitoring women at risk for preterm labor. *N Engl J Med*. 1998;338(1):15–19.

Eilts B. Medical abortion, canine and feline. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:357–376.

Freshman JL. Post-partum metritis/subinvolution of placental sites (SIPS). In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:417–422.

Gobello C, et al. Use of cabergoline to treat primary and secondary anestrus in dogs. *J Am Vet Med Assoc*. 2002;220:1653.

Gobello C. Dopamine agonists, anti-progestins, anti-androgens, long-term-release GnRH agonists and anti-estrogens in canine reproduction: a review. *Theriogenology*. 2006;66:1569.

Görlinger S, et al. Treatment of fibroadenomatous hyperplasia in cats with aglepristone. *J Vet Intern Med*. 2002;16:710.

Gregory C. Episioplasty/Vulvoplasty in the bitch and queen. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:131–138.

Grundy S. Ovarian remnant syndrome/hyperestrogenism. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:395–407.

Grundy SA. Infectious causes of pregnancy loss: feline. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:459–466.

Hagman R, Greko C. Antimicrobial resistance in *Escherichia coli* isolated from bitches with pyometra and from urine samples from other dogs. *Vet Rec*. 2005;157:193–196.

Hagman R, et al. Differentiation between pyometra and cystic endometrial hyperplasia/mucometra in bitches by prostaglandin F 2α metabolite analysis. *Theriogenology*. 2006;66(2):198–206.

Hagman R, et al. A breed-matched case-control study of potential risk-factors for canine pyometra. *Theriogenology*. 2011;75:1251–1257.

Hammel S, et al. Results of vulvaplasty for treatment of recessed vulva in dogs. *J Am Anim Hosp Assoc*. 2002;38:79.

Kruger EF. Pregnancy diabetes. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:423–425.

Kruger EF. Pregnancy ketosis. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:433–435.

Levy X. Feline mammary hyperplasia. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:337–343.

Levy X. Eclampsia. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:127–130.

Lightner B, et al. Episioplasty for the treatment of perivulvar dermatitis or recurrent urinary tract infection in dogs with excessive perivulvar skin folds: 31 cases (1983-2000). *J Am Vet Med Assoc*. 2001;219:1577.

Lopate C. Pyometra, cystic endometrial hyperplasia (hydrometra, mucometra, hematometra). In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017:53–62.

Lulich J. Endoscopic vaginoscopy in the dog. *Theriogenology*. 2006;66:588.

Maenhoudt C, Santos NR, Fontaine E. Results of GnRH agonist implants in oestrous induction and oestrous suppression in bitches and queens. *Reprod Domest Anim*. 2012;47(6):393–397.

Morresey P. Reproductive effects of canine herpesvirus. *Compendium*. 2004;4:804.

Noakes DE, Dhaliwal GK, England GC. Cystic endometrial hyperplasia/pyometra in dogs: a review of the causes and pathogenesis. *J Reprod Fertil Suppl*. 2001;57:395–406.

Pelican KM, et al. Ovarian control for assisted reproduction in the domestic cat and wild felids. *Theriogenology*. 2006;66(1):37–48.

Piewbang C, et al. Viral molecular and pathological investigations of Canid herpesvirus 1 infection associated respiratory disease and acute death in dogs. *Acta Vet Brno*. 2017;67(1):11–24.

Rubion S, et al. Treatment with a subcutaneous GnRH agonist containing controlled release device reversibly prevents puberty in bitches. *Theriogenology*. 2006;66:1651.

Schlafer DH, Gifford AT. Cystic endometrial hyperplasia, pseudoplacentation, endometrial hyperplasia, and other cystic conditions of the canine and feline uterus. *Theriogenology*. 2008;70:349–358.

Slater LA, Davidson AP, Dahlinger J. Theriogenology question of the month: semen peritonitis. *J Am Vet Med Assoc*. 2004; 225:1535.

Themmen AP, et al. The use of anti-Müllerian hormone as diagnostic for gonadectomy status in dogs. *Theriogenology*. 2010;86(6):1467–1474.

Trigg TE, et al. A review of advances in the use of GnRH agonist deslorelin in control of reproduction. *Theriogenology*. 2006;66:1507–1512.

Volkmann D, et al. The use of deslorelin implants for the synchronization of estrous in diestrous bitches. *Theriogenology*. 2006;66:1497.

von Dehn B. Infectious causes of pregnancy loss, canine: toxoplasmosis/neosporosis, cryptosporidium, herpes virus, brucellosis, minute virus. In: Greco DS, Davidson AP, eds. *Blackwell's five minute veterinary consultant clinical companion: small animal endocrinology and reproduction*. Wiley Blackwell; 2017: 437–458.

Wanke MM, Delpino MV, Baldi PC. Use of enrofloxacin in the treatment of canine brucellosis in a dog kennel (clinical trial). *Theriogenology*. 2006;66(6):1573–1578.

Wanke MM. Canine brucellosis. *Anim Reprod Sci*. 2014;82:195–207.

Wiebe VJ, Howard JP. Pharmacologic advances in canine and feline reproduction. *Top Companion Anim Med*. 2009;24(2):71–99. https://doi.org/10.1053/j.tcam.2008.12.004. In ed AP Davidson.

CHAPTER 56

Clinical Conditions of the Dog and Tom



CRYPTORCHIDISM

Cryptorchidism, a common congenital genital defect in male dogs (uncommonly tomcats), is diagnosed if either or both testes are not present in the scrotum at puberty; testes normally descend into the canine scrotum by 6 to 16 weeks of age. In the author's experience, descent can occur as late as 10 months of age, but these dogs should not be considered normal; late descent is a heritable defect as well as nondescent. Cats have prenatal testicular descent; however palpation of scrotal testes in neonatal kittens is difficult due to their small size. The testicular hormone insulin-like factor 3 (also called *relaxin-like factor*), produced by pre- and postnatal Leydig cells, mediates the transabdominal testicular descent from the caudal pole of the kidney to the inguinal canal. It induces growth and differentiation of the gubernaculum from the caudal suspensory ligament. The transabdominal migration of the fetal testis is independent of androgens, whereas the inguinoscrotal descent is subsequently mediated by testosterone, which causes regression of the cranial suspensory ligament. During the inguino-scrotal phase of migration, there is shortening of the gubernaculum and eversion of the cremaster muscle.

Unilateral cryptorchidism does not result in infertility due to the scrotal testis. Bilaterally cryptorchid dogs and cats are infertile due to the lack of normal spermatogenesis resulting from their intraabdominal temperature (~5° > scrotal). In both cases, because interstitial cells continue to produce testosterone, libido and secondary sex characteristics are normal. Cryptorchidism in dogs is inherited as a sex-limited autosomal recessive trait; cryptorchidism in cats is assumed to be heritable as well (Zhao, 2010). Unilaterally affected animals should not be bred. Both parents of affected individuals should be implicated as carriers. Because of the heritability, and the fact that intraabdominal testes have a higher incidence of neoplasia (9-14×) and subsequent torsion, bilateral orchiectomy is recommended. Bilateral orchiectomy is required to reduce testosterone-mediated behaviors. Attempts at medical therapy to induce testicular descent with gonadotropins or testosterone have been unsuccessful and are not ethical. Orchiopexy is also considered unethical in veterinary medicine; the American Kennel Club bans any dog with orchiopexy from competition. In humans, the increased incidence of neoplasia in the formerly intraabdominal cryptorchid testis persists postorchiopexy, making the procedure contraindicated medically in veterinary patients as well as being unethical. Failure of one testis to develop (true monorchidism) can occur in dogs but is rare.

In a cryptorchid cat, examination of the penis for presence of spines is an excellent diagnostic technique. Penile spines are testosterone-dependent, becoming atrophied 6 weeks postcastration. Cryptorchidism in the dog is best confirmed with appropriate hormonal testing and ultrasonography. Baseline serum testosterone levels vary normally; single levels are not diagnostic. Serum testosterone before and 48 hours after human chorionic gonadotropin (hCG) injection (250 IU IM) has been used to support complete castration if < 20 pg/mL (0.0693 nmol/L); a twofold increase suggests the presence of testicular tissue; the test results are variable and not always reliable. hCG is of human origin, therefore the potential for hypersensitivity exists. Gonadotropic-releasing hormone (GnRH) stimulation testing using commercial bovine GnRH products is based on inducing a measurable testosterone increase. GnRH is administered at 2 µg/kg IM, with blood sampling pre- and 2–3 hours postinjection; castrated dogs have testosterone concentrations <0.1 ng/mL (0.3467 nmol/L) and should not stimulate, but test results are variable and not always reliable. The luteinizing hormone (LH) test is not marketed for evaluating cryptorchidism in the dog or tom; however, it can be reliable in the author's experience. A high LH (>1 ng/mL) suggests the dog or tom is castrated. A low LH (<1 ng/mL) suggests the dog or tom is intact, with testosterone providing negative feedback to GnRH, FSH, and LH (Wheeler and Kutzler, 2010). Recently marketed, the qualitative Anti-Müllerian Hormone (AMH) test for dogs and cats is meant to distinguish between intact (cryptorchid) neutered males after they have reached the age of sexual maturity. A negative AMH test is consistent with

a neutered male, whereas a positive AMH test indicates the presence of testes.

Ultrasound localization of cryptorchid testis(es) can confirm the condition in pediatric dogs and cats with unilateral or bilateral involvement, and assist the surgeon in planning the approach (i.e., inguinal versus cranial abdominal). The retained testes can be positioned anywhere between the ipsilateral kidney and the scrotum. The right testis is more commonly cryptorchid. A systematic evaluation of the region from the caudal renal pole to the inguinal canal can identify an oval, homogenously echogenic structure with a mildly hyperechoic border representing the parietal and visceral tunics. The epididymis is usually distinctly less echoic than the testicular parenchyma, as in the scrotal testis. The cryptorchid testis will maintain the anatomic structure of the mediastinum testis, a hyperechoic slash, and normal testicular echogenicity despite being reduced in size as compared with a scrotal testis (Fig. 56.1, *A*, 56.1, *B*, Video 56.1). Ultrasound is also the method of choice to localize cryptorchidism in adult dogs and cats whose neutering status is unknown or suspected to be incomplete.

TESTICULAR TORSION

Other than malignant transformation, the most common complication of uncorrected cryptorchidism in the dog is testicular torsion, which occurs with an increased incidence in neoplastic intraabdominal testes, and presents as an acute abdomen. Ultrasound is commonly performed in dogs with acute abdominal distress. Cryptorchid testes can be positioned anywhere between the ipsilateral kidney and the inguinal canal, but tend to gravitate to the mid ventral abdomen when enlarged. Testicular torsion can appear similar to orchitis with a diffuse hypoechoic appearance to the testis; malignant transformation and gangrenous change can make their appearance less recognizable (Fig. 56.2, *A*, 56.2, *B*). Doppler examination reveals aberrant blood flow. Immediate surgical intervention for removal is indicated.

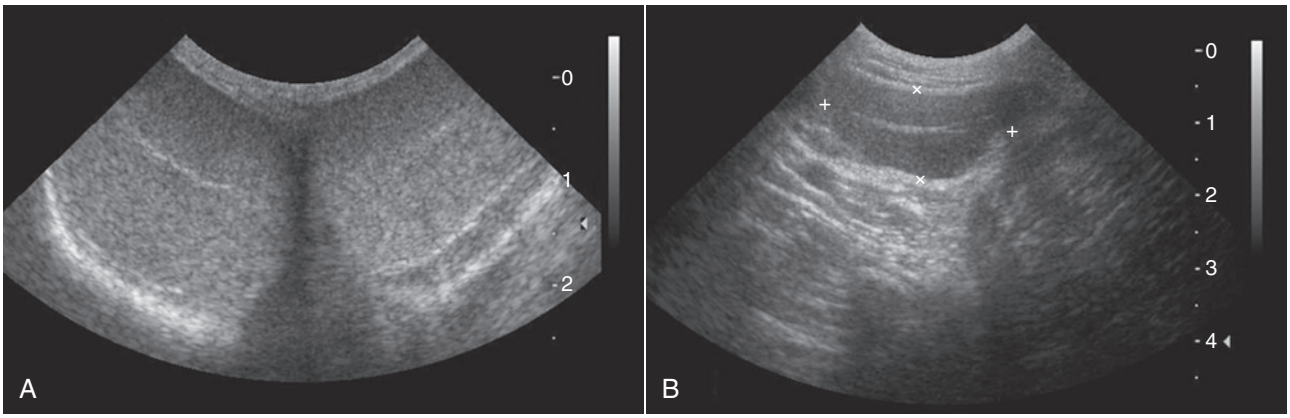


FIG 56.1
Testicular ultrasound. **(A)** Side-by-side image of normal scrotal testes. **(B)** Sagittal view of cryptorchid testis (*cursors*). Note the uniform parenchymal echotexture (similar to the spleen), mediastinum testis (hyperechoic central linear structure), and relatively smaller size in the intraabdominal (cryptorchid) testis.

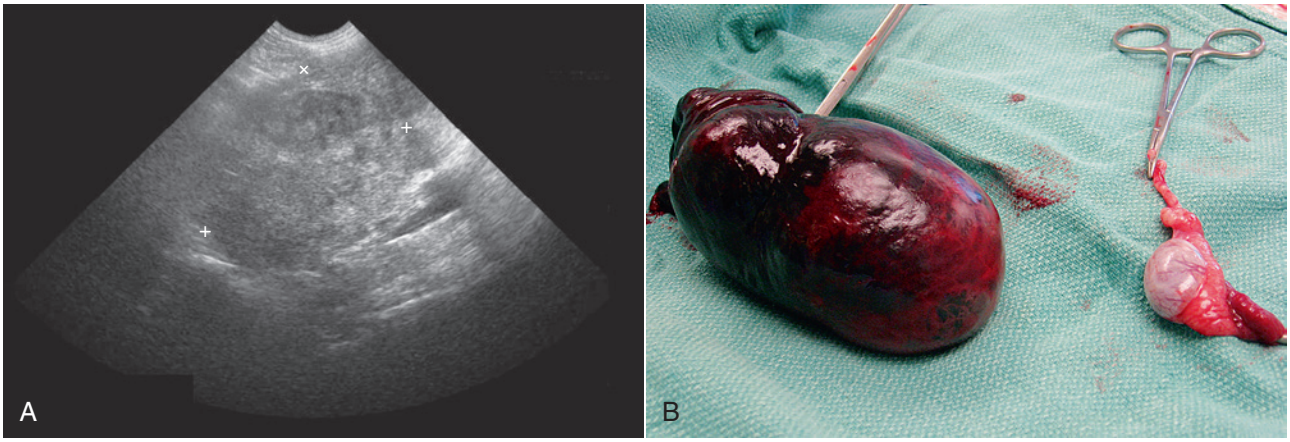


FIG 56.2
Ultrasound image of an intraabdominal mass. **(A)** A midabdominal testis (*cursors*) with complex echotexture. **(B)** A Sertoli cell tumor was identified within the enlarged and torsed intraabdominal testis after exploratory and castration. The normal scrotal testis for comparison, left.

PERSISTENT PENILE FRENULUM

Under the influence of androgens, the surfaces of the glans penis and the preputial mucosa normally separate before or within weeks of birth. If this separation does not occur, connective tissue persists between the penis and the prepuce. In dogs the persistent penile frenulum is usually located on the ventral midline of the penis. A persistent penile frenulum may cause no clinical signs, or it may be associated with preputial discharge or excessive licking of the prepuce. Persistent frenulum may cause the penis to deviate ventrally or laterally so that the dog or tomcat is unable or unwilling to mate, or it may interfere with normal tumescence (Fig. 56.3). The diagnosis is made by visual examination. Treatment is surgical excision, which can often be done using just sedation with local anesthesia as the frenulum tends to be a sheer, avascular membrane.

URETHRAL PROLAPSE

Urethral prolapse occurs most commonly in Bulldogs, French Bulldogs, and Boston Terriers, and is likely familial. Eversion of the urethral mucosa at the distal tip of the penis results in refractory hemorrhage. The condition may be associated with the increased intraabdominal pressure associated with the brachycephalic syndrome. Surgical revision is indicated as the condition will not resolve spontaneously. Preventing erection during recovery is important; breeding these dogs can cause relapse, and castration should be suggested for both therapeutic and ethical reasons.

SCROTAL DERMATITIS

Scrotal dermatitis can result from trauma, contact irritants or hypersensitivities, excessively warm bedding/heating pads, burns, frostbite, envenomation, shaving, allergic dermatopathies, or intrascrotal pathology inciting excoriation such as orchitis or epididymitis (Fig. 56.4). Scrotal dermatitis can cause thermal insult acutely affecting spermatogenesis. Chronic scrotal dermatitis can result in infertility, with visible lichenification and hyperpigmentation of the ventral scrotum. Physical examination of a dog with abnormal semen should always include close visual evaluation of the ventral scrotum. Scrotal mast cell tumors can incite local inflammation.

Appropriate topical and systemic therapies should be instituted, and prevention of excoriation by the use of Elizabethan collars encouraged. Nonsteroidal antiinflammatory drugs such as carprofen (Rimadyl® Pfizer), meloxicam (Metacam® Boehringer Ingelheim), firocoxib (Previcox® Merial), or grapiprant (Galliprant® Aratana) are useful. Narcotics (Tramadol) may be necessary short term for adequate analgesia. Broad spectrum antibiotics appropriate for pyoderma, such as cephalexin or cefpodoxime proxetil (Simplicef® Pfizer), are appropriate. The use of corticosteroids should be avoided. Normalization of spermatogenesis can take more than 60 days.

BALANOPOSTHITIS

Inflammation or infection of the preputial cavity and penis, balanoposthitis, is common in dogs and rare in cats. Normal scant white smegma in an intact male dog should not be mistaken for balanoposthitis. The causative organisms are usually members of the normal preputial flora, although overgrowth of one organism or a predominance of *Pseudomonas spp* can occur. Balanoposthitis usually causes no clinical signs other than a purulent preputial discharge that varies from mucoid to copious green pus accompanied by excessive licking. The discharge associated with balanoposthitis is not sanguineous unless the cause is neoplasia or accumulated foreign material. Lymphoid follicular hyperplasia is commonly also present and thought to develop as a result of chronic irritation (Fig. 56.5, *A*).

The diagnosis of balanoposthitis is made by physical examination of the penis and preputial cavity all the way to the fornix, in a search for foreign material, neoplasia,

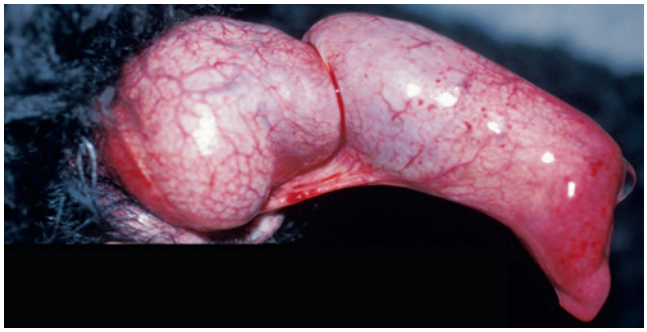


FIG 56.3
Penile persistent frenulum; postsemen collection.



FIG 56.4
Marked scrotal edema and inflammation secondary to crotalid envenomation and abscessation of the bite site.

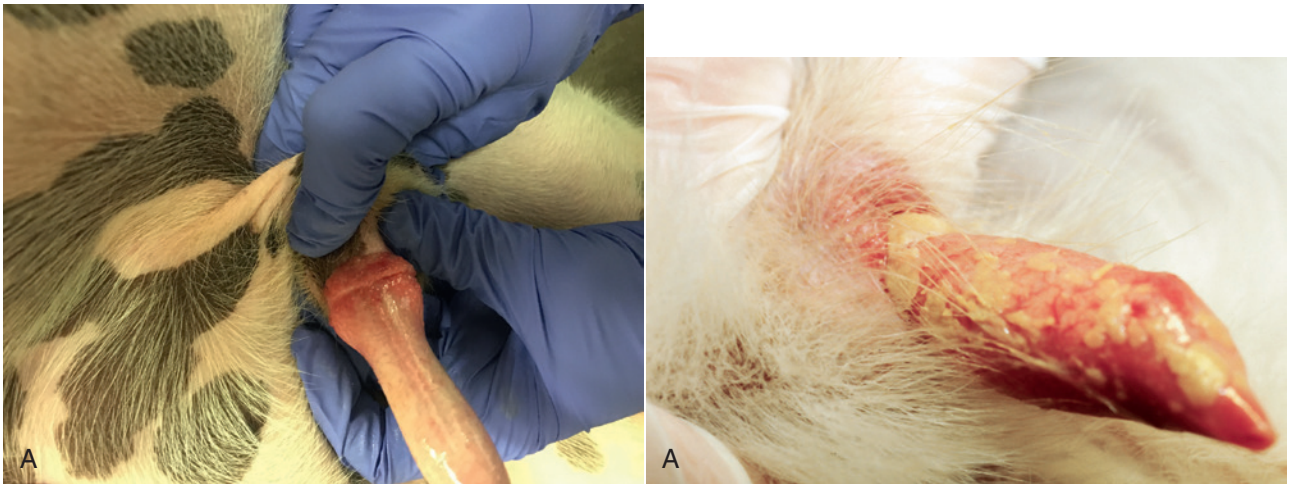


FIG 56.5
(A) Lymphoid follicular hyperplasia at the base of the penis. **(B)** Balanoposthitis. (**B** Courtesy Dr. P. Olson)

ulceration, or inflammatory nodules (Fig. 56.5, *B*). Cultures and cytologic studies are rarely helpful unless a mycotic infection or neoplastic process is suspected.

The treatment of balanoposthitis is usually conservative. The hair should be clipped from the preputial orifice and from the surrounding area if discharge has been accumulating there. Flushing the preputial cavity with dilute, gentle antiseptic solutions (e.g., chlorhexidine, povidone-iodine) can be helpful. Topical antibacterial or combination corticosteroid antibacterial medications may be instilled into the preputial cavity. In persistent or refractory cases, cytology, culture, and endoscopic examination of the prepuce and urethra should be considered. Systemic antibiotics short term can be considered, as well as nonsteroidal antiinflammatory therapy. Preputial discharge from benign prostatic hyperplasia, prostatitis, urethritis, or cystitis should be ruled out if the penis and prepuce appear normal. Penile mass lesions can cause excessive preputial discharge. Transmissible venereal tumor (TVT) is the most commonly reported penile tumor in dogs. Cytologic evaluation of TVT is supportive; biopsy is diagnostic (Fig. 56.6). The macroscopic appearance of TVT and penile papilloma virus may be similar. Penile papillomatosis often resolves spontaneously after biopsy of a lesion.

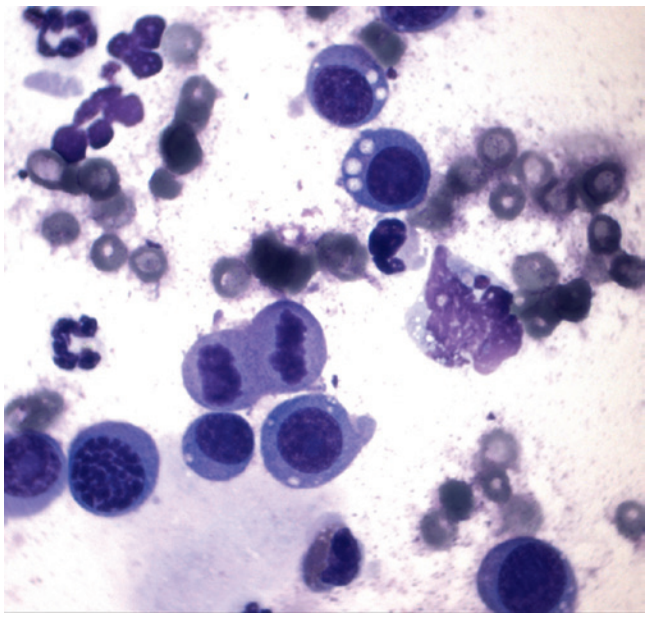


FIG 56.6
Cytology resulting from a fine needle aspirate of a penile transmissible venereal tumor. Note mitotic figure in center of field. (Courtesy Dr. J. Sykes)

PRIAPISM, PARAPHIMOSIS, AND PHIMOSIS

Priapism is a persistent penile erection without sexual stimulation (Fig. 56.7). Priapism is categorized as either nonischemic (arterial, high flow) or ischemic (veno-occlusive, low flow). Ischemic priapism is considered an emergency as rapid penile necrosis can result; the condition is usually very painful. Either condition can result in significant trauma to the penile tissues.

Priapism can be confused with paraphimosis. Paraphimosis occurs when the penis cannot be ensheathed in the prepuce and is most commonly associated with previous but not ongoing sexual stimulation. Paraphimosis can be associated with problematic detumescence after breeding or semen collection. The penis can remain erect, or it may be markedly edematous from chronic extrusion. The urethra is usually not damaged. The unexposed penis and the uninvolved prepuce are normal and nonpainful. Long-standing paraphimosis may result in gangrene or necrosis. Paraphimosis may



FIG 56.7
Chronic canine nonischemic priapism. (Courtesy Dr. J. Lavely)

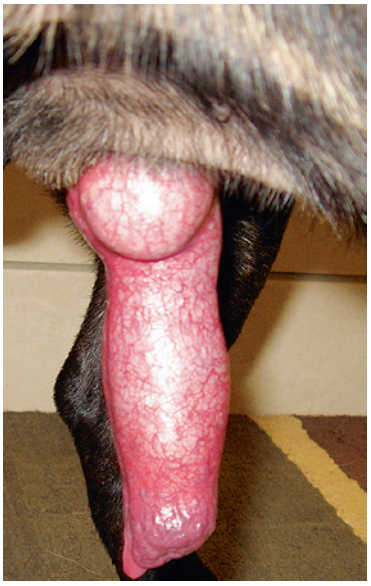


FIG 56.8
Erect canine penis post semen collection; the penile mucosa is normal in appearance.

result from too small of a preputial orifice, inadequate length of the prepuce, weakened preputial muscles, or trauma. Paraphimosis most commonly occurs in dogs after manual semen collection, as the exposed penile mucosa becomes dry during the postejaculation period (when the normal copulatory tie would occur) from exposure to air without lubrication (Fig. 56.8). Return of the penis within the prepuce is hampered, and severe edema of the exposed distal penile tissues can occur (Fig. 56.9). Clinicians should always check the stud dog before he leaves the examination room for this development. Lubricating the exposed penile tissues with water soluble gel and gentle manipulation of the prepuce is indicated. Paraphimosis may occur in longhaired cats when the penis becomes entangled in the preputial hairs; otherwise, it is uncommon in cats.



FIG 56.9
Paraphimosis, postcopulation, secondary to a small preputial opening which prevented detumescence. Note the injected, edematous penile mucosa.



FIG 56.10
Ruptured tunica albuginea causing a mass effect in the canine penis.

Priapism should also be differentiated from other causes of penile swelling, such as a hematoma, trauma, or mass lesions (Figs. 56.10, 56.11, 56.12). Penile hematomas usually form as a result of trauma or bleeding disorders. Simple visual inspection and palpation of the penis are usually sufficient to differentiate the conditions. An ultrasound and/or color-flow Doppler examination may help differentiate these disorders from priapism. Ultrasound of the perineum and the entire penile shaft is indicated to evaluate for anatomic abnormalities such as neoplasia, fracture of the os penis, hematoma formation, or thromboemboli. Priapism can be confirmed ultrasonographically (Figs. 56.13 and 56.14).



FIG 56.11
Penile laceration.



FIG 56.12
Lymphosarcoma, canine penile mucosa.

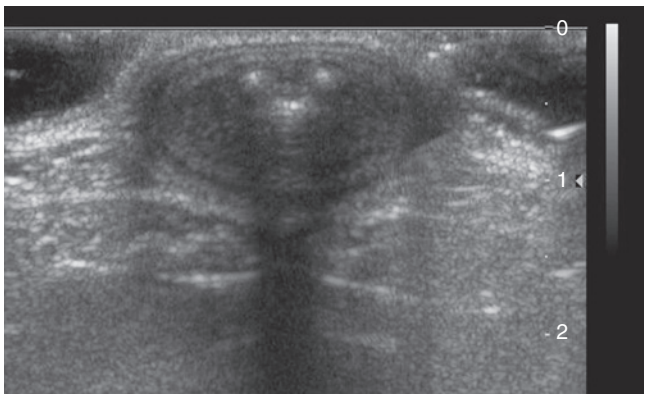


FIG 56.13
Transverse ultrasound image of the canine penis at the level of the bulbus glandis. The os penis produces a hard shadow dorsally. Detumescence.



FIG 56.14
Transverse ultrasound image of the erect canine penis at the level of the bulbus glandis. Priapism. Arrow indicates blood accumulation during tumescence.

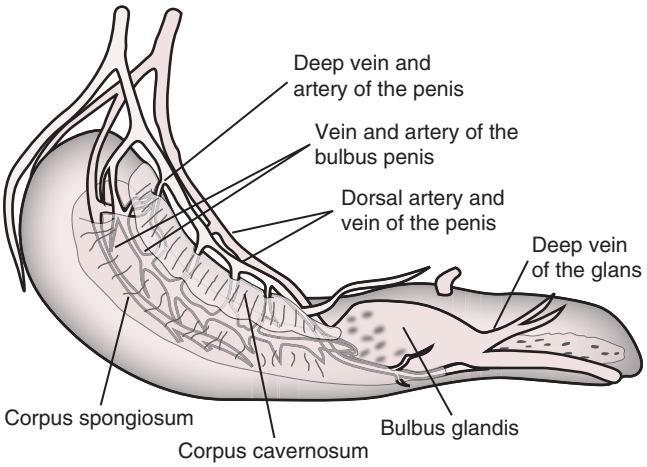


FIG 56.15
Schematic representation of relevant vascular anatomy of the canine penis. (Courtesy Dr. J. Lavely.)

The canine erection is mediated through the pelvic nerve, which arises primarily from the first and second sacral nerves (S1-S2) and is composed of parasympathetic nerve fibers. Stimulation of the pelvic nerve increases penile blood pressure, partially inhibits venous drainage, and dilates penile arteries resulting in an erection. The pudendal nerve, which arises from the sacral nerves S1-S3, is involved as well, by stimulating contraction of the extrinsic penile muscles. The hypogastric nerve, a sympathetic nerve originating from the lumbar L1-L4 spinal cord segments, may also have a regulatory role in the canine erection. The hypogastric nerve is responsible for ejaculation and prostatic fluid secretion. Sympathetic chain fibers inhibit erection. Sympathetic chain fiber stimulation increases arterial resistance, decreases corpus cavernosal pressure, and decreases venous resistance. The sympathetic inhibition of the erectile process is mediated by the α_1-adrenergic system (Fig. 56.15).

True priapism (ischemic or nonischemic) can be associated with vascular disorders (efferent or afferent) or neuropathy, or it can be idiopathic. A dysregulatory hypothesis for the pathophysiology of priapism has been postulated. Dysnergic neurostimulations of inflow and outflow penile blood vessels cause prolonged vascular or smooth muscle spasms. This dysregulation may occur at the level of the penis or at other regulatory levels of penile erection, including the central (spinal cord L1-4, S1-3) or peripheral nervous system (Lavely, 2009).

Distinguishing ischemic (proceeds to gangrene) versus nonischemic priapism and identifying and treating the underlying cause is important. If determined to be ischemic, prompt aspiration of the corpora cavernosa under sedation or anesthesia with or without irrigation should be done. Intracavernosal injections of phenylephrine should be considered. However, this may carry some risk as appropriate dosages in dogs and cats have not been determined. Starting with low dosages (1-3 mcg/kg) and cardiovascular monitoring, therefore, is important. Providing lubrication is important to limit tissue damage secondary to exposure and excoriation. An Elizabethan collar may be indicated. If intracavernosal drainage and injections are not successful or significant tissue damage has occurred, then penile amputation and perineal urethrostomy may become necessary.

Nonischemic priapism can resolve spontaneously. Thus conservative therapy, protecting penile integrity with lubrication, and an Elizabethan collar are recommended. Several systemic medications are of potential benefit, although very little controlled data exists regarding efficacy of systemic drug therapy. Gabapentin, terbutaline, or pseudoephedrine should be tried. If detumescence is not achieved after several days of treatment with one drug, switching to another may be successful.

Ischemic priapism has been reported in cats; penile amputation and perineal urethrostomy may be indicated. A traumatic cause should be considered in cats if they have a recent history of mating; it has also been reported after orchiectomy. Surgical treatment making several small incisions bilaterally in the tunica albuginea of the corpora cavernosa penis and in some parts of the corpora cavernosa followed by irrigation with heparinized saline has been reported to have some success. Skin sutures were then placed closing the approach, but the tunica albuginea was not closed. Nonischemic feline priapism can respond to medical management as in the dog (Fig. 56.16).

Phimosis is a condition in which the penis is trapped within the preputial cavity. It usually occurs as a congenital defect in which the preputial opening is abnormally small and the penis cannot protrude. Phimosis is uncommon in cats and dogs. It may be recognized in young animals as a cause of a urinary outflow tract obstruction or of the dribbling of urine that has accumulated in the preputial cavity. Phimosis may be recognized in an affected postpubertal male unable to copulate. It is treated by conservatively surgically enlarging the preputial orifice. The preputial hairs of longhaired cats may entangle the preputial orifice, causing clinical signs similar to phimosis, and is treated by clipping the preputial hairs.

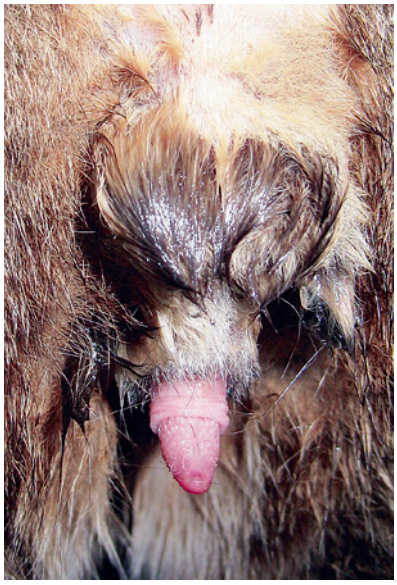


FIG 56.16
Feline priapism in a tom cat overdosed with ace promazine.

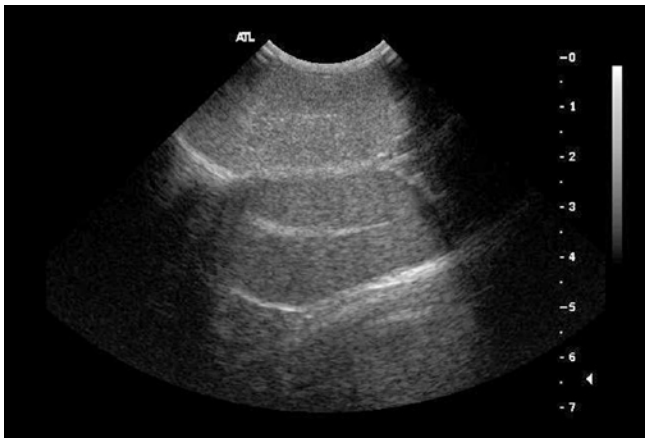


FIG 56.17
Ultrasound image of normal canine testes, sagittal view.

TESTICULAR NEOPLASIA IN STUD DOGS

Unless the dog is a valuable and still fertile stud, the discovery of a testicular mass warrants castration. If the dog is still breeding and the tumor is limited to one testis, unilateral castration can be performed. Testicular neoplasia is rare in the tom cat. Risk factors for testicular neoplasia in the dog are age (>10 years) and cryptorchidism. The early diagnosis of testicular neoplasia is often incidental and based on careful palpation of the scrotal testes. Ultrasound can detect testicular masses too small for manual detection and is therefore indicated annually in valuable breeding dogs. The normal testis is uniform in texture with echogenicity similar to the spleen (Fig. 56.17). The mediastinum testis is a thin, centrally

located, very hyperechoic line. The epididymis (head, body, tail) is less echogenic than the testis. The ductus deferens is difficult to visualize. The spermatic cord is adjacent to the head of the epididymis and has obvious, tortuous, small diameter veins. Testicular neoplasms appear as variably circumscribed masses, hypo- to hyperechoic, which may obscure the mediastinum testis (Fig. 56.18). The appearance is not specific for tumor type; masses tend to change from hypoechoic to mixed echogenicity with growth likely due to necrosis and hemorrhage. Testicular tumors commonly cause enlargement of the testis with chronicity; some cause paraneoplastic syndromes.

In dogs, Sertoli cell tumors, Leydig cell (interstitial cell) tumors, and seminomas occur with about equal frequency in scrotal testes; intraabdominal testicular neoplasia is most commonly the Sertoli cell tumor. Sertoli cell and interstitial (Leydig) cell tumors can produce hormones, particularly estrogen, which can cause paraneoplastic syndromes. Although these tumors usually are clinically silent, the production of estrogen, progesterone, and corticosteroids has also been described. Estrogen excess and feminizing syndromes may occur from the peripheral aromatization of testosterone or from the direct production of estradiol by the tumor itself. These include atrophy of the contralateral testis, bone marrow suppression, pendulous prepuce, gynecomastia, alopecia, hyperpigmentation, and squamous metaplasia of the prostate. Preputial mucosal cytology can show an estrogen effect similar to estrus in the bitch (superficial cells predominate) (Fig. 56.19). Gynecomastia and a pendulous prepuce have been referred to as feminization. Bone marrow suppression induced by estrogen is characterized by anemia, thrombocytopenia, and/or leukopenia. Thrombocytopenia occurs first. Some of the clinical signs may be related to anemia or hemorrhage as a result of the thrombocytopenia. A complete blood count is indicated to assess the possibility of bone marrow toxicity. Because most affected dogs are geriatric, a preoperative biochemical panel and urinalysis are also reasonable. Hyperestrogenism can cause atrophy of the unaffected testis resulting in azoospermia, which can be noted clinically before a testicular mass is diagnosed.

After castration, histopathology of the testicular mass with evaluation of the local lymphatics is indicated. Most testicular neoplasia in the dog is cured by castration as the potential for distant metastasis is low; local metastasis (intra-abdominal via regional lymphatics) tends to occur late with chronicity.

MICROBIOLOGY AND MALE FERTILITY

Previously fertile stud dogs producing small litter size or failing to impregnate normal bitches with good husbandry and normal breeding behavior should have semen evaluation performed (see semen collection, Chapter 54). If the semen is abnormal and associated with inflammatory cells or pain during ejaculation, it should be submitted for aerobic, anaerobic, and *Mycoplasma* spp. culture, and *B. canis* testing should always be performed (see Chapter 54). Semen is judged to be abnormal if no semen (aspermia), no sperm (azoospermia), or inadequate numbers of sperm (<200-400 million plus per ejaculate [oligospermia]) are present; if sperm motility is less than 75% to 90% progressively motile (asthenospermia); if sperm morphology reveals greater than 10% to 15% abnormal (teratospermia) forms; and especially if the semen contains excessive numbers of other cells such as white blood cells, macrophages, or red blood cells (pyospermia, hemospermia). Physical examination and clinical pathologic evaluation of the subfertile or infertile stud dog should take place *after* semen collection is accomplished; the results will usually direct subsequent diagnostics (Fig. 56.20).

Bacterial infection of the testes (orchitis), epididymides (epididymitis), or scrotum can cause alterations in



FIG 56.18
Intratesticular neoplasia: seminoma. The well-circumscribed round mass within the testicular parenchyma is homogenous with a single cystic region. The mediastinum testis is disrupted.

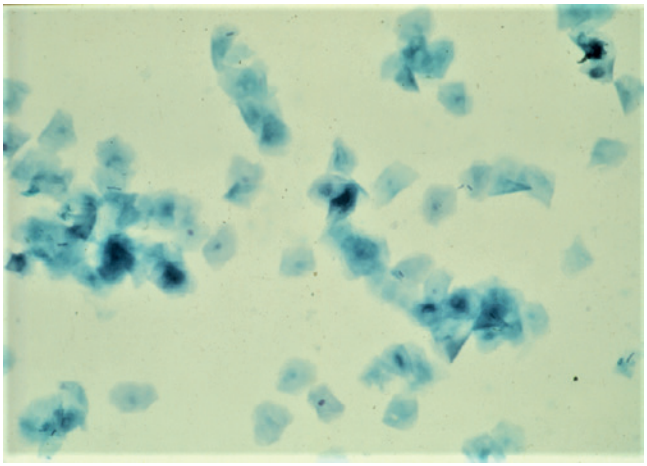


FIG 56.19
Preputial cytology showing estrogen effect on the mucosal epithelial cells. Note angular cytoplasmic margins, pyknotic or absent nuclei.

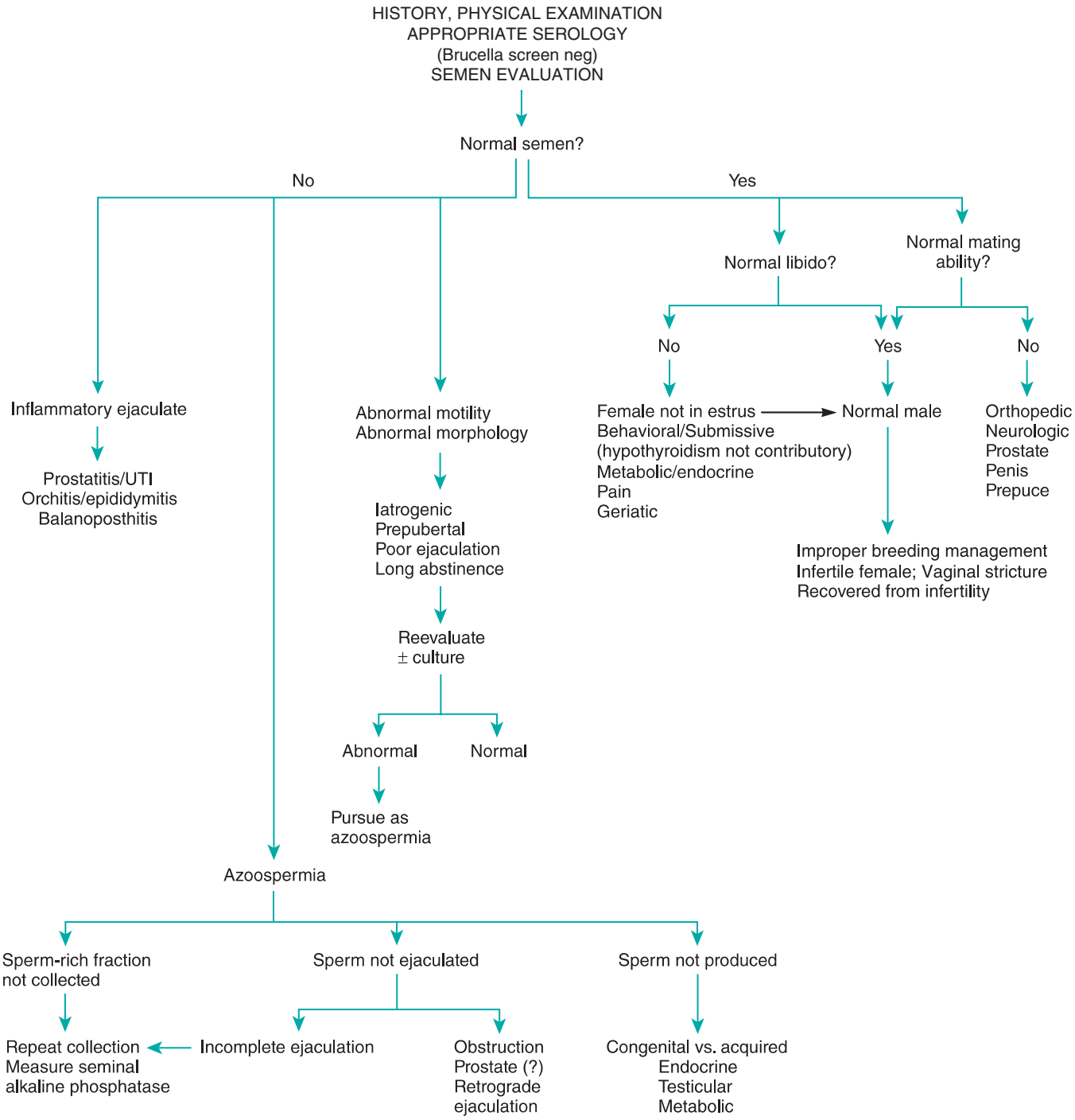


FIG 56.20
Flowchart illustrating the diagnostic pathway for male infertility.

spermatogenesis secondary to the destructive properties of the organisms themselves and as a result of local swelling and hyperthermia. Focal lesions can become generalized. Infectious prostatic disorders can cause abnormal semen due to the prostatic fluid component. The normal bacterial flora of the prepuce and distal urethra are the same organisms most frequently isolated from normal canine semen and also from dogs with bacterial orchitis, epididymitis, or prostatitis. The normal flora of the distal urethra and prepuce consist predominantly of aerobic organisms, but anaerobic organisms are also found. *Pasteurella multocida,* β-hemolytic streptococci, and *E. coli* are the organisms most commonly isolated from dogs (Table 56.1). Similar data are available for tomcats (Table 56.2). Because of this, collecting semen for culture can be misleading because normal urethral flora will contaminate the sample. The number of

TABLE 56.1

Bacterial Isolates From the Prepuce and Semen of Stud Dogs

PREPUCE	SEMEN	SEMEN
(n = 232 samples from 15 dogs; Bjurström et al.)	(n = 232 samples from 15 dogs; Bjurström et al.)	(n = 95 dogs; Root Kustritz et al., 2005)
Pasteurella multocida	*Pasteurella multocida*	Aerobic Organisms in 28% of Samples
β-hemolytic *Streptococci*	β-hemolytic *Streptococci*	β-hemolytic *Streptococci*
E. coli	*E. coli*	*Pasteurella multocida*
Coagulase neg *Staphylococci*	*Pasteurella* spp.	hemolytic *E. coli*
Staphylococcus intermedius	*Streptococcus* spp.	nonhemolytic *E. coli*
Streptococcus spp.	*Staphylococcus intermedius*	*Achromobacter*
Pasteurella spp.		*Actinomyces pyogenes*
Coryneforms		*Bacillus* spp.
Enterococci		Coagulase pos *Staphylococcus*
Pseudomonas spp.		*Hemophilus*
Proteus		*Klebsiella*
		Proteus
		Pseudomonas
		Staphylococcus intermedius
		Anaerobic Organisms in 14% of Samples
		Bacteroides spp.
		Peptostreptococcus
		Propionibacterium
		Clostridium
		Fusobacterium
		Streptococcus morbillorum
Mycoplasma present in 11% of samples and 80% of dogs	*Mycoplasma* present in 3% of samples and 27% of dogs	*Mycoplasma* present in 58% of samples
No bacterial growth in 14% of samples	No bacterial growth in 70% of samples	No bacterial growth in 18% of samples

colony-forming units (CFUs) per milliliter of semen attributable to urethral contamination (normal urethral flora) reportedly varies from 100 to 10,000. A separate culture of the material from a urethral swab obtained just before ejaculation could be used to identify urethral organisms. Quantitative culture of the urethra can then be compared with quantitative culture of the semen. Gentle cleansing and drying of the prepuce should precede semen collection; semen should be collected with sterile equipment (artificial vagina and collection tubes). Semen evaluation should not be performed on these samples because of the spermicidal effects of cleansing and sterilizing agents. Greater than 3 logs increase (semen versus urethra) in the number of an organism identified in both the semen and urethral cultures could be considered significant. Quantitative aerobic, anaerobic, and *Mycoplasma* cultures of both the urethra and semen are often prohibitively expensive. Specific sampling of the urine (representing the prostatic component), prostate, epididymi, and testes can be more efficient and meaningful, and can be facilitated by ultrasound-guided technique. Cytologic samples of these areas can also be acquired; suppurative inflammation of the prostate, epididymi, and testes is characterized by infiltration of neutrophils and macrophages. Concluding that an infertile or subfertile dog has infectious etiology on the basis of a positive routine ejaculate culture is unjustified without supportive data. Dogs with infectious orchitis, epididymitis, and/or prostatitis tend to have clinical signs supporting the etiology (heat, pain, redness, and swelling of the affected organ) readily apparent on the physical examination, as well as abnormal semen (Fig. 56.21). Semen collection may be difficult due to pain associated with ejaculation.

TABLE 56.2

Bacterial Isolates From the Prepuce and Semen of Tomcats With Normal Semen

PREPUCE	SEMEN
n = 29 samples	n = 29 samples
hemolytic *E. coli*	hemolytic *E. coli*
Pseudomonas aeruginosa	*Pseudomonas aeruginosa*
Proteus mirabilis	*Proteus mirabilis*
Klebsiella oxytoca	*Klebsiella oxytoca*
Streptococcus spp.	*Streptococcus* spp.
Nonhemolytic *E. coli*	*Streptococcus enterococcus*
Enterococcus	Nonhemolytic *E. coli*
Bacillus spp.	*Staphylococcus* spp.
Serratia odorifera	
Streptococcus enterococcus	
Staphylococcus spp.	
Yersinia intermedia	
Acinetobacter spp.	
No aerobic bacterial growth in 10% of samples	No aerobic bacterial growth in 3% of samples

From Johnston SD et al.: Ovarian and testicular function in the domestic cat: Clinical management of spontaneous reproductive disease, *Anim Reprod Sci* 42:261, 1996.



FIG 56.21
Erythemic, enlarged, painful and warm scrotum in a dog found to have acute bacterial epididymitis.

INFECTIOUS ORCHITIS AND EPIDIDYMITIS

Brucellosis

The primary acute clinical signs of canine brucellosis in the male dog involve the portions of the reproductive tract that participate in maturation, transport, and storage of spermatozoa. Epididymitis is common, with associated orchitis and scrotal dermatitis and resultant deterioration of semen quality and fertility. Chronically, testicular atrophy and infertility can occur. The organism can be found in the prostate gland and urethra and is shed intermittently in the urine. Antisperm antibodies develop in association with brucellosis-induced epididymal granulomas and can further contribute to infertility. Pyospermia develops 3 to 4 months postinfection. Chronic infections in either sex can result in uveitis or endophthalmitis, lymphadenitis, splenomegaly, discospondylitis, and occasionally dermatitis and meningoencephalitis have been reported. Bacteremia can persist for years, and subclinically infected dogs can remain infectious for long intervals. Large numbers of organisms are shed in the vulvar discharge of bitches 4 to 6 weeks postabortion. The highest concentration of organisms is shed in the semen of infected dogs 2 to 3 months after infection, with lesser amounts in the semen for years. Urine can serve as a contaminated vehicle because of the proximity of the urinary and genital tracts in the dog, with shedding present for months to years; this is more prevalent in males (see Chapter 55, Brucellosis diagnostics) (Wanke, 2004).



FIG 56.22
Sagittal ultrasound image of acute epididymitis; the epididymis (*arrows*) is mottled and enlarged (dog of Fig. 56.21).

Other Infectious Agents

Orchitis and epididymitis not associated with brucellosis can occur separately or in concert. Male dogs are typically presented because their owners noticed an enlarged scrotum. Scrotal enlargement can be due to scrotal neoplasia, scrotal dermatitis, scrotal edema, intrascrotal effusion or hemorrhage, testicular enlargement, or epididymal enlargement. Testicular or epididymal enlargement can be due to an acute infectious process or to infiltrative disease, which can be granulomatous or neoplastic. Careful palpation of the scrotum and contents may differentiate the source of enlargement; ultrasound evaluation is very helpful in recognizing pathology (Figs. 56.22, 56.23, 56.24, 56.25).

Infertile or subfertile males with contributory physical and ultrasonographic findings and positive reproductive tract cultures should be treated with appropriate antibiotic



FIG 56.23
Transverse ultrasound image showing scrotal edema (*arrow*) and increased testicular echogenicity in a dog with acute orchitis.

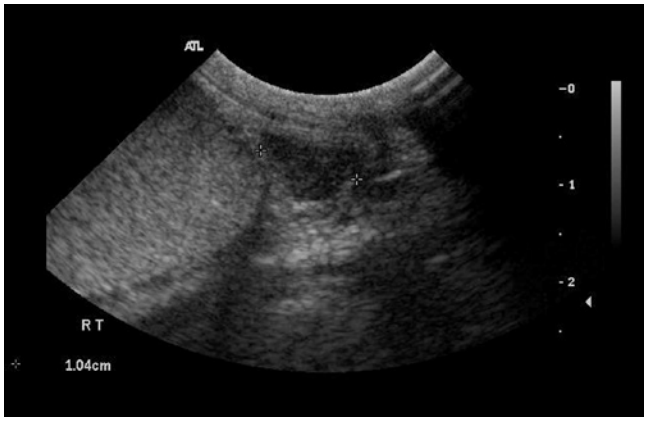


FIG 56.24
Sagittal ultrasound image showing epididymal enlargement and hypoechogenicity in a dog with an epididymal abscess (*cursors*); the abscess is thick walled, with flocculent contents.



FIG 56.25
Sagittal ultrasound image showing testicular enlargement due to a mass within the testicular parenchyma.

therapy based on sensitivity profiles, keeping in mind penetration into the prostate gland. Appropriate antimicrobial therapy should continue for a minimum of 2 to 8 weeks, longer in the case of chronic bacterial prostatitis (see later section). The prognosis for fertility is guarded (but not hopeless) even with therapy—thermal damage from heat associated with inflammation impacts spermatogenesis, and the potential for sperm autoantibody formation exists after such an inflammatory process; clients should be warned of this potential complication.

PROSTATIC DISORDERS IN THE VALUABLE STUD DOG

BENIGN PROSTATIC HYPERPLASIA AND CYSTIC BENIGN PROSTATIC HYPERPLASIA

Prostatic disease is common in dogs but rare in cats. Prostatic hyperplasia occurs predictably in all intact male dogs after the age of 5 and is due to the effect of dihydrotestosterone on the prostatic parenchyma. Dihydrotestosterone causes symmetric, eccentric prostatic parenchymal hyperplasia that can become cystic. Because prostatic enlargement is eccentric, urethral compression (as seen in men) is unlikely. Tenesmus secondary to colonic compression from prostatomegaly can be seen. The most common clinical signs of benign prostatic hyperplasia (BPH) and cystic benign prostatic hyperplasia (CBPH) are blood (of prostatic origin) dripping from the urethra, hemospermia, and hematuria. The prostate is not painful upon palpation. Fertility is not impaired, but attempts at cryopreservation are compromised because the presence of hemoglobin increases sperm cell membrane fragility during the freeze/thaw process.

BPH and CBPH have a characteristic ultrasonographic appearance; a symmetric parenchymal striation with increased echogenicity is apparent, with variable hypoechoic to anechoic intraparenchymal cystic structures evident (Figs. 56.26 and 56.27). Cytology and biopsy can be used to confirm the diagnosis. The presence of intraparenchymal cysts might increase the potential for prostatic abscessation. Castration is curative.

Medical antiandrogen therapy is advised if cryopreservation is desired, defecation is difficult, or the owners find the clinical signs objectionable. Urinary outflow compromise, prostatic pain, or semen quality deterioration should prompt closer evaluation for more serious prostatic disorders such as prostatitis, prostatic neoplasia, or both. Antiandrogen therapy using the 5α-reductase inhibitor finasteride (Proscar, Propecia [Merck]) is a potentially effective option. Conversion of testosterone to dihydrotestosterone is inhibited, causing a reduction in prostatic size and cysts beginning in 1 to 8 weeks. The dose can be extrapolated from the human dose: 1.25 to 5 mg/dog orally q24h, although higher doses (0.10-0.20 mg/kg orally q24h) have been evaluated without problems other than the expense. A generic form of the drug appears to be equally effective and is less

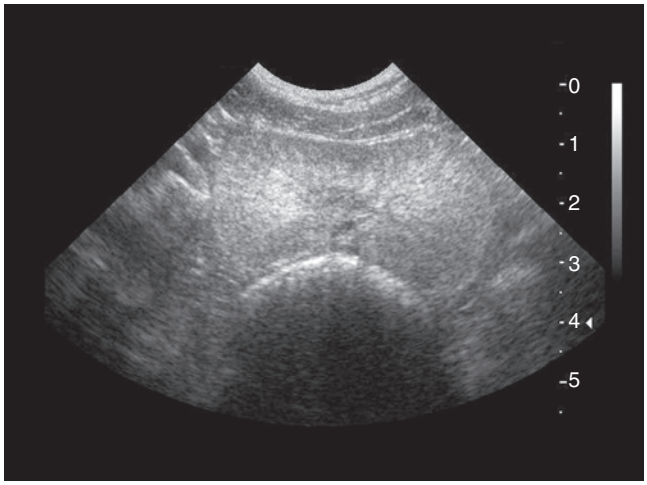


FIG 56.26
Benign prostatic hyperplasia (BPH). A transverse ultrasound image of an intact canine prostate; multiple "wagon wheel" striations radiating from the urethra to the capsule, a typical ultrasonographic finding for BPH.

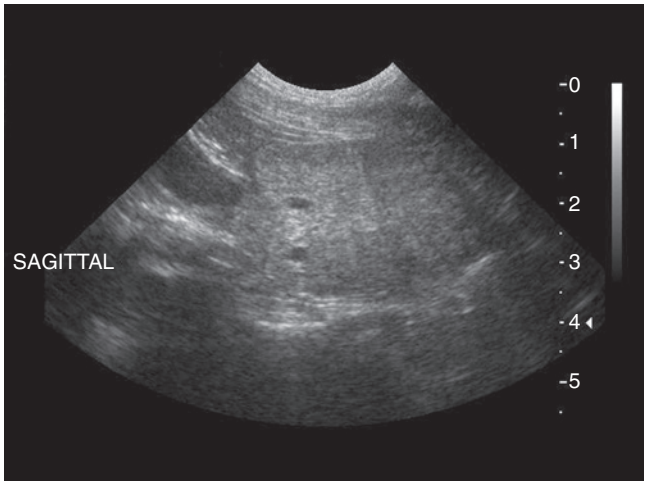


FIG 56.27
Cystic benign prostatic hyperplasia (CBPH). A sagittal ultrasound image of a canine prostate with anechoic parenchymal cysts.

expensive. Libido and semen quality are not compromised, but the prostatic fluid component of the ejaculate is markedly diminished. The effect of this on fertility with natural breedings, where prostatic fluid volume during the ejaculatory tie forces the sperm-rich component of the ejaculate into the uterus, is not known. Artificial insemination, either vaginal or transcervical, using semen extenders could be utilized if fertility seems compromised in dogs on finasteride. Alternative medical therapies such as estrogenic or progestational compounds are not advised, owing to their negative effect on testosterone concentration and spermatogenesis and induction of prostatic metaplasia (estrogen), potential for myelosuppression (estrogen), insulin and glucose dysregulation (progesterone), and mammary neoplasia (estrogen).

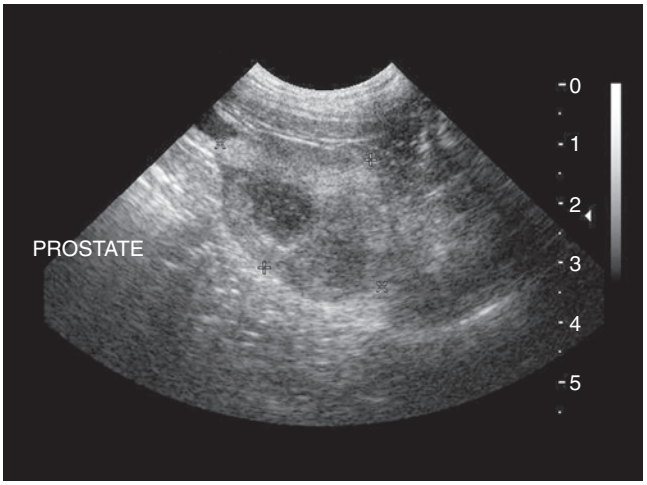


FIG 56.28
Prostatitis with abscess. A sagittal ultrasound image of an intact canine prostate (*cursors*); a hypoechoic nodule is visible within the parenchyma. The parenchymal echo texture is mixed.

Finasteride is not licensed for use in dogs but has achieved common clinical use (Laroque et al., 1994).

Infectious Prostatitis

Bacterial infection of the prostate gland can be acute and fulminate or chronic and progressive. Prostatic abscessation can occur. The prostate is painful on palpation; sublumbar lymphadenomegaly can be present. Dogs are commonly febrile, anorexic, and lethargic. Ejaculation can be painful, and affected dogs may be reluctant to breed. The semen is typically abnormal, with suppurative inflammation, hemospermia, necrospermia (dead sperm), and decreased volume evident. Because prostatic fluid normally refluxes into the urinary bladder, urinary tract infection is usually present whenever there is bacterial prostatitis. Pyuria and bacteriuria should always prompt evaluation of the prostate in any intact male dog. The most common route of infection is ascension of urethral flora, but the hematogenous route of infection is also possible. The organisms most commonly isolated from the infected prostate are *E. coli, Staphylococcus, Streptococcus,* and *Mycoplasma* spp. Occasionally, *Proteus* spp., *Pseudomonas,* or anaerobic organisms are found. Mycotic prostatitis is uncommon and usually limited to endemic regions. Septic prostatitis is best diagnosed on the basis of the findings from physical examination, followed by ultrasonography and cytology and culture of the prostate, with specific attention to any cystic structures within the parenchyma (Fig. 56.28).

Acute septic prostatitis is a serious disorder and can lead to sepsis and death. Treatment must be prompt and aggressive. Fluid therapy is necessary to correct dehydration and shock. Large prostatic abscesses are treated most effectively by surgical drainage and omentalization. Abscesses may also be drained by fine-needle aspiration under ultrasound guidance. Pending the results of culture and susceptibility,

treatment with a fluoroquinolone and potentiated amoxicillin should be initiated. Antibiotic penetration in acute prostatitis is not as problematic as in the normal prostate; in acute prostatitis, inflammation alters the blood-prostate barrier, allowing most antibiotics to penetrate. A negative culture of the urine or prostate should be obtained once therapy has been initiated to confirm effectiveness. Antibiotic treatment for acute prostatitis should be continued for a minimum of 4 weeks. Urine or prostatic fluid should be recultured a week after discontinuing antibiotic therapy and again 2 to 4 weeks later to be certain the infection has resolved. Castration should be considered. Medical castration with finasteride is an acceptable alternative if the dog stabilizes rapidly and is valuable for breeding. Relapse is common and can be diminished with the use of finasteride chronically.

Acute septic prostatitis can result in the later development of chronic septic prostatitis. Recurrent urinary tract infections imply chronic septic prostatitis. Chronic septic prostatitis may be asymptomatic, with deteriorating semen quality the only sign. The prostate may be painful, firm, and irregular on palpation. Ultrasonographic findings are nonspecific but typically will be of mixed echotexture, with hyperechoic areas reflecting fibrosis. The ultrasonographic appearance can be similar to that of prostatic neoplasia. Additionally, multiple prostatic pathologies can be present in an individual patient. The diagnosis of chronic septic prostatitis requires cytologic and microbiologic examination of urine and prostatic tissue, which may be obtained by ultrasound-guided fine-needle aspiration. Chronic bacterial prostatitis may be difficult to clear because the blood-prostate barrier is quite effective in preventing many drugs from penetrating into the prostatic parenchyma. In chronic prostatitis, only highly lipophilic agents cross into the prostate. Erythromycin, clindamycin, oleandomycin, trimethoprim-sulfonamide, chloramphenicol, carbenicillin, enrofloxacin, and ciprofloxacin are the agents most capable of achieving therapeutic concentrations in the prostate. Ciprofloxacin penetrates well into human prostate tissues, but its prostate/blood concentration ratios are not as high as enrofloxacin in dogs. Antibiotic therapy should be based on culture and susceptibility results from urine and prostatic tissue. Treatment should be continued for at least 4 weeks. Cultures should be repeated during and for several months after discontinuing antibiotic therapy to ascertain whether resistance to antibiotics or persistent infection has developed. Castration (surgical or medical) improves the response to treatment of chronic bacterial prostatitis. It has been suggested that, to avoid creating sequestration of infectious material in an involuting gland, castration should be postponed until a negative urine or prostatic culture is obtained while on antibiotic therapy.

Prostatic Neoplasia

Prostatic neoplasia is more common in neutered dogs; the disease is likely of basal cell (ductal or uroepithelial) origin and is not responsive to antiandrogen therapy. Prostatic neoplasia is suggested by the ultrasonographic findings of intraprostatic mineralization and complex parenchymal changes (Fig. 56.29). It is a disease of aged dogs, usually diagnosed late in its course, and has a poor prognosis. Urethral stent placement can provide temporary relief of obstruction secondary to prostatic neoplasia.

ACQUIRED INFERTILITY

Immune-Mediated Orchitis

Immune-mediated orchitis is characterized by an insidious onset of subfertility progressing to infertility in a previously normal male and occurs more commonly in the dog. A history of recent small litter size production and failure to impregnate bitches is common. Physical examination is normal, but the testes can be noted to be slightly small and soft, making the epididymi prominent by comparison. Ultrasound is the best method for serial testicular size determination, serial evaluations best to confirm atrophy is present (Fig. 56.30). Libido is intact. No history of infectious or systemic disease (including *Brucella spp* evaluation), fever, trauma, or toxins is present. Recent medications and supplements should be recorded to ensure none are contributory (see semen evaluation, Chapter 54).

Semen evaluation usually finds increased teratospermia, oligospermia progressing to azoospermia, and the presence of mononuclear cells. An increased number of sperm with morphologic abnormalities in the midpiece and tail are often present (Fig. 56.31). These cells have abnormal motility (asthenospermia). Early in the course, lymphocytic-plasmacytic inflammation can be found on histopathology (Fig. 56.32). Later, a lack of spermatogenesis without any evidence of an inflammatory process is present (Fig. 56.33). Testicular biopsy can confirm the disorder early in the course but is prognostic only; therapy is unrewarding.

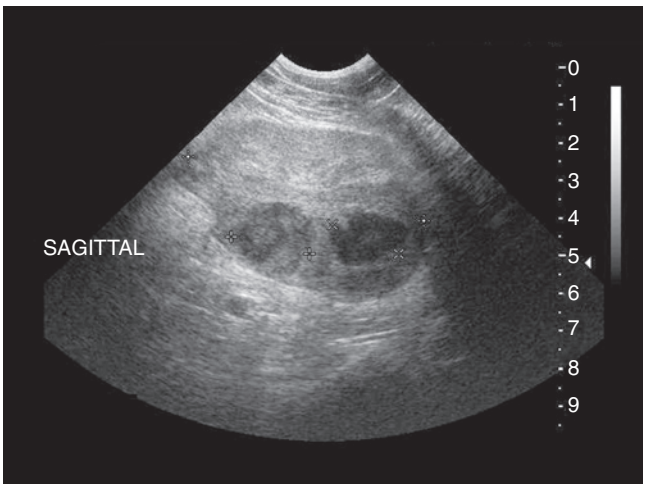


FIG 56.29
Prostatic adenocarcinoma. A sagittal image of an intact canine prostate showing characteristic BPH striations ventrally, but hypoechoic nodules (*cursors*) present within the dorsal parenchyma, illustrating the lack of specificity of ultrasound in prostatic disease. This is an unusual case of adenocarcinoma in an intact dog.



FIG 56.30
Ultrasonographic testicular measurement; *cursors* mark testicular length and width in sagittal.



FIG 56.31
Canine sperm cell showing a coiled tail (Dag defect) adjacent to two normal sperm cells.

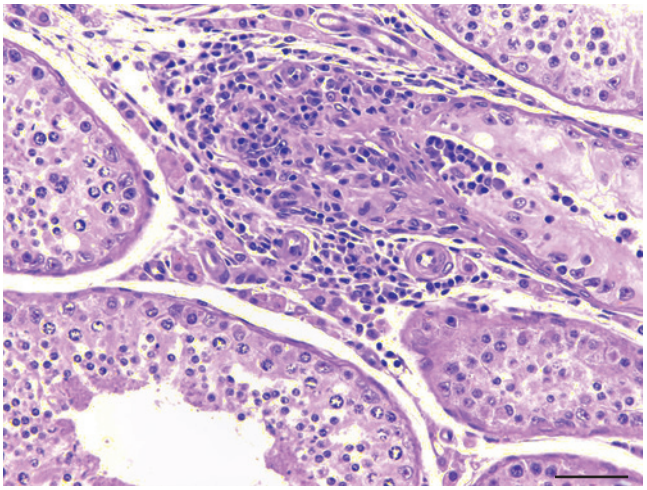


FIG 56.32
Lymphoplasmacytic inflammation shown in a testicular biopsy performed on a Toy Poodle with acquired infertility.

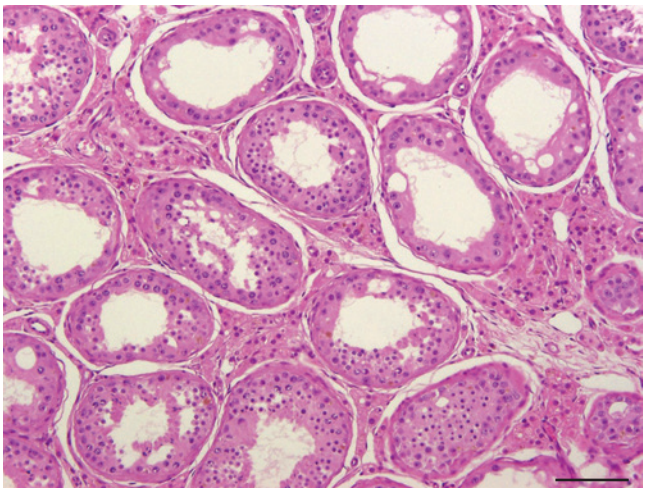


FIG 56.33
Complete lack of spermatogenesis shown in a testicular biopsy of a littermate Toy Poodle with acquired infertility.

Testicular biopsy has not been associated with a subsequent increase of antisperm antibodies. Testicular fine-needle aspiration cytology (60 mL syringe, 21 or 23-gauge butterfly needle) can be performed to evaluate normal spermatogenesis, spermatogenic arrest, Sertoli cell population, and inflammatory cell presence (Romagnoli and Schlafer, 2006) The etiology is unknown; microscopic breakdown of the sperm-bloodstream barrier is likely. Any attempt at immunosuppression inevitably targets spermatogenesis, and even staged therapy is problematic. Monitoring for other immune-mediated endocrinopathies is indicated, but their occurrence is uncommon. The disorder is noted in some breeds more frequently, suggesting a genetic component that could be associated with the degree of inbreeding present; breeding affected individuals is controversial (Davidson et al., 2015).

OBSTRUCTIVE DISORDERS OF EJACULATION

Azoospermia, a lack of sperm cells in the ejaculate, suggests a lack of spermatogenesis, spermatogenic arrest, or bilateral obstruction of the outflow of semen from the epididymi, usually in the ductuli deferentes. Incomplete ejaculation must be ruled out, because stud dogs can withhold the sperm-rich second fraction of the ejaculate voluntarily, especially if not comfortable with the collection process or clinician, or an estrual bitch is not present. Semen alkaline phosphatase (originating from the canine epididymis) can

be evaluated in azoospermic samples; a level of greater than 5000 IU/L suggests patency of the duct system and that a complete ejaculate was obtained. Cytologic examination of fine-needle aspirate of the testes (described earlier) can help evaluate for the presence of spermatogenesis in azoospermic dogs with low semen alkaline phosphatase by the identification of spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa; if normal, an obstructive lesion is more likely. Prostatic evaluation is indicated as both ductuli deferentes course through the prostate into the prostatic urethra. Ultrasound of the reproductive tract should be performed evaluating the prostate, epididymi, and urethra for abnormalities that could interfere with semen outflow (epididymal spermatocele, prostatitis).

Retrograde Ejaculation

Normally, semen flows antegrade into the urethra, and a small amount passes retrograde into the urinary bladder. Excessive retrograde flow can result in oligospermia and is confirmed by evaluating the number of sperm in urine before and after ejaculation. Treatment with α-andrenergic agonists (ephedrine, norfenefrine, phenylpropanolamine hydrochloride) can be attempted to increase urethral sphincter pressure; neither testosterone nor estrogen should be used. Urine is toxic to sperm cells, so stud dogs should be encouraged to empty their bladders before semen collection or natural breeding.

DEFECTS OF SPERMATOGENESIS

Testicular fine-needle aspirate and cytology can also assist in the diagnosis of defects in spermatogenesis. Hypospermatogenesis and maturation defects can be detected. Defective spermatogenesis can occur secondary to direct thermal scrotal insult (scrotal dermatitis), systemic disease, fever and hyperthermia from prolonged exercise, certain drugs and toxins, and endocrinopathies. The effect of these etiologies on spermatogenesis can be reversible. Cimetidine, ketoconazole, sex steroids, glucocorticoids, anticholinergics, thiazide diuretics, propranolol, digoxin, spironolactone, diazepam, and chlorpromazine have been implicated. Re-collection and evaluation 60 days (or more) later is necessary to permit a new cycle of spermatogenesis to be identified in the ejaculate.

In addition to a careful general and focused (scrotum, testes, epididymi, and prostate) physical examination, testicular ultrasound should be performed in every patient with unexplained acquired infertility and abnormal semen analysis. It allows diagnosis of more pathologic conditions than physical examination. Subtle differences in testicular or epididymal size or symmetry, or changes in testicular or epididymal consistency, warrant an ultrasonographic evaluation that can disclose pathology (i.e., orchitis, epididymitis, testicular neoplasia) sometimes before reproductive performance has been irreversibly affected. The presence of a functional testicular neoplasia (most commonly Sertoli cell tumor) can adversely affect spermatogenesis in the unaffected testis; early unilateral castration can be curative if significant testicular atrophy has not occurred (Fig. 56.34).



FIG 56.34
Ultrasonographic identification of a small Sertoli cell tumor (*cursors*). Ultrasound guided fine needle aspirate and cytology are often helpful in identifying tumor type.

CONGENITAL INFERTILITY

HERITABLE TERATOSPERMIA

Genetic sperm defects such as acrosome defects, head defects, midpiece abnormalities, and tail defects have been described in several species including dogs and cats. Increased fertility problems in purebred dogs suggests this could be related to reduced genetic variability.

DISORDERS OF SEXUAL DIFFERENTIATION

Malformation and dysfunctionality of the reproductive tract can result from abnormalities of chromosomal sex, causing intersex conditions. Intersex animals commonly have ambiguous or inappropriate external genitalia that can be discovered readily by careful physical examination. Sexual differentiation occurs during fetal development and is dependent upon a normal chromosomal complement, followed by normal gonad and genitalia formation. The Y chromosome, containing the SRY gene, is the sex-determining chromosome. If it is present and normal, a male develops; if absent or abnormal, the fetus develops into a female or an intersex. Once fetal gonads have developed, the fetal phenotypic sexual characteristics develop as a consequence of hormones secreted.

Physical findings in individuals with disorders of sexual differentiation can include an os clitoris (commonly causing vestibulitis), hypospadias (commonly associated with incontinence and exposure phimosis), cryptorchidism, and displacement of the prepuce (caudally) or vulva (cranially). Os clitorises have been noted as an incidental finding during coxofemoral joint radiography; the reproductive status of the individuals was not reported. Normal estrous cycles can be lacking in individuals with anomalous differentiation.



FIG 56.35
Cranially displaced and malformed vulva in a female puppy exposed in utero to progestins.

Defects in the development of the internal tubular genital tract of females can also result from developmental abnormalities during embryogenesis. Ovaries, testes, or ovotestes can be present. A definitive diagnosis is based on karyotyping and histopathology of the reproductive tract. Most of these animals are sterile.

Neutering is still indicated to avoid behavioral and paraneoplastic conditions associated with hormone production. Iatrogenic causes of disorders of sexual differentiation include therapy with progestagens during pregnancy (Fig. 56.35).

In males, congenital causes of infertility should be considered in aspermic animals that have no history of siring a litter. Abnormalities of the hypothalamic-pituitary-gonadal axis, such as hypogonadotropic hypogonadism, and disorders of sexual differentiation, such as intersex, are possible causes. Males with hypogonadism have abnormally small testes with diminished (or absent) spermatogenesis and testosterone production. The secretory capacity of pituitary gonadotropins can be assessed by determining LH levels (Status-LH [Synbiotics/Pfizer]) before and 1 hour after administration of GnRH (1-2.2 μg/kg intramuscularly); normal intact male dogs have a serum LH from 0.20 to less than 20.0 ng/mL. Evaluation of resting and post-hCG or GnRH stimulation testosterone levels is often hampered by reference range variation among laboratories and the overlap between normal basal testosterone levels and hypotestosteronism. Examination of the libido of the dog or the penile spines in the tomcat can be more informative regarding the presence of testosterone.

Suggested Readings

Bjurström L, et al. Long-term study of aerobic bacteria in the genital tract in stud dogs. *Am J Vet Res*. 1992;53:670.

Chenowith PJ. Genetic sperm defects. *Theriogenology*. 2005;64:457–468.

Davidson AP, Baker TW. Reproductive ultrasound of the dog and tom. *Top Companion Anim Med*. 2009;24:64–70.

Davidson AP, von Dehn BJ, Schlafer DH. Adult-onset lymphoplasmacytic orchitis in a Labrador retriever stud dog. *Top Companion Anim Med*. 2015;30(1):31–34.

Gartley CJ. Canine semen abnormalities: orchitis/epididymitis. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:509–512.

Goodman M. Canine prostate disease: benign prostatic hyperplasia, cystic benign prostatic hyperplasia, prostatitis. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:483–489.

Gunn-Moore DA, et al. Priapism in seven cats. *J Small Anim Pract*. 1995;36:262–266.

Hess M. Documented and anecdotal effects of certain pharmaceutical agents used to enhance semen quality in dogs. *Theriogenology*. 2006;66:613.

Laroque PA, et al. Effects of chronic oral administration of a selective 5α-reductase inhibitor, finasteride, on the dog prostate. *Prostate*. 1994;24(2):93–100.

Lavely JA. Priapism in dogs. *Top Companion Anim Med*. 2009;24:49–54.

Lyle S. Disorders of sexual differentiation. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:103–116.

O'Brien D, Rodriguez C. Reproductive malignancies. In: Greco DS, Davidson AP, eds. *Blackwell's five-minute veterinary consult clinical companion: endocrinology and reproduction*. Wiley Blackwell; 2017:491–508.

Peters MAJ, et al. Aging, testicular tumours and the pituitary-testis axis in dogs. *J Endocrinol*. 2000;166:153.

Pettersson A, et al. Age at surgery for undescended testis and risk of testicular cancer. *N Engl J Med*. 1835;356:2007.

Rijsselaere T, et al. New techniques for the assessment of canine semen quality: a review. *Theriogenology*. 2005;64:706.

Rochat MC. Priapism a review. *Theriogenology*. 2001;56:713–722.

Romagnoli S, et al. Clinical use of testicular fine needle aspiration cytology in oligozoospermic and azoospermic dogs. *Reprod Domest Anim*. 2009;44(s2).

Romagnoli S, Schlafer DH. Disorders of sexual differentiation in puppies and kittens: a diagnostic and clinical approach. *Vet Clin North Am Small Anim Pract*. 2006;36:573.

Root Kustritz, et al. Effect of administration of prostaglandin F2alpha or presence of an estrous teaser bitch on characteristics of the canine ejaculate. *Theriogenology*. 2007;67:255.

Root Kustritz, et al. Relationship between inflammatory cytology of canine seminal fluid and significant aerobic bacterial, anaerobic bacterial or *Mycoplasma* cultures of canine seminal fluid: 95 cases (1987-2000). *Theriogenology*. 2005;64:1333.

Ström-Holst B, et al. Characterization of the bacterial population of the genital tract of adult cats. *Am J Vet Res*. 2003;64:963.

Wanke MM. Canine brucellosis. *Anim Reprod Sci*. 2004;82:195–207.

Wheeler R, Kutzler M. LH testing is accurate for diagnosing the presence or absence of testicular tissue in dogs. *Clin Theriogenol*. 2010;1:382.

Zhao X, Du ZQ, Rothschild MF. An association study of 20 candidate genes with cryptorchidism in Siberian Husky dogs. *J Anim Breed Genet*. 2010;127(4):327–331.

CHAPTER 57

Neonatology and Pediatrics



Average reported neonatal mortality rates (greatest during the first week of life) vary, ranging in reports from 9% to 26%. Veterinary intervention in the prenatal, parturient, and postpartum periods can increase neonatal survival by controlling or eliminating factors contributing to puppy morbidity and mortality. Poor prepartum condition of the dam, dystocia, congenital malformations, genetic defects, postnatal injury, chilling, overheating, malnutrition, parasitism, and infectious disease all contribute to neonatal morbidity and mortality. Optimal husbandry favorably impacts neonatal survival by managing labor and delivery to reduce stillbirths, controlling parasitism, reducing infectious disease exposure, preventing injury and environmental extremes, and optimizing nutrition of the dam and neonates. Proper genetic screening for selection of breeders (both the sire and the dam) minimizes inherited congenital defects. Breeders should select for sires that have normal fecundity, producing normal-sized litters that survive to weaning.

NEONATAL RESUSCITATION

Cardiopulmonary resuscitation for neonates who fail to breathe spontaneously is challenging yet potentially rewarding. Maintaining a neonatal resuscitation kit is ideal (Box 57.1). Optimal neonatal resuscitation after birth (if the dam fails to do so) or cesarean section involves the same ABCs (airway, breathing, circulation) as any cardiopulmonary resuscitation (Box 57.2) (Video 57.1). Intervention for resuscitation of neonates after vaginal delivery should take place if the dam's actions fail to stimulate respiration, vocalization, and movement within 1 minute of birth. After removing amniotic membranes from the neonatal muzzle, promptly clear the airways by gentle suction with a bulb syringe or DeLee mucous trap while the neonate's head is lowered (Figs. 57.1, 57.2, *A*, 57.2, *B*, 57.2, *C*). Neonates should not be swung to clear airways because of the potential for cerebral hemorrhage from concussion (Grundy et al., 2009). After checking for a heartbeat, drying and stimulating the neonate to promote respiration are performed next (Fig. 57.3). The use of doxapram as a respiratory stimulant is unlikely to improve hypoxemia associated with hypoventilation and is not recommended (Moon et al., 2000). Spontaneous breathing and vocalization at birth are positively associated with survival through 7 days of age (Video 57.2). Ventilatory support should include constant flow-by O_2 delivery by face mask (Fig. 57.4, *A*). If this is ineffective after 1 minute, positive pressure with a snugly fitting mask, or endotracheal intubation and rebreathing bag (using a 2-mm endotracheal tube or a 12- to 16-gauge intravenous [IV] catheter), is advised (Fig. 57.4, *B*). Anecdotal success with Jen Chung acupuncture point stimulation has been claimed when a 27-ga or acupuncture needle is inserted into the nasal philtrum at the base of the nares and rotated when bone is contacted (Fig. 57.5). An improvement in heart rate should follow ventilation support; myocardial hypoxemia is the most common cause of neonatal bradycardia or asystole. Atropine is currently *not* advised in neonatal resuscitation. The mechanism of bradycardia is hypoxemia-induced myocardial depression rather than vagal mediation, and anticholinergic-induced tachycardia can actually exacerbate myocardial oxygen deficits. If no heartbeat is detected, direct transthoracic cardiac compressions are advised as the first step; epinephrine diluted 1:9 is the drug of choice for cardiac arrest/standstill (0.0002 mg/g administered best by the IV or intraosseous [IO] route) (Moon et al., 2000). Venous access in the neonate is challenging; the single umbilical vein is one possibility if not thrombosed. The proximal humerus, proximal femur, and proximomedial tibia offer intraosseous sites for drug administration (Fig. 57.6, *A*, 57.6, *B*).

Chilled neonates can fail to respond to resuscitation. Loss of body temperature occurs rapidly when a neonate is damp. Keeping the neonate warm is important during resuscitation and in the immediate postpartum period. During resuscitation, placing the chilled neonate's body into a warm water bath (95° F-99° F) can improve response (Fig. 57.7). Working under a heat lamp or within a Bair hugger warming device is helpful. After resuscitation, neonates should be placed in a warm box (a Styrofoam picnic box with ventilation holes is ideal) with warm bedding until they can be placed with

BOX 57.1

Neonatal Resuscitation Equipment Kit

- Syringes (tb)
- Drugs (epinephrine 0.1 mg/mL +/– 0.01 mg/mL, 2.5%-5% Dextrose, Ceftiofur*)
- Oxygen sources
- Suction (pediatric bulb syringes, DeLee mucous traps)
- Small face masks
- Towels (small)
- Heat sources (Baer, warm water blanket, infrared lamp, hair dryer, warm water bottles)
- Puppy box (Styrofoam) with heat support
- Multiple clean mosquito forceps & small scissors
- 3-0 monofilament suture for umbilical cord ligation
- Tincture of iodine 2%
- Bowls for warm water baths
- Pediatric/neonatal stethoscope
- Doppler
- Neonatal gram scale

*Naxcel®/Ceftiofur Protocol
Reconstitute with 20 mL bacteriostatic or sterile water to 50 mg/mL solution
Stable for 12 hours at room temperature (once reconstituted)
Stable for 7 days if refrigerated (once reconstituted)
Stable for 8 weeks if frozen (once reconstituted)
Freeze remainder in 1-mL increments in labeled RTT
Neonatal dose is 2.5 mg/kg (0.0025 mg/gram) SC bid for 3-5 days



FIG 57.1
Removal of amniotic membranes from the muzzle of a neonate.

BOX 57.2

Neonatal Resuscitation Protocol

A, B, Cs—Airway, Breathing & Circulation

A. Clear airway of amniotic membrane and fluid by suction. Do not swing. Place with head below thorax to improve drainage.
B. Gentle brisk towel drying to stimulate respiration. If not breathing, start positive pressure ventilation using snug face mask and 21% O_2.
C. Circulation: If HR is slow, improve ventilation/oxygenation.

Is Resuscitation Effective?

1. Is the puppy vocalizing?
2. Is the mucous membrane color improving?
3. Is the puppy moving?

Keep in mind that even a nonviable puppy can have red color in the mucous membranes from the maternal circulation and fetal hemoglobin.

Rxs if ABCs Fail

- Epinephrine (1:10,000 or 0.1 mg/mL); give 0.0002 mg/g (e.g. 500 g neonate would receive 0.1 mg (0.1 mL) IV, IO, IC. Smaller neonates could require further dilution of epinephrine to 0.01 mg/mL
- Atropine not advised
- Doxapram not advised
- Acupressure if poor respiration: 27 ga or acupuncture needle into the nasal philtrum, insert and turn

Prolonged Problematic Case

Hypothermic? Warm water bath at 95-98° F
Hypoglycemic? Rx Dextrose 2.5%-5.0% Dextrose IV, IO

Reasons to Stop

1. No pulse after 10 minutes (check with Doppler or pediatric stethoscope)
2. Agonal breathing for more than 20 minutes
3. Severe congenital defect

their dam. Neonatal dogs and cats lack thermoregulatory mechanisms until 4 weeks of age, so the ambient temperature must be high enough to facilitate maintenance of a body temperature of at least 97° F (36° C). Hypothermia negatively impacts immunity, nursing, and digestion. Postresuscitation, exogenous heat should be supplied, best in the form of an overhead heat lamp. Heating pads run the risk of burning neonates incapable of moving away from excessively hot surfaces. Chilled older neonates must be rewarmed slowly (30 minutes) to avoid peripheral vasodilation and dehydration. Tube feeding should be delayed until the neonate is euthermic; hypothermia induces ileus, and regurgitation and aspiration can result. Thermal support should continue through 4 weeks of life (Fig. 57.8, Box 57.3).

Neonates lack glucose reserves and have minimal capacity for gluconeogenesis. Providing energy during prolonged resuscitation efforts becomes critical. Clinical hypoglycemia involves blood glucose levels less than 30 to 40 mg/dL and is best treated with IV or IO dextrose at a dose of 0.1 to 0.2 mL of a 2.5% to 5.0% (25-50 mg/mL) dextrose solution. Single administration of parenteral glucose is adequate if the puppy can then be fed or if it nurses. Because of the potential for phlebitis if administered intravenously, 50% dextrose solution should only be applied to mucous membranes; however, circulation must be adequate for absorption from the mucosa. Neonates repeatedly administered dextrose should be monitored for hyperglycemia because of immature

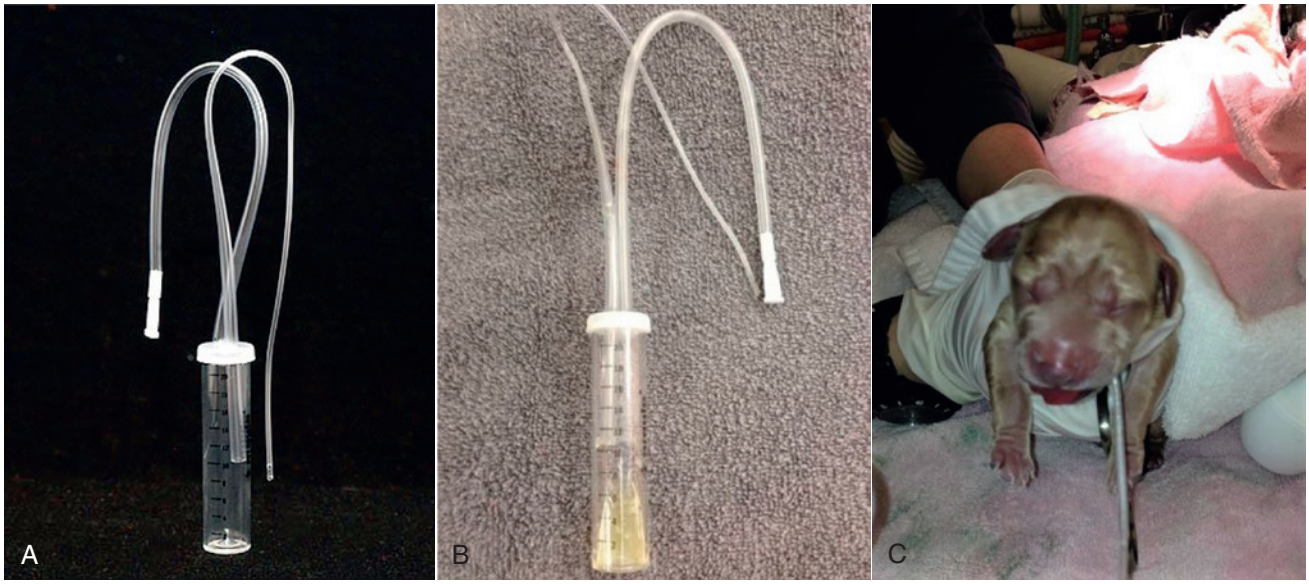


FIG 57.2
DeLee mucous trap. **(A)** Empty. **(B)** Full of fluid recovered from the neonate's airway. **(C)** Note the capped line is inserted in the resuscitators mouth, the open line into the neonatal proximal trachea.



FIG 57.3
Rubbing the neonatal muzzle stimulates respiration.

BOX 57.3

Normal Rectal Temperature of Neonates, First 4 Weeks of Life, and Associated Ambient Temperature Required

Neonatal Normal Body Temperature (Rectal)		
Week 1	95-99° F	35-37.2° C
Week 2-3	97-100° F	36.1-37.8° C
At weaning	99-101° F	37.2-38.3° C
Environmental Warmth Required		
Week 1	84-89° F	35-37.2° C
Weeks 2-3	80° F	26.7° C
Week 4	69-75° F	20.6-23.9° C
Week 5	69° F	20.6° C

metabolic regulatory mechanisms. If a neonate is too weak to nurse or suckle, a mixture of a warmed, balanced crystalloid (½ strength saline) and 2.5% dextrose may be administered subcutaneously at a dose of 1 mL/30 g of body weight until the pup can be fed or nurses. Note that 5% dextrose in lactated Ringer's or Normosol solution is hypertonic and contraindicated with dehydration. Subcutaneous administration of glucose can result in abscessation (Fig. 57.9). A balanced warmed nutrient-electrolyte solution or colostrum from the dam can be administered orally by stomach tube every 15 to 30 minutes until the neonate is capable of suckling.

The umbilicus of neonates should be treated with 2% tincture of iodine immediately after birth or resuscitation to reduce contamination and prevent ascent of bacteria into the peritoneal cavity (omphalitis, peritonitis); the alcohol-based tincture of iodine promotes faster desiccation of the umbilicus than water-based Betadine (Fig. 57.10, *A*, 57.10, *B*, 57.10, *C*, 57.10, *D*; *see* Videos 57.1, 57.2).

After resuscitation or within the first 24 hours of a natural delivery, a complete physical examination with vital signs should be performed by a veterinarian, technician, or knowledgeable breeder (Boxes 57.4 and 57.5). The oral cavity, hair coat, limbs, digits, umbilicus, and urogenital structures should be visually inspected. In the normal neonate, the



FIG 57.4
(A) Flow-by oxygen provided by a small mask. **(B)** Positive pressure ventilation using a snugly fitting mask.



FIG 57.5
Jen Chung acupressure.

BOX 57.4

Normal Values of Body Temperature, Heart Rate, and Respiratory Rate in the Neonate

	Puppies	Kittens
Body temperature	95-99° F 35.0-37.2° C	95-99° F 35.0-37.2° C
Heart rate	200 beats/min	200-250 beats/min
Respiratory rate	10-18/min	10-18/min

BOX 57.5

Immediate Postresuscitation Neonatal Management

Check for congenital defects: cleft palates, urogenital, abdominal wall.
Umbilical care: ligate with suture, remove distally at about 0.5-1 cm from abdomen and dip entire cord remaining in 2% tincture of iodine bottle.
Be sure each puppy nurses effectively (weigh before and after) as soon as possible. If this is delayed, consider tube feeding. Best to acquire colostrum from the dam.
Do not leave neonates unattended with a dam recovering from anesthesia for 24-36 hours postsurgery, as she may be clumsy or even aggressive. Place the puppies/kittens in with dam every 1-2 hours to nurse under supervision.
Canine serum can be given to puppies or kittens that failed to receive colostrum (0.10 mL/g puppy; 0.15 mL/g kitten) weight divided prn; PO within the first 24 hours, or SC if post-24 hours (intestinal absorption diminished > 24 h).
Ceftiofur 0.0025 mg/g SC bid × 5 days may be given to puppies that may have aspirated meconium or had a stressful delivery and are at risk for sepsis.



FIG 57.6
Intraosseous catheter placement in the neonate. **(A)** Proximal humerus. **(B)** Proximal femur.



FIG 57.7
Warm water bath during the resuscitation of a chilled neonate.



FIG 57.8
Post resuscitation, neonates are kept warm in an insulated styrofoam box with a warm air blanket.

mucous membranes should be pink and moist, a suckle reflex present, the coat full and clean, and the urethra and anus patent (Fig. 57.11). The thorax should be auscultated; vesicular breath sounds and a lack of murmur are normal; subtle murmurs, if present, should resolve within 24 hours. The abdomen should be pliant and not painful. A normal neonate will squirm and vocalize when examined, and will nurse and sleep quietly when returned to the dam. Normal neonates will attempt to right themselves and orient by rooting toward their dam. Neonates are highly susceptible to environmental stress, infection, and malnutrition. Proper husbandry is critical and should include daily examination of each neonate for vigor and recording of weight. Severe congenital defects can result in morbidity and mortality; breeders may elect euthanasia if the prognosis is poor or the cost of therapy prohibitive. The hematologic values for



FIG 57.9
Subcutaneous abscess at the site of glucose administration.



FIG 57.11
Checking the neonatal suckle reflex in the immediate postpartum period.



FIG 57.10
(A) Clamping and cutting the umbilicus. **(B)** Saturating the ligated umbilicus in 2% tincture of iodine. **(C)** Appearance of correctly ligated umbilicus postsaturation in 2% tincture of iodine. **(D)** Normal appearance of the umbilicus 24 h postpartum.

growing healthy dogs and cats are presented in Tables 57.1 and 57.2; the biochemical parameters from birth to approximately 8 weeks of age and up to 12 months of age in puppies in Tables 57.3 and 57.4; and the biochemical parameters from birth to approximately 8 weeks of age and up to 12 months of age in kittens in Tables 57.5 and 57.6.

Drug therapy in pediatric dogs and cats is impacted by neonatal physiology and morphology. Absorption of oral drugs is altered by high gastric pH and increased mucous content, decreased gastrointestinal motility, and decreased bile production. Drug distribution is impacted by neonatal increased body water content and decreased fat content. Lower plasma proteins decrease drug binding. The blood brain barrier is incomplete. Decreased renal and hepatic metabolic and excretory capacity persists until 4 to 6 months of age.

ANOMALIES APPARENT AT THE NEONATAL EXAM

A developmental anomaly resulting in extrusion of a portion of the gastrointestinal tract outside of the body wall, occurring within the umbilical canal (omphalocele) or lateral to the umbilical canal (gastroschisis), has been reported in humans and occurs in both dogs and cats (Fig. 57.12). The condition is usually hopeless in small pediatric veterinary patients presented to the veterinarian hours after birth; however, a 30% to 70% survival rate is reported in humans with immediate postpartum surgical intervention; the diagnosis is made prepartum with abdominal ultrasound based on the recognition of fetal gastric wall (rugal) structures or intestinal contents in an abnormal location. Earlier surgical intervention before inevitable septic contamination occurs may improve the prognosis in veterinary patients.

Gastrointestinal abnormalities are suggested by poor weight gain, regurgitation of milk through the nares, respiratory signs, and abnormal defecation. Congenital palate defects occur in dogs with an incidence of up to 25% (Fig. 57.13, *A*). Secondary cleft palate is a congenital oronasal fistula resulting in incomplete closure of the hard and soft palate. Secondary cleft palate occurs alone or in combination with primary cleft palate involving the lip and premaxilla (Fig. 57.13, *B*). Cleft palate results from incomplete fusion of the palatine shelves, most critical at 25 to 28 days gestation,



FIG 57.12
Omphalocele, with and without placental attachment to the umbilicus.

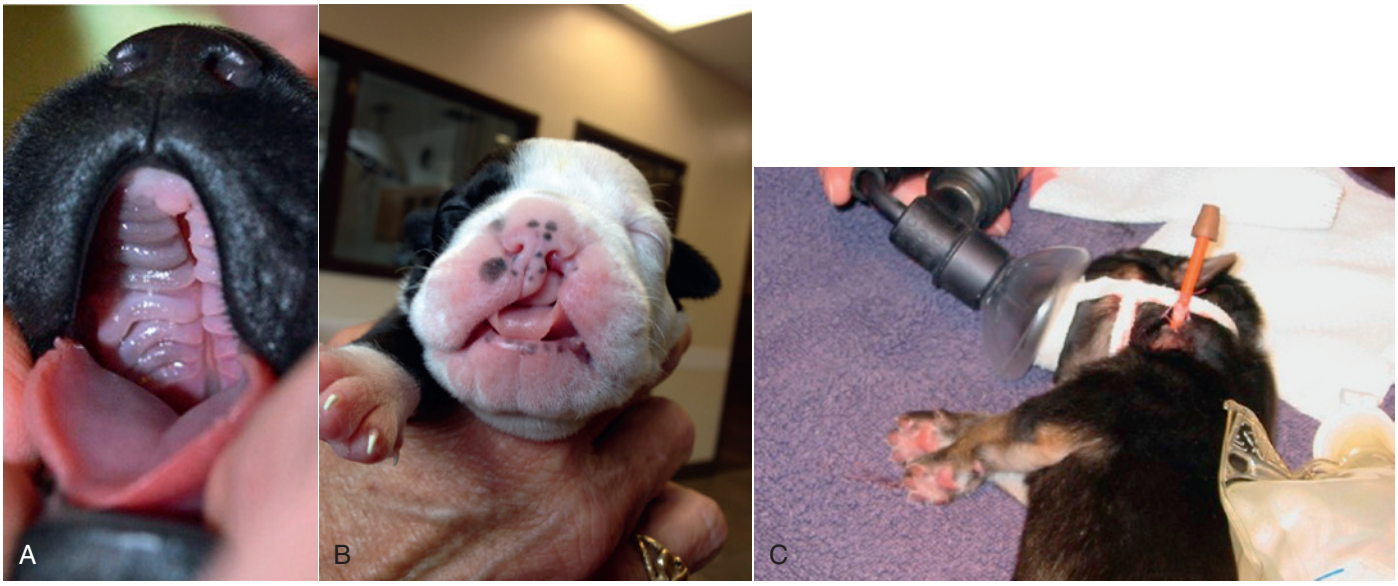


FIG 57.13
(A) Secondary cleft soft and hard palate. **(B)** Primary cleft palate involving the upper lip and maxilla. **(C)** Esophageal feeding tube placed in a neonate with a secondary cleft palate.

TABLE 57.1

Hematologic Values for Growing, Healthy Beagle Dogs

HEMATOLOGIC PARAMETER	AGE (IN WEEKS)				
	BIRTH*	1*	2*	3*	4*
RBC ($\times 10^6/\mu L$)	4.7-5.6 (5.1)	3.6-5.9 (4.6)	3.4-4.4 (3.9)	3.5-4.3 (3.8)	3.6-4.9 (4.1)
Hemoglobin (g/dl)	14.0-17.0 (15.2)	10.4-17.5 (12.9)	9.0-11.0 (10.0)	8.6-11.6 (9.7)	8.5-10.3 (9.5)
PCV (%)	45.0-52.5 (47.5)	33.0-52.0 (40.5)	29.0-34.0 (31.8)	27.0-37.0 (31.7)	27.0-33.5 (29.9)
MCV (fl)	(93.0)	(89.0)	(81.5)	(83.0)	(73.0)
MCH (pg)	(30.0)	(28.0)	(25.5)	(25.0)	(23.0)
MCHC (%)	(32.0)	(32.0)	(31.5)	(31.0)	(32.0)
nRBC/100 WBC	0-13 (2.3)	0-11 (4.0)	0-6 (2.0)	0-9 (1.6)	0-4 (1.2)
Reticulocytes (%)	4.5-9.2 (6.5)	3.8-15.2 (6.9)	4.0-8.4 (6.7)	5.0-9.0 (6.9)	4.6-6.6 (5.8)
Total WBC ($\times 10^3/\mu L$)	6.8-18.4 (12.0)	9.0-23.0 (14.1)	8.1-15.1 (11.7)	6.7-15.1 (11.2)	8.5-16.4 (12.9)
Segmented neutrophils	4.4-15.8 (8.6)	3.8-15.2 (7.4)	3.2-10.4 (5.2)	1.4-9.4 (5.1)	3.7-12.8 (7.2)
Band neutrophils	0-1.5 (0.23)	0-4.8 (0.50)	0-1.2 (0.21)	0-0.5 (0.09)	0-0.3 (0.06)
Lymphocytes	0.5-4.2 (1.9)	1.3-9.4 (4.3)	1.5-7.4 (3.8)	2.1-10.1 (5.0)	1.0-8.4 (4.5)
Monocytes	0.2-2.2 (0.9)	0.3-2.5 (1.1)	0.2-1.4 (0.7)	0.1-1.4 (0.7)	0.3-1.5 (0.8)
Eosinophils	0-1.3 (0.4)	0.2-2.8 (0.8)	0.08-1.8 (0.6)	0.07-0.9 (0.3)	0-0.7 (0.25)
Basophils		0-0.2 (0.01)			0-0.15 (0.01)
Platelets ($\times 10^3/\mu L$)	178-465 (302)	282-560 (352)	210-352 (290)	203-370 (272)	130-360 (287)

MCH, Mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *nRBC/100 WBC*, number of nucleated red blood cells per 100 white blood cells; *PCV*, packed cell volume; *RBC*, red blood cells; *total WBC*, total white blood cell count. Values in parentheses are mean values.

*Normal ranges and/or mean values from Earl Fl, Melveger BA, Wilson RL: The hemogram and bone marrow profile of normal neonatal and weanling beagle dogs. *Lab Anim Sci* 23:690-695, 1973.

†Mean values from Anderson AC, Gee W: Normal blood values in the beagle, *Vet Med* 53:135-138, 156, 1958.

From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

attributed to genetic (recessive or incompletely dominant polygenic inheritance), teratogenic (drugs, supplements), nutritional (folic acid deficiency), or infectious (viral) factors. Affected neonates are diagnosed by visual inspection of the face and oral cavity, and ineffective nursing/suckling results. These neonates fail to thrive, developing aspiration pneumonia and rhinitis. Feeding by orogastric tube is indicated until the puppy reaches a size permitting oral surgery, traditionally advised at 8 to 12 weeks of age. Palatoplasty in such young puppies remains difficult due to patient size and anticipated postoperative orofacial growth, often necessitating multiple surgeries. Esophagostomy or gastrostomy tube placement can facilitate feeding over time but require significant client commitment and can still result in aspiration (Fig. 57.13, *C*). Palatal prostheses are problematic in dogs. Methods to improve survival of pet puppies with cleft palates are sought by clients; survival to reproductive age in congenitally affected dogs providing a research model for the human condition avoids the need for iatrogenic or teratogenically induced models. A successful method to manage nutrition in affected dogs until adult size is attained, facilitating a single later surgical correction, has been reported. Feeding the dam's colostrum for 24 hours followed by artificial bitch milk replacer by intermittent orogastric tube is instituted. At 4 weeks of age, transition to a dry (unsoaked) commercial pediatric dog food is made. Water is made available through an overhead ball-point tube cap system. Surgery can be delayed until the puppy has achieved enough growth or may never become necessary, as some degree of closure of the cleft occurs with time (Figs. 57.14, *A*, 57.14, *B*, 57.14, *C*, 57.14, *D*, 57.15) (Davidson et al., 2014).

Enteric duplication or agenesis can be confirmed ultrasonographically in pediatric patients. Duplication is rare, can occur anywhere in the intestinal tract, and the clinical signs may be nonspecific (abdominal distension, discomfort). A fluid-filled juxta intestinal formation with variable peristalsis and contents can be seen with ultrasound. Enteric agenesis usually results in severe, life-threatening clinical signs in the neonatal period (Fig. 57.16). Ultrasonographic findings usually include marked fluid and gas distention of bowel proximal to the defect.

Text continued on p. 1020

6*	8	12†	16†	20†	24†	28†	40†	44†	52†
4.3-5.1 (4.7)	4.5-5.9 (4.9)	(6.34)	(6.38)	(6.93)	(7.41)	(8.45)	(8.69)	(8.47)	(7.68)
8.5-11.3 (10.2)	10.3-12.5 (11.2)	(14.3)	(15.0)	(16.0)	(16.7)	(17.7)	(18.2)	(18.8)	(18.1)
26.5-35.5 (32.5)	31.0-39.0 (34.8)	(40.9)	(43.0)	(44.9)	(47.6)	(48.8)	(50.8)	(50.2)	(49.3)
(69.0)	(72.0)	(64.6)	(67.4)	(64.8)	(64.2)	(57.8)	(58.4)	(59.3)	(63.5)
(22.0)	(22.5)	(22.8)	(23.5)	(23.0)	(22.5)	(20.5)	(20.9)	(22.1)	(23.6)
(31.5)	(32.0)	(35.3)	(34.8)	(35.6)	(35.1)	(36.1)	(35.9)	(37.3)	(37.1)
0	0-1 (0.2)								
2.6-6.2 (4.5)	1.0-6.0 (3.6)								
12.6-26.7 (16.3)	12.7-17.3 (15.0)	(17.1)	(16.3)	(14.6)	(15.6)	(15.5)	(14.4)	(13.9)	(14.0)
4.2-17.6 (9.0)	6.2-11.8 (8.5)	(9.8)	(9.0)	(8.9)	(9.1)	(9.1)	(9.9)	(8.7)	(8.1)
0-0.3 (0.05)	0-0.3 (0.08)	(0.08)	(0.1)	(0.02)	(0.02)	(0.08)	(0.02)	(0.02)	(0.04)
2.8-16.6 (5.7)	3.1-6.9 (5.0)	(5.7)	(5.9)	(4.5)	(5.3)	(4.8)	(3.4)	(4.0)	(4.7)
0.5-2.7 (1.1)	0.4-1.7 (1.0)	(0.9)	(0.9)	(0.8)	(0.7)	(0.7)	(0.5)	(0.6)	(0.5)
0.1-1.9 (0.5)	0-1.2 (0.4)	(0.4)	(0.4)	(0.3)	(0.5)	(0.8)	(0.6)	(0.5)	(0.5)
275-570 (371)	240-435 (324)								

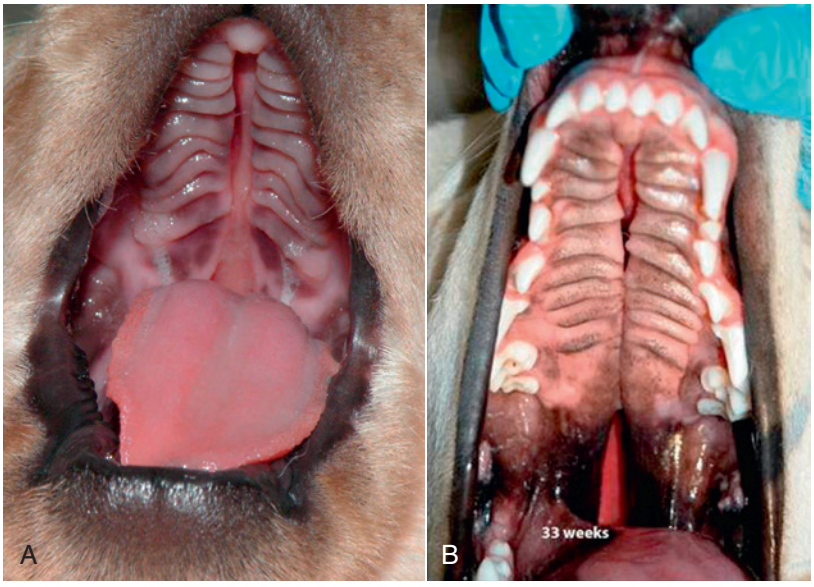


FIG 57.14
Series of images of a secondary cleft palate in a Labrador Retriever. **(A)** 2 days of age. **(B)** 33 weeks of age.

Continued

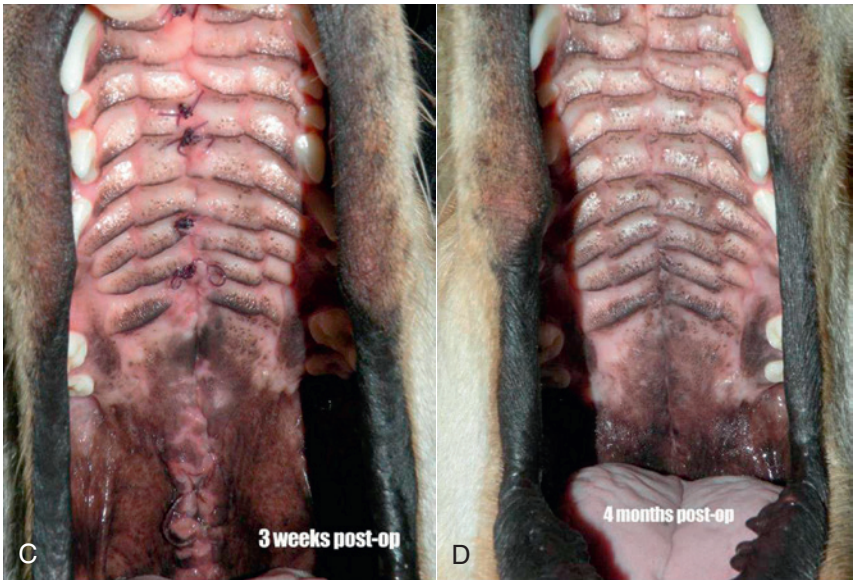


FIG 57.14, cont'd
(C) 21 days postsurgical revision at 14 months of age. **(D)** 4 months postrevision.

TABLE 57.2

Hematologic Values for Growing, Healthy Cats

HEMATOLOGIC PARAMETER	AGE (IN WEEKS)				
	0-2*	2-4*	4-6*	6-8*	8-9*
RBC ($\times 10^6/\mu L$)	5.29 ± 0.24	4.67 ± 0.10	5.89 ± 0.23	6.57 ± 0.26	6.95 ± 0.09
Hemoglobin (g/dL)	12.1 ± 0.6	8.7 ± 0.2	8.6 ± 0.3	9.1 ± 0.3	9.8 ± 0.2
PCV (%)	35.3 ± 1.7	26.5 ± 0.8	27.1 ± 0.8	29.8 ± 1.3	33.3 ± 0.7
MCV (fl)	67.4 ± 1.9	53.9 ± 1.2	45.6 ± 1.3	45.6 ± 1.0	47.8 ± 0.9
MCH (pg)	23.0 ± 0.6	18.8 ± 0.8	14.8 ± 0.6	13.9 ± 0.3	14.1 ± 0.2
MCHC (%)	34.5 ± 0.8	33.0 ± 0.5	31.9 ± 0.6	30.9 ± 0.5	29.5 ± 0.4
Total WBC ($\times 10^3/\mu L$)	9.67 ± 0.57	15.31 ± 1.21	17.45 ± 1.37	18.07 ± 1.94	23.68 ± 1.89
Segmented neutrophils	5.96 ± 0.68	6.92 ± 0.77	9.57 ± 1.65	6.75 ± 1.03	11.00 ± 1.41
Band neutrophils	0.06 ± 0.02	0.11 ± 0.04	0.20 ± 0.06	0.22 ± 0.08	0.12 ± 0.09
Lymphocytes	3.73 ± 0.52	6.56 ± 0.59	6.41 ± 0.77	9.59 ± 1.57	10.17 ± 1.71
Monocytes	0.01 ± 0.01	0.02 ± 0.02	0	0.01 ± 0.01	0.11 ± 0.06
Eosinophils	0.96 ± 0.43	1.40 ± 0.16	1.47 ± 0.25	1.08 ± 0.20	2.28 ± 0.31
Basophils	0.02 ± 0.01	0	0	0.02 ± 0.02	0

MCH, Mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *nRBC/100 WBC*, number of nucleated red blood cells per 100 white blood cells; *PCV*, packed cell volume; *RBC*, red blood cells; *total WBC*, total white blood cell count.

*Normal ranges ± one standard deviation from Meyers-Wallen VN, Haskins ME, Patterson DF: Hematologic values in healthy neonatal, weanling, and juvenile kittens. *Am J Vet Res* 45:1322-1327, 1984.

†Normal ranges from Anderson L, Wilson R, Hay D: Haematological values in normal cats from four weeks to one year of age. *Res Vet Sci* 12:579-583, 1971.

From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

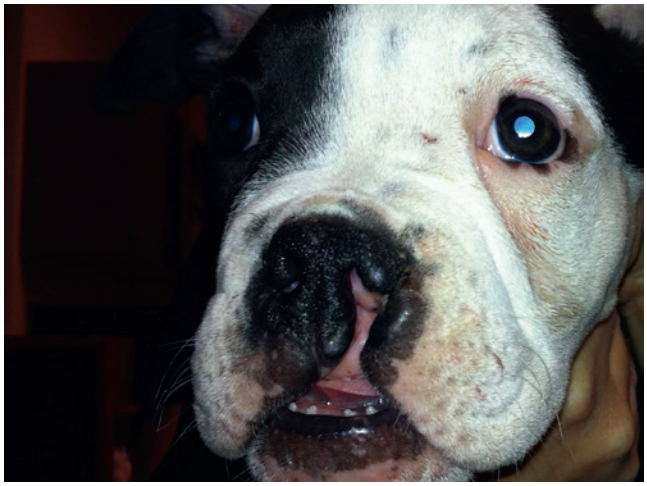


FIG 57.15
Adult Bulldog mix with primary cleft palate; the soft and hard palate were normal.



FIG 57.16
Atresia ani, an anorectal malformation in a 4-week-old Boxer puppy. Abdominomegaly secondary to fecal accumulation was present.

12-13*	16-17*	20†	30†	44†	52†
7.43 ± 0.23	8.14 ± 0.27	7.4 ± 0.7	8.0 ± 0.5	7.9 ± 0.8	7.7 ± 0.8
10.1 ± 0.3	11.0 ± 0.4	10.7 ± 1.2	12.1 ± 1.8	13.0 ± 2.1	13.3 ± 1.8
33.1 ± 1.6	34.9 ± 1.1	33.4 ± 3.3	37.1 ± 3.4	37.3 ± 3.5	36.6 ± 3.6
44.5 ± 1.8	43.1 ± 1.5	45 ± 5.2	46 ± 3.5	47 ± 3.4	47 ± 3.9
13.7 ± 0.4	13.5 ± 0.4				
31.3 ± 0.9	31.6 ± 0.8	32 ± 2.0	33 ± 3.3	34 ± 3.0	36 ± 3.1
23.20 ± 3.36	19.70 ± 1.12	15.9 ± 6.0	21.9 ± 6.8	18.3 ± 7.8	24.0 ± 12.5
11.00 ± 1.77	9.74 ± 0.92				
0.15 ± 0.07	0.16 ± 0.07				
10.46 ± 2.61	8.78 ± 1.06	6.2 ± 2.1	5.3 ± 1.2	6.1 ± 2.0	5.5 ± 2.7
0	0.02 ± 0.02				
1.55 ± 0.35	1.00 ± 0.19				
0.03 ± 0.03	0				

TABLE 57.3

Puppy Biochemical Parameters From Birth to Approximately 8 Weeks of Age

	DAYS 1-3	DAYS 8-10	WEEKS 4-5 DAYS 28-33	WEEKS 7-8 DAYS 50-58
Albumin (g/dL)	1.76-2.75	1.71-2.5	2.17-2.97	2.38-3.22
ALP (U/L)	452-6358	195-768	153-490	153-527
ALT (U/L)	9.1-42.2	4.1-21.4	4.3-17.4	10.3-24.3
Bilirubin (mg/dL)	0.04-0.38	0.01-0.18	0.02-0.15	0.01-0.11
BUN (mg/dL)	29.5-118	29.1-66.7	13.1-46.2	16.8-61.4
Calcium (mg/dL)	10.4-13.6	11.2-13.2	10.4-13.2	10.8-12.8
Cholesterol (mg/dL)	90-234	158-340	177-392	149-347
Creatinine (mg/dL)	0.37-1.06	0.28-0.42	0.25-0.83	0.26-0.66
GGT (U/L)	163-3558	—	—	—
GLDH (U/L)	1.8-17.0	0.2-17.7	1.2-9.0	1.6-7.3
Glucose (mg/dL)	76-155	101-161	121-158	122-159
TP (g/dL)	3.7-5.77	3.26-4.37	3.71-4.81	4.04-5.33
Triglycerides (mg/dL)	45-248	52-220	36-149	39-120
Phosphorus (mg/dL)	5.26-10.83	8.35-11.14	8.66-11.45	8.35-11.14

Adapted from Center SA et al.: Effect of colostrum ingestion on gamma-glutamyltransferase and alkaline phosphatase activities in neonatal pups. *Am J Vet Res* 52(3):499-504, 1991; Kuhl S et al.: Reference values of chemical blood parameters for puppies during the first 8 weeks of life, *Dtsch Tierärztl Wschr* 107:438-443, 2000; Harper EJ et al.: Age-related variations in hematologic and plasma biochemical test results in Beagles and Labrador Retrievers. *J Am Vet Med Assoc* 223(10):1436-1442, 2003.
From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

TABLE 57.4

Puppy Biochemical Parameters Up to 12 Months of Age

	2-3 MONTHS	4-6 MONTHS	7-12 MONTHS
Albumin (g/dL)*	2.6-3.7	2.6-3.7	2.6-3.7
ALP (U/L)	88-532	126-438	4-252
ALT (U/L)	≤29	≤32	5-45
Amylase (U/L)*	≤1683	≤1683	≤1683
AST (U/L)	7-19	3-23	2-26
Bilirubin (mg/dL)	0.01-0.13	0.01-0.13	≤0.3
BUN (mg/dL)*	9.8-37.3	9.8-37.3	9.8-37.3
Calcium (mg/dL)	10.4-13.6	10-13.2	10.4-12
Chloride (mEq/L)*	99-120	99-120	99-120
Cholesterol (mg/dL)	99.6-499.6	99.6-499.6	135-278
CK (U/L)	31-255	40-192	≤134
Creatinine (mg/dL)	0.39-0.49	0.27-0.88	0.21-0.89
GGT (U/L)	≤6.2	≤4.3	≤3.2
Globulins (g/dL)	1.9-2.5	2.2-3.5	2.2-4.5
Glucose (mg/dL)	97.1-166.2	97.1-166.2	76-119
GLDH (U/L)	1.6-9.6	1.9-8.7	1.2-8.0

TABLE 57.4

Puppy Biochemical Parameters Up to 12 Months of Age—cont'd

	2-3 MONTHS	4-6 MONTHS	7-12 MONTHS
LDH (U/L)	68-290	≤442	9-269
Lipase (U/L)	≤241	≤139	≤154
Magnesium (mEq/L)*	1.4-5.2	1.4-5.2	1.4-5.2
Phosphorus (mg/dL)	6.4-11.3	5.6-9.6	3.5-7.8
Potassium (mEq/L)	4.5-6.3	3.9-6.1	4.2-5.6
Sodium (mEq/L)	140-156	139-159	138-158
Total protein (g/dL)	4.3-5.8	4.5-7.3	4.9-6.7
Triglycerides (mg/dL)	19.1-205.5	19.1-205.5	40-169
TLI (µg/L)	5-35		

*Parameters for which significant age variation was not found in puppies.
Adapted from the following source: Harper EJ et al.: Age-related variations in hematologic and plasma biochemical test results in Beagles and Labrador Retrievers. *J Am Vet Med Assoc* 223(10):1436-1442, 2003.
From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

TABLE 57.5

Kitten Biochemical Parameters From Birth to 8 Weeks of Age

				WEEK 4	WEEK 8
	DAY 0	DAY 1	DAY 7	DAY 28	DAY 56
Albumin (g/dL)	2.5-3.0	1.9-2.7	2.0-2.5	2.4-4.9	2.4-3.0
ALP (U/L)	184-538	1348-3715	126-363	97-274	60-161
ALT (U/L)	7-42	29-77	11-76	14-55	12-56
Amylase (U/L)	310-837	310-659	187-438	275-677	407-856
AST (U/L)	21-126	75-263	15-45	15-31	14-40
Bilirubin (mg/dL)	0.1-1.1	0.1-1.6	0.0-0.6	0.0-0.3	0.0-0.1
BUN (mg/dL)	26-45	34-94	16-36	10-22	16-33
Calcium (mg/dL)	9.4-13.9	9.6-12.2	10.0-13.7	10.0-12.2	9.8-11.7
Cholesterol (mg/dL)	65-141	48-212	119-213	173-253	124-221
CK (U/L)	91-2300	519-2654	107-445	125-592	102-1512
Creatinine (mg/dL)	1.2-3.1	0.6-1.2	0.3-0.7	0.4-0.7	0.6-1.2
GGT (U/L)	0-2	0-9	0-5	0-1	0-2
Glucose (mg/dL)	55-290	65-149	105-145	117-152	94-143
LDH (U/L)	176-1525	302-1309	117-513	98-410	62-862
Lipase (U/L)	12-43	21-131	8-46	4-86	6-70
Phosphorus (mg/dL)	5.9-11.2	4.9-8.9	6.7-11.0	6.7-9.0	7.6-11.7
TP (g/dL)	3.8-5.2	3.9-5.8	3.5-4.8	4.5-5.6	4.8-6.5
TS (g/dL)	3.1-4.4	3.2-5.2	3.0-4.6	4.0-6.0	4.1-6.2
Triglycerides (mg/dL)	23-132	30-644	129-963	43-721	16-170

Adapted from Levy JK, Crawford PC, Werner LL: Effect of age on reference intervals of serum biochemical values in kittens. *J Am Vet Med Assoc* 228(7):1033-1037, 2006.
From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

TABLE 57.6

Kitten Biochemical Parameters Up to 12 Months of Age

	<3 MONTHS	4-6 MONTHS	7-12 MONTHS
ALT (U/L)	10-50	≤77	≤85
ALP (U/L)	≤564	37-333	21-197
Amylase (U/L)*	≤1800	1800	≤1800 (≤2200 Oriental breeds)
AST (U/L)	≤20	≤30	≤30 (≤40 Oriental breeds)
Bilirubin (mg/dL)†	≤4	≤4	≤4
BUN (mg/dL)‡	17-35	17-35	17-35
Calcium (mg/dL)*	9.2-12.0	9.2-12.0	9.2-12.0
Chloride (mEq/L)	97-125	102-122	104-124
Creatinine (mg/dL)	0.16-1.26	0.33-1.21	—§
CK (U/L)	≤188	≤160	≤128
GGT (U/L)*	≤4	≤4	≤4
GLDH (U/L)*	≤7	≤7	≤7 (≤16 Oriental breeds)
Glucose (mg/dL)‡	70-150	70-150	70-150
LDH (U/L)	68-280	≤442	9-269
Lipase (U/L)	≤280	≤280	≤280
Magnesium (mEq/L)*	1.2-5.2	1.2-5.2	1.2-5.2
Potassium (mEq/L)	3.7-6.1	4.2-5.8	3.7-5.3
Phosphorus (mg/dL)	6.5-10.1	6-10.4	4.5-8.5
Sodium (mEq/L)*	143-160	143-160	143-160
Total protein (g/dL)#	—	3.3-7.5	3.3-7.5
TLI (µg/L)	17-49¶		

*Parameters for which significant age variation has not been found in kittens.
†Adult values reached after 1 week of age.
‡Adult values reached after 8 weeks of age.
§Reference ranges have not been reported for kittens over 6 months of age; 0.8-2.3 mg/dl (adult).
#Adult levels are reached between 6 months and 1 year of age.
¶Data from Steiner JM: Diagnosis of pancreatitis. *Vet Clin North Am Small Anim Pract* 33:1181-1195, 2003.
Adapted from Kraft W, Hartmann K, Dereser R: Dependency on age of laboratory values in dogs and cats. Part 1: Activities in serum enzymes. *Tierärztl Prax* 23:502-508, 1995; Kraft W, Hartmann K, Dereser R: Age dependency of laboratory values in dogs and cats. Part II: serum electrolytes. *Tierärztl Prax* 24:169-173, 1996; Kraft W, Hartmann K, Dereser R: Age dependency of laboratory values in dogs and cats. Part III: bilirubin creatinine & proteins in serum. *Tierärztl Prax* 24:610-615, 1996.
From von Dehn B: Pediatric clinical pathology. In Davidson AP (ed) Pediatrics. *Vet Clin of North Amer: Small Animal Practice.* 31;44(2):205-219, 2014.

Umbilical hernias can be significant if large enough to permit bowel evisceration and strangulation. More commonly, omentum becomes trapped in a small umbilical hernia in pediatric dogs and cats; closure of the hernia then results in a benign mass effect often alarming to clients. Evaluation of a painful or enlarging umbilical mass with ultrasound permits differentiation of omentum from entrapped bowel, which has a typical enteric appearance.

Omphalitis resulting from bacterial umbilical contamination in the postpartum period places the neonate at risk for bacterial septicemia. The umbilicus should be closed and dry 24 hours postpartum; erythema or drainage indicates antibiotics should be instituted due to the potential for peritonitis (Fig. 57.17, *A*). Excessive umbilical attention by the dam can result in exposure of the subcutaneous (SC) tissues with risk of peritonitis (Fig. 57.17, *B*).

Anasarca, a lethal congenital edema, can occur with concurrent cardiovascular abnormalities. Generalized SC edema, with intrathoracic and intraperitoneal fluid accumulation, are present (Fig. 57.18). Congenital hereditary lymphedema causes edema of the extremities and sometimes head, and is associated with morphologic lymphatic abnormalities.

Incompletely developed immune systems during the first 10 days of life make neonates vulnerable to systemic infection (most commonly bacterial and viral). Adequate ingestion of colostrum must occur promptly postpartum for neonates to acquire passive immunity, as transplacental transfer is <5%. The intestinal absorption of immunoglobulin (IgG)

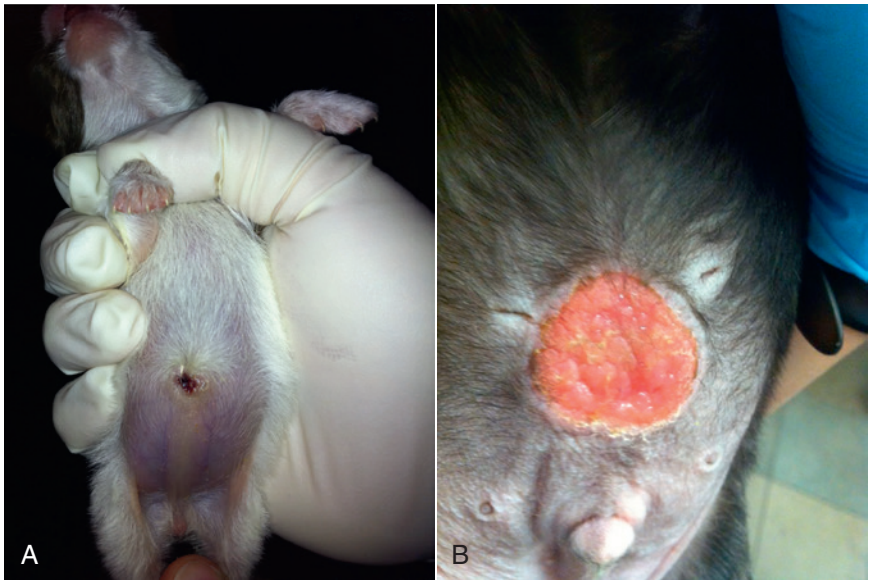


FIG 57.17
(A) Erythemic, moist umbilicus suggesting omphalitis. **(B)** Excoriation of the umbilicus secondary to excessive maternal grooming.



FIG 57.18
Littermates, low birth weight neonate on the left.

generally ceases by 24 hours after parturition. Colostrum-deprived canine neonates should be given 100 mL/kg (0.10 mL/gram) of serum from an immunocompetent adult to achieve adequate IgG levels. Kittens should receive 150 mL/kg (0.15 mL/gram). Blood typing is important with cats. The serum can be given orally if within the first 24 hours of life, otherwise it must be given parenterally, preferably subcutaneously, divided with both routes (Levy et al., 2001; Poffenbarger et al., 1991). Neonates should be encouraged to suckle promptly after resuscitation is completed; this usually necessitates close monitoring after a cesarean section, because the dam is still groggy from anesthesia.

FADING NEONATES

Neonatal bacterial septicemia can cause rapid deterioration resulting in death if not recognized and treated promptly. Factors that reportedly predispose a neonate to septicemia include endometritis in the dam, prolonged delivery/dystocia, feeding of replacement formulas, use of ampicillin, stress, low birth weight (<350 g for a medium-size breed of puppy, <100 g for a kitten), and chilling (body temperature <96° F) (see Fig. 57.18). The organisms most frequently associated with septicemia are *E. coli,* streptococci, staphylococci, and *Klebsiella* spp. Umbilical contamination is the most likely route of entry. Omphalitis leads to peritonitis, bacteremia, and pneumonia. Abscessation can occur later at other sites (Fig. 57.19). Premortem diagnosis can be challenging; clinical signs may not be noted owing to sudden death. Commonly, a decrease in weight gain, failure to suckle, hematuria, persistent diarrhea, unusual vocalization, abdominal distention and pain, and sloughing of the extremities indicate septicemia may be present. Prompt therapy with broad-spectrum bactericidal antibiotics; improved nutrition via supported nursing, tube, or bottle feeding; maintenance of body temperature; and appropriate fluid replacement are indicated. The third-generation cephalosporin antibiotic ceftiofur sodium (Naxcel [Upjohn]) is an appropriate choice for neonatal septicemia. It minimally alters normal intestinal flora and is usually effective against the causative organisms. Ceftiofur sodium should be administered at a dose of 0.0025 mg/gram SC q12h for no longer than 5 days. Because neonates less than 48 hours old have reduced thrombin levels, presumptive therapy with vitamin K_1 may be used



FIG 57.19
Neonatal ophthalmia; accumulation of purulent fluid under the eyelid of a 7-day-old neonate likely secondary to bacteremia.

(0.01-1 mg SC per neonate). The prognosis is guarded but not hopeless.

Incompatible blood types of the parental cats have recently been implicated as a cause of feline neonatal mortality. This incompatibility arises when queens with Type B blood give birth to kittens who inherited the sire's blood Type A. Type B is rare in mixed breed and Siamese cats but is much more common in certain purebreds such as British Shorthair and Devon Rex cats. Type B cats have naturally occurring anti-A antibodies. When the kittens nurse and absorb these antibodies, the kittens' own red blood cells are hemolyzed, leading to anemia and organ failure. The clinical course is determined by the severity of the hemolytic reaction. In all cases, the kittens are born healthy and nurse vigorously. Some kittens may die suddenly in the first day, whereas others linger longer and fade during the first week of life. Clinical neonatal isoerythrolysis (NI) is suggested by pale mucous membranes and dark red-brown urine, and is confirmed by documenting hemolytic anemia and the blood types of the parents. If NI is suspected, the kittens are removed from the queen and fostered on a Type A queen or bottle-fed for the first 2 days of life. NI can be avoided in catteries by testing the blood types of breeding animals and avoiding matings of Type B queens with Type A toms.

Canine herpes virus (CHV) is a commonly blamed cause for fading puppy syndrome resulting in neonatal death (see Chapter 55). Premortem diagnosis of CHV infection in neonates can be challenging. Postmortem diagnostics include appropriate histopathology, virus isolation, or PCR. Pathognomonic changes occurring in the kidneys include multifocal petechial hemorrhages, although this can be seen with bacterial septicemia and associated thromboembolic disorders as well. Intranuclear inclusion bodies can be difficult to find. Diagnosis by virus isolation or CHV-specific PCR is confirmatory and desirable, especially before litter mortality reaches 100%. Until recently, treatment of CHV infection in neonates has been reported to be unrewarding and rare, with recovery suspected to be associated with residual cardiac and neurologic damage. Treatment with immune serum from affected dams is reported to be ineffective in infected puppies. Successful treatment with the antiviral agent acyclovir (Zovirax [Novopharm]) has been reported (Davidson et al., 2003). Acyclovir is an antiviral agent with activity against a variety of viruses including herpes simplex. Acyclovir is preferentially taken up by susceptible viruses and converted into the active triphosphate form, inhibiting viral DNA replication. Acyclovir is poorly absorbed after oral administration and is primarily hepatically metabolized. Acyclovir can increase the toxicity of nephrotoxic drugs. The half-life in humans is approximately 3 hours. Its use in veterinary medicine is not well established, and it should be used with caution and only in situations where indicated. The safety and effectiveness in humans younger than 2 weeks of age is not established. The dose was extrapolated from that for humans (20 mg/kg by mouth [PO] q6h × 7 days).

ORPHANS' SPECIAL NEEDS

Kittens and puppies under 3 weeks of age lack voluntary elimination and must have the micturition and defecation reflexes stimulated multiple times daily using a cotton ball with mineral oil on the anogenital area. Sibling suckling secondary to the lack of normal nursing can cause dermatologic lesions; separation of the neonates in an orphaned litter may be necessary until solid food is introduced. Neonates have minimal body fat reserves and limited metabolic capacity to generate glucose from precursors. Glycogen stores are depleted shortly after birth, making adequate nourishment from nursing vital. Even minimal fasting can result in hypoglycemia. Hypoglycemia can also result from endotoxemia, septicemia, portosystemic shunts (PSS), and glycogen storage abnormalities. Oral fluid and glucose replacement may be preferable if the neonate has an adequate swallowing reflex and is not clinically compromised. The neonatal caloric requirement is 133 cal/kg/day during the first week of life, 155 cal/kg/day for the second, 175 to 198 cal/kg/day for the third, and 220 cal/kg/day for the fourth. Bottle or intermittent esophageal tube feeding must be commenced until weaning (Fig. 57.20). Commercially manufactured milk replacement formulas are usually superior to homemade versions, but none are equal to the dam's milk (Heinze et al., 2014). The use of milk obtained from the dam should be considered and is superior if available. Most replacement formulas lack appropriate calcium, amino acids, and essential fatty acids. An osmotic diarrhea (usually yellow, curdled fecal appearance) can result from overfeeding formula; constipation can also occur necessitating diluting the product

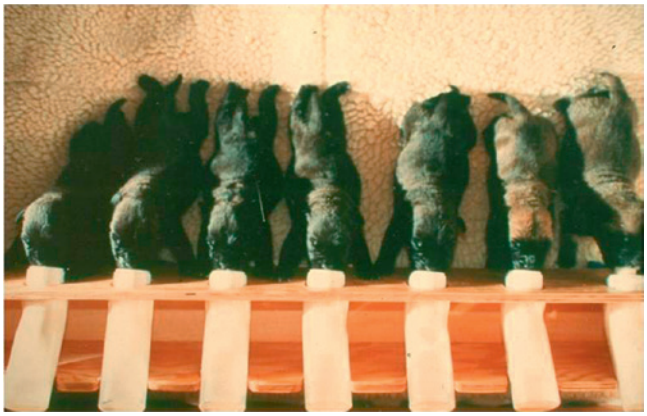


FIG 57.20
Bottle-feeding apparatus, Bull Mastiff litter.



FIG 57.21
Esophagram, 14-day-old neonate with regurgitation of milk through the nares. Congenital megaesophagus.

25% to 50% with water or a balanced crystalloid solution. Neonates should gain weight steadily from the first day after birth (a transient mild loss from birth weight is acceptable on day 1), with puppies gaining 1 to 3 g/day/lb (2.2 kg) of anticipated adult weight and kittens 50 to 100 g/wk. Neonatal weights should be recorded daily for the first 2 weeks, then every 3 days until 1 month of age. Healthy, well-nourished neonates are quiet and sleep when not nursing. The normal neonatal weight gain is an increase of 5% to 10% body wt/day. The limited size of neonatal stomach, and propensity for regurgitation/aspiration if overdistension from overfeeding occurs, necessitates multiple small feedings around the clock. Most commercial milk replacers deliver approximately 1.0 kcal/mL; maximum comfortable stomach capacity approximates 4 mL/100 g body weight.

PEDIATRIC SYSTEMIC ABNORMALITIES

Cardiovascular Disorders

Ventricular septal defects, mitral valve disorders, and arteriovenous fistulas are the most common congenital cardiac defects. Cardiac defects can arise from environmental stress, infection, or intoxication of the dam; however, the heritability of many has been documented. Clinical signs are often not apparent until after weaning, although affected neonates may not be as vigorous as normal littermates. Accurate cardiac auscultation should be possible at and after 6 to 8 weeks of age; echocardiography is the preferred mode of evaluation once adequate pediatric size is attained, usually at 3 to 4 months of age.

Respiratory Disorders

Primary ciliary dyskinesia, the rare immotile cilia syndrome, should be suspected in neonates exhibiting persistent or recurrent mucopurulent nasal discharge, coughing, and abnormal breath sounds without other demonstrable cause. The presence of a cleft palate, persistent right aortic arch, and congenital megaesophagus should be ruled out (Fig. 57.21). Abnormal mucociliary transport and neutrophil function result in chronic rhinitis, tracheobronchitis, and bronchopneumonia. Situs inversus can also be present. The long-term prognosis, even with supportive therapy, is poor. Neonatal dyspnea with evidence of gastrointestinal disorders can occur secondary to congenital peritoneopericardial or pleuroperitoneal diaphragmatic hernias. Thoracic wall abnormalities, such as pectus excavatum, a sternal intrusion into the thorax, can cause dyspnea and is variably associated with poor growth. Surgical correction of thoracic wall abnormalities is indicated if the neonate is symptomatic once adequate body size is attained. Reports of a neonatal respiratory distress syndrome secondary to a deficiency of surfactant exist; affected neonates died within 5 days of age. Surfactant deficiency secondary to prematurity is predictably problematic. Proper timing of elective cesarean sections is vital to avoid premature delivery of surfactant deficient neonates. The administration of corticosteroids to term pregnant bitches does not result in the formation of surfactant (Sipriani et al., 2009). Radiography of the term pregnant bitch should permit visualization of fetal dentition (Fig. 57.22).

Musculoskeletal Disorders

Neonates can be born with hind limb hyperextension of unknown etiology; because their joints are lax, simple bandaging in a flexed position for 2 to 3 days can resolve the condition (Fig. 57.23). Puppies with noticeable flattening of the sternum at 3 to 4 weeks of age are called "swimmer puppies" by breeders. Swimmer puppies fail to develop normal stepping ambulation at 14 to 21 days of life, moving instead by paddling their limbs laterally and caudally. Compression and deformation of the sternum and thorax occurs concurrently (Fig. 57.24, *A*). Obese puppies from small litters, raised on slippery surfaces, are predisposed. Treatment should be instituted immediately upon diagnosis, consisting



FIG 57.22
Lateral radiograph of term pregnant bitch. Arrow indicates mineralized fetal dentition.



FIG 57.23
Cocker Spaniel neonate with pelvic limb hyperextension; cardboard tube keeps the pelvic limbs in flexion.









FIG 57.24
(A) "Swimmer puppy" showing flattened sternum and box-shaped thorax.
(B) Lateral view of pelvic limb hobble.
(C) Ventral view of forelimb hobbles.
(D) Dorsal view of forelimb hobbles. Gait improvement was seen after 5 days in the hobbles.

of caloric restriction, physical therapy, and improved traction in the nest box. Placement of loose hobbles helps control limb movements and promotes normal ambulation within days (Fig. 57.24, *B*, 57.24, *C*, 57.24, *D*). The prognosis for swimmer puppies treated before 4 to 5 weeks of age is good.

Urogenital Disorders

Dysuria, urinary incontinence, or hematuria/pyuria can accompany neonatal urogenital disorders. The presence of a persistent urachus causes micturition through the umbilicus. Urachal diverticula can predispose the bladder to recurrent infection because of abnormal urine flow in the region; surgical excision is indicated. The diagnosis is confirmed with ultrasound (Fig. 57.25, *A*, 57.25, *B*). Renal dysplasia is a heritable problem in several canine breeds; ultrasound can identify the typical marked morphologic abnormalities in puppies at 6 to 8 weeks of age in breeds at risk (Fig. 57.26) Congenital renal polycystic disease of brachycephalic cats can similarly be identified with ultrasound in 8- to 12-week-old kittens (Fig. 57.27). Until reliable genetic markers are available for the various breed-specific congenital renal dysplasias, ultrasound provides the best method of screening young dogs and cats for these disorders; clinical signs are usually not present until early adulthood when uremia develops. Neonatal urolithiasis, with or without associated urinary tract infection, can cause outflow obstruction and

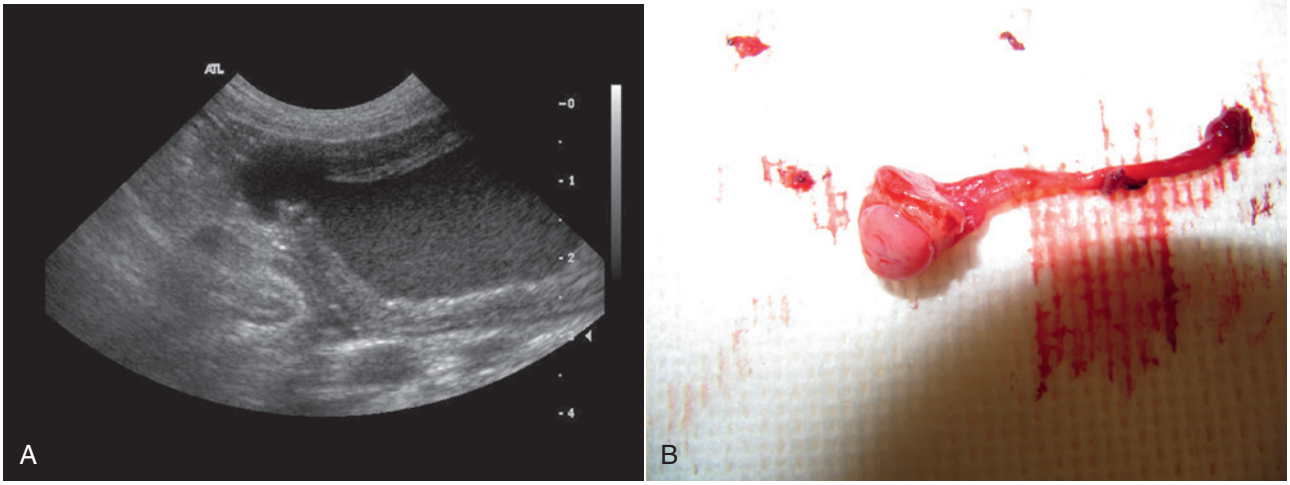


FIG 57.25
(A) Sagittal ultrasound image of a urachal diverticulum at the apex of the urinary bladder. **(B)** Gross specimen, urachal diverticulum and patent urachus. (Image courtesy T.W. Baker.)

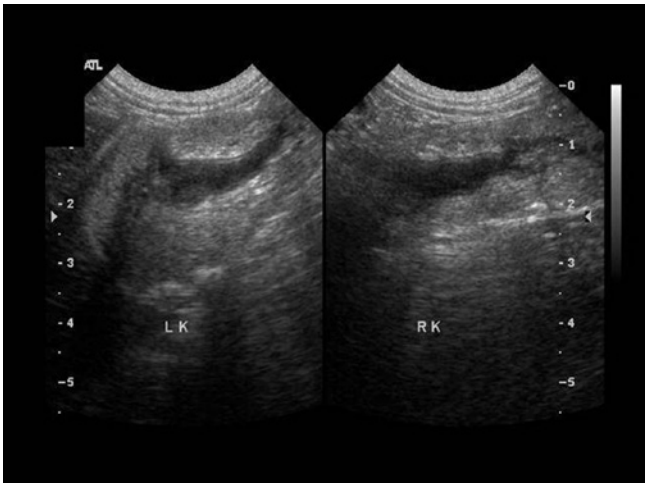


FIG 57.26
Sagittal ultrasound image of congenital canine renal dysplasia. Note the lack of normal renal morphology; the corticomedullary interface is not well defined. (Image courtesy T.W. Baker.)

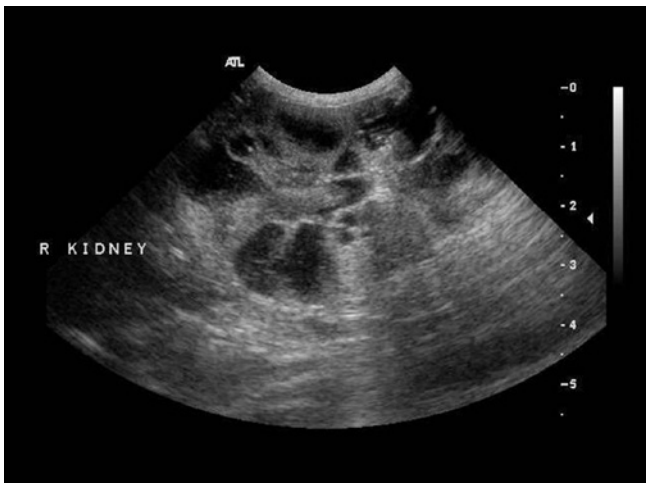


FIG 57.27
Transverse ultrasound image of feline polycystic renal disease; numerous parenchymal cysts are evident. The renal papilla is evident in the center of the image. (Image courtesy T.W. Baker.)

signs of acute abdominal pain. Lower urinary tract infection in neonates has the potential for ascending and causing pyelonephritis if not detected and controlled, making ultrasound-guided cystocentesis preferable when acquiring urine from pediatric patients with signs of lower tract disease.

Ectopic ureters can cause incontinence during the postpartum period; clinical signs are most evident after weaning when the dam is no longer cleaning the puppy. An ectopic ureter is defined as one which distally enters the genitourinary tract in any location other than the trigone of the bladder. Ectopic ureters are the most common cause of urinary tract infection in young dogs. Breeds reported to be at risk include the Golden Retriever, Labrador Retriever, Siberian Husky, Newfoundland, and English Bulldog. The condition should be considered heritable. Ectopic ureters are uncommon in male dogs and, if present, these animals often do not have clinical signs. This fact could be due to the increased length of the urethra in male dogs. Ectopic ureters are extremely rare in cats. Ectopic ureters can be intramural (tunnel along the bladder wall) or extramural (independent of the bladder wall) with the former being far more common in dogs.

A diagnosis of ectopia can be made by excretory urography, fluoroscopic urethrography or ureterography, abdominal ultrasonography, cystoscopy, helical computed tomography, or a combination of these diagnostic procedures. Other congenital abnormalities can also occur in dogs with ectopic ureters, including but not limited to renal agenesis or dysplasia, and hydronephrosis and/or hydroureter; therefore, it is essential to evaluate the entire urinary system using ultrasonography if cystoscopy is the only other diagnostic utilized before surgery. Accompanying urethral sphincter mechanism anomalies are commonly present in dogs with ectopia, making the prognosis for complete resolution of incontinence after resolution of the ectopic ureter guarded. Visualization of a nonvascular fluid-filled structure with a hyperechoic wall passing dorsal to the urinary bladder or obvious insertion of the structure into the proximal urethra suggest the diagnosis (Fig. 57.28, *A*, 57.28, *B*). Visualization of distinct ureteral walls, which contain smooth muscle and display pulsatile motion, supports ureteral abnormalcy such as ectopia (Video 57.3). Hydroureter and hydronephrosis can eventually result from an uncorrected ectopic ureter due to flow impedance at the abnormal site of insertion (Fig. 57.28, *C*). Urinary tract infection is commonly associated with ectopia due to urinary stasis in part of the tract and, if not detected and treated, can progress to pyelonephritis and ureteritis causing permanent

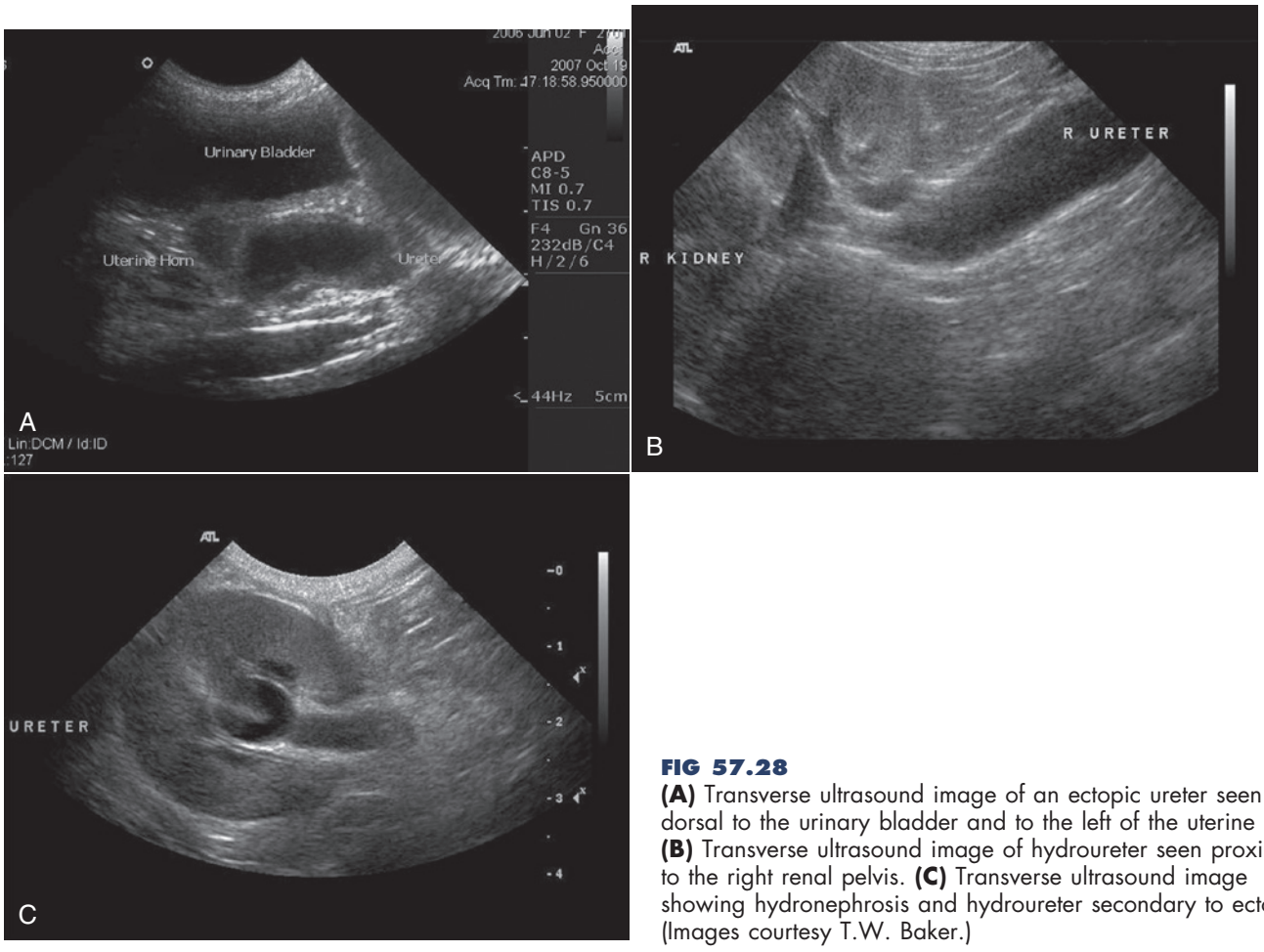


FIG 57.28
(A) Transverse ultrasound image of an ectopic ureter seen dorsal to the urinary bladder and to the left of the uterine horn. **(B)** Transverse ultrasound image of hydroureter seen proximal to the right renal pelvis. **(C)** Transverse ultrasound image showing hydronephrosis and hydroureter secondary to ectopia. (Images courtesy T.W. Baker.)

damage to the urinary tract. Traditionally, treatment for dogs with ureteral ectopia is surgical correction (revision), and postoperative success rates vary between 50% to 75%. It has been reported that dogs weighing <20 kg have a better outcome postoperatively. Minimally invasive therapies have also been utilized in dogs with ectopic ureters such as cystoscopic-guided laser ablation for the ectopic ureter (Fig. 57.29, Video 57.4). Nephrectomy is reserved for advanced cases with irreversible renal damage ipsilaterally and normal function contralaterally, or cases with severe financial constraints. Removal of affected individuals from breeding programs and avoidance of similar pedigrees in breeding should always be discussed with the owners. Ongoing studies exist evaluating the mode of inheritance. Postoperative persistent incontinence can be managed in many cases pharmacologically with the α-adrenergic stimulant phenylpropanolamine (1.0-1.5 mg/kg PO q8-12h), or estrogen compounds that increase sensitivity of α-adrenergic receptors in the urethra (compounded diethylstilbestrol, DES, at 0.02 mg/kg PO tapered to 1-3 times weekly or estriol (Incurin [Merck] 2 mg PO daily for 14d then tapered). Time-released phenylpropanolamine is more effective than short-acting phenylpropanolamine in refractory cases of incontinence. Combination therapy with phenylpropanolamine and an estrogen compound can be superior if either fails when used as a single agent. Gonadotropin-releasing hormone (GnRH) analogues recently have been shown to improve continence in ovariectomized female dogs, most likely through interaction with GnRH, FSH, and LH receptors in the lower genitourinary tract (Reichler et al., 2003). A postoperative urine culture should always be determined before assuming that persistent incontinence is due to residual anatomic abnormalities.

Female puppies presented with mucopurulent vulvar discharge should be evaluated for the benign condition called "puppy vaginitis", a misnomer as it is not an inflammatory condition. The discharge can be accompanied by mild perivulvar dermatitis. The puppy is not typically attentive to the discharge, and there is not any associated change in urinary behavior (dysuria or polakiura). Clients often have a difficult time deciding if a puppy has normal urinary behavior or not. The age of onset ranges from 6 weeks to puberty, the duration runs days to months, and the disorder is often intermittent. Cytologic examination of the discharge is suppurative. Vaginal cultures (aerobic) generally fail to grow anything but normal flora in small mixed numbers. Similar organisms could be cultured from a littermate without signs. A urinalysis, acquired by cystocentesis, is characteristically normal (a decreased urine specific gravity is typical for young dogs lacking adult concentrating abilities), and urine culture, if performed, is negative. The clinician needs to perform enough diagnostics to rule out more significant causes of vulvar discharge and feel comfortable with the diagnosis of benign puppy vaginitis. Important rule-outs (some of which are associated with inflammation) include urinary tract infection, urine scalding, perivulvar dermatitis, redundant dorsal vulvar folds, the onset of the initial estrous cycle, vaginal foreign bodies (i.e., foxtails), and urogenital anatomic anomalies (ectopia, disorders of sexual differentiation, significant strictures distal to the urethral papilla). The specific etiology of puppy vaginitis is unknown. An imbalance of juvenile vaginal glandular epithelium is postulated. The condition is reported in the literature to resolve both with puberty and with ovariohysterectomy, two very different events endocrinologically, therefore neither is likely to truly cause resolution. Puppy vaginitis diminishes with maturity. Cleansing the perivulvar area with gentle antiseptic wipes is advised. There is no association between puppy vaginitis and adult chronic vaginitis or urinary incontinence postovariohysterectomy.

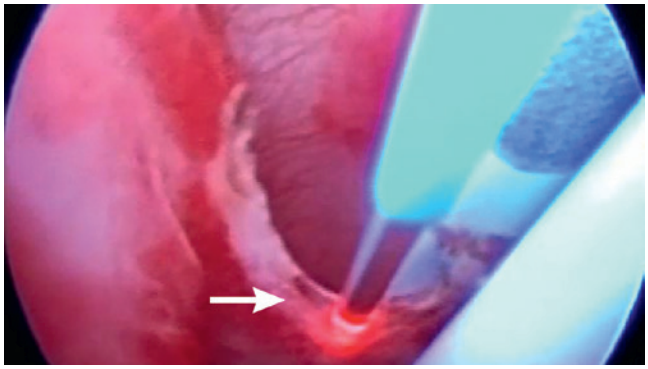


FIG 57.29
Laser ablation (*arrow*) of the bladder mucosa creating an opening for an intramural ectopic ureter.

Gastrointestinal Disorders

Pediatric patients should be presumptively dewormed at 2, 4, and 6 weeks of age for parasites (roundworms) acquired via transplacental transmission. In endemic regions, *Neospora caninum,* Babesiosis, Leishmaniasis, and Dirofilarial microfilariae can also be transmitted transplacentally. Transmammary transmission and environmental contamination with parasites can continue postpartum. Repeated deworming (every 2 weeks) is required because of this and because of the parasites' life cycles. Fecal evaluation should follow completion of routine anthelmintics at 7 to 8 weeks of age, usually when the puppy has been transferred to its new owner and veterinarian. Abnormal stools at any age should prompt a fecal parasite evaluation. Clinically significant endoparasitisms of young dogs and cats include roundworms (*Toxocara canis, Toxocara cati, Toxascaris leonina),* hookworms *(Ancylostoma caninum, Ancylostoma tubeforme, Uncinaria stenocephala),* tapeworms *(Dipylidium caninum, Echinococcus granulosus, Taenia spp.), Strongyloides stercoralis*, and protozoal organisms such as coccidia (*Isospora spp*.), *Cryptosporidium parvum*, and *Giardia sp*. Clinical signs are variable and range from asymptomatic to life-threatening; most common clinical signs include diarrhea, weight loss, or failure to gain. *Ancylostoma caninum* can be associated with severe hemorrhagic enteritis and anemia in puppies. Diagnosis of endoparasitic infestations is most commonly made by fecal flotation, and centrifugation techniques may improve

diagnostic accuracy. *Strongyloides stercoralis* may be demonstrated by either the Baermann flotation technique or observation of larvae in fresh fecal smears. Giardia infections can be diagnosed by observation of motile trophozoites in fresh fecal smears or by detection of cysts using a zinc sulfate fecal flotation; however, a more recently developed fecal ELISA test that detects Giardia antigen is the preferred diagnostic test.

Parasitic infections also reach pathogenic levels in kittens in the first month of life. Coccidia infection, which may be inapparent in adults, can cause severe diarrhea and malnutrition, resulting in rapid weight loss, hypoglycemia, and dehydration. Coccidia are highly contagious and survive in the environment despite extensive decontamination efforts. Coccidia infection is readily diagnosed by fecal floatation and should be considered in kittens that develop diarrhea in this age range or older. Treatment is with sulfadimethoxine (50 mg/kg PO first day, then 25 mg/kg PO every day for 5-20 days until asymptomatic and fecal flotation negative), which is coccidiostatic, not coccidiocidal. Recovery from coccidia infection requires an intact immune response, so treatment failures can often be traced to concurrent immunosuppressive conditions such as malnutrition, overcrowding, and poor hygiene. If coccidiosis is diagnosed in a group of cats, all of the animals should be treated. Ascariasis (round worms) also becomes significant in this age group, and large worm burdens can lead to malnutrition and poor growth.

Because maternally acquired ascaridiasis is so common, all puppies and kittens should receive routine deworming treatments with pyrantel pamoate (10 mg/kg orally, repeated in 2 weeks), regardless of fecal test results. Control of many helminth infections can be easily accomplished by monthly administration of combined anthelmintic and heartworm preventative, for example, ivermectin plus pyrantel pamoate. Treatment of Dipylidium infections must include adequate flea control as well as an appropriate anthelmintic such as praziquantel. Coccidial infections are treated with sulfa-containing drugs such as sulfadimethoxine or trimethoprim sulfa; although very frequently diagnosed and treated in the clinical setting, most canine coccidial infections are likely self-limiting. Fenbendazole is the recommended treatment for Giardia infection (50 mg/kg PO q24h for 3-7 days); although metronidazole is commonly used, it is proven less effective than fenbendazole and has greater potential for side effects in immature animals. A Giardia vaccine is also available, and it has been suggested that it may be effective in clearing refractory infections; however vaccination against Giardia failed to decrease incidence of diarrhea associated with giardiasis in one field study (Payne et al., 2002).

Diarrhea not associated with endoparasitism is not uncommon in pediatric patients after weaning; overfeeding with consequential bacterial overgrowth syndrome is the most common cause. Decreasing the amount fed, sometimes with a short course of antibiotics (amoxicillin), is effective. Infectious agents associated with diarrhea in young dogs and cats are typically either bacterial or viral. Viral infections in dogs include *canine parvovirus, canine distemper, coronavirus,* and *rotavirus,* whereas *parvovirus (Feline Panleukopenia), coronavirus,* and *retroviruses (FeLV, FIV)* are important in young cats. Bacterial organisms responsible for neonatal diarrhea can include *Salmonella spp., Escherichia coli, Clostridium spp., Yersinia enterocolitica,* and *Campylobacter spp*. Diagnosis in most patients is usually uncomplicated, and is based on typical clinical signs, serology, or demonstration of virus in feces, or specialized fecal cultures for certain bacterial organisms. It is often best to run tests for these disorders at the same time through the use of a "fecal diagnostics panel" now available at many commercial laboratories. A single fecal sample is submitted to the lab, and tests for each of these disorders are done at the same time (commonly immunologic tests and PCR tests) (see Chapter 27).

Several breeds of dogs have a reported genetic predilection to small intestinal disease. Normally, the small bowel appears sonographically as four distinct layers (Fig. 57.30, *A*, 57.30, *B*). The bowel lumen is hyperechoic, as gas and ingesta are compressed. The layer just outside the lumen is the mucosa; it is hypoechoic and normally the thickest appearing section. Outside the mucosa is the submucosa; it is hyperechoic to the mucosa and about one third the thickness. The muscularis, the bowel muscle layer, is outside of the submucosa and appears as a very thin hypoechoic black line. Reactive mesenteric lymph node enlargement is common in puppies (Fig. 57.30, *C*) An immunoproliferative enteropathy is seen in the Basenji breed, which is characterized by lymphangectasia, intermittent diarrhea, weight loss, hypoalbuminemia and hyperglobulinemia, and lymphoplasmacytic mucosal infiltrates throughout the gastrointestinal tract. Histopathology is diagnostic; however, abdominal ultrasonography can identify bowel in which disruption of the normal layering has occurred. Chinese Sharpei dogs have been identified with a lymphoplasmacytic-eosinophilic infiltrative enteropathy characterized by poor weight gain, weight loss, or intermittent diarrhea episodes, with onset of signs typically between 2 to 6 months of age. Infiltrative enteropathies can be characterized ultrasonographically as having changes in the normal bowel wall layering.

PSS are congenital malformations of the hepatic portal venous drainage system and can have either a familial (i.e., genetic) or random occurrence. Congenital PSS can be either intrahepatic or extrahepatic; breed predilections for extrahepatic shunts include Yorkshire Terrier, Maltese, Poodle, Miniature Schnauzer, Dachshund, Lhasa Apso, Pekingese, Pug, and Shih Tzu, whereas intrahepatic shunts are more commonly identified in large breed dogs such as Golden Retrievers, German Shepherds, Irish Wolfhounds, Irish Setters, and Samoyeds. PSS are uncommon in cats. Ultrasonography provides a rapid and noninvasive method for screening patients suspected to have congenital PSS. It is noninvasive and requires no anesthesia, however diagnostic accuracy is highly operator-dependent, and the PSS will be confirmed in only approximately 60% to 80% of cases. The liver may be small and difficult to image in patients with congenital PSS. Imaging the liver from the standard ventral approach can be

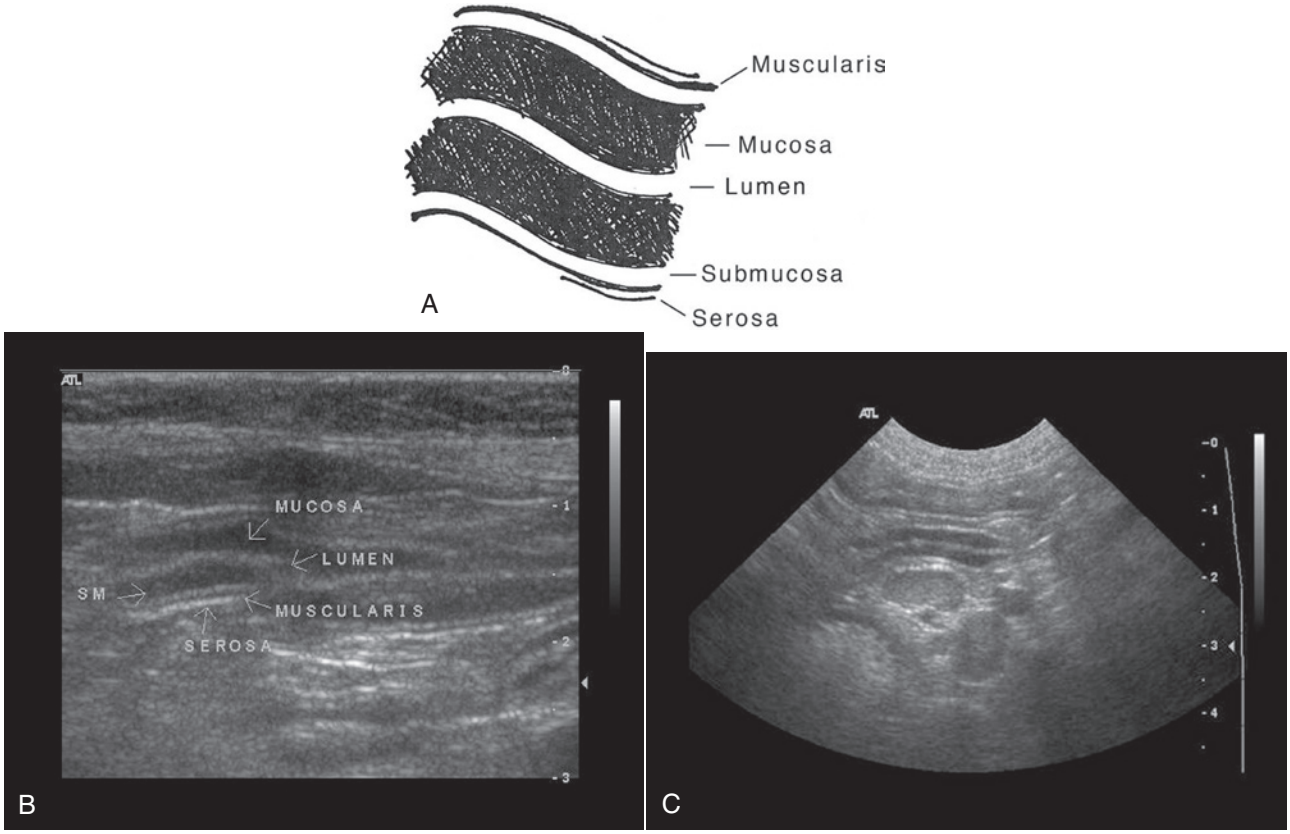


FIG 57.30
(A) Schematic of normal small bowel wall layering. The normal mucosa is the thickest layer, the submucosa less thick, and the muscularis thinner; the serosa is the thinnest layer. **(B)** Sagittal ultrasound image of small bowel with thick (normal) mucosa, less thick submucosa (SM), thin muscularis, and thinner bright serosa. **(C)** Transverse ultrasound image of sublumbar lymph nodes in the pediatric dog. Note the nodes have homogenous parenchyma and would be considered normal. (Courtesy T.W. Baker.)

improved in some cases by using the left ventral intercostal and right dorsal intercostal approaches (Fig. 57.31, *A*, 57.31, *B*, Video 57.5). The presence of ascites can facilitate the study, as can adding fluid to the stomach and positioning the patient to shift gas away from the scan head and shift abdominal organs caudally. Although scintigraphy (transcolonic portal scintigraphy or transplenic portography) is considered the most reliable noninvasive method of documenting a PSS, its availability is limited to specialty and university practices, and its use dictates special handling of the radioactive patient for at least 12 hours. Mesenteric portography, although more invasive and requiring general anesthesia, is a highly reliable method of confirming and localizing a PSS. Management is dictated by the shunt characteristics (see Chapter 27).

Intussusception is not uncommon in young dogs and cats, occurring most frequently at the ileocecocolic junction in dogs and in the jejunum in cats. Pediatric patients are prone to intussusception because they lack the intrinsic enteric neural mechanisms for aboral motility present in adult animals; instead, gastrointestinal motility is pressure-dependent and based on the sequential ingestion of food. Fasting or vomiting result in ileus and increase the risk of intussusception.

The classic transverse ultrasonographic appearance of intussusception is a multilayered series of concentric rings representing the invaginated bowel wall layers; the outer layer can be edematous (hypoechoic) and the inner layers more normal in appearance (Fig. 57.32, *A*, 57.32, *B*, 57.32, *C*, Video 57.6) Discomfort is typically displayed with abdominal palpation or when scan head pressure is placed over the affected area of bowel. Doppler evaluation of the bowel and associated mesenteric vessels can provide information about bowel viability. Serial examinations are important when evaluating the pediatric patient with a palpable abdominal mass, unanticipated clinical deterioration, or increased abdominal pain. If an intussusception is diagnosed in the pediatric veterinary patient in a timely fashion, reduction rather than resection might be possible.

Neurologic Disorders

Neonatal neurologic disorders can be inherited, or can result from intrauterine teratogens or trauma during parturition. Cerebral damage from resuscitation has been reported (see

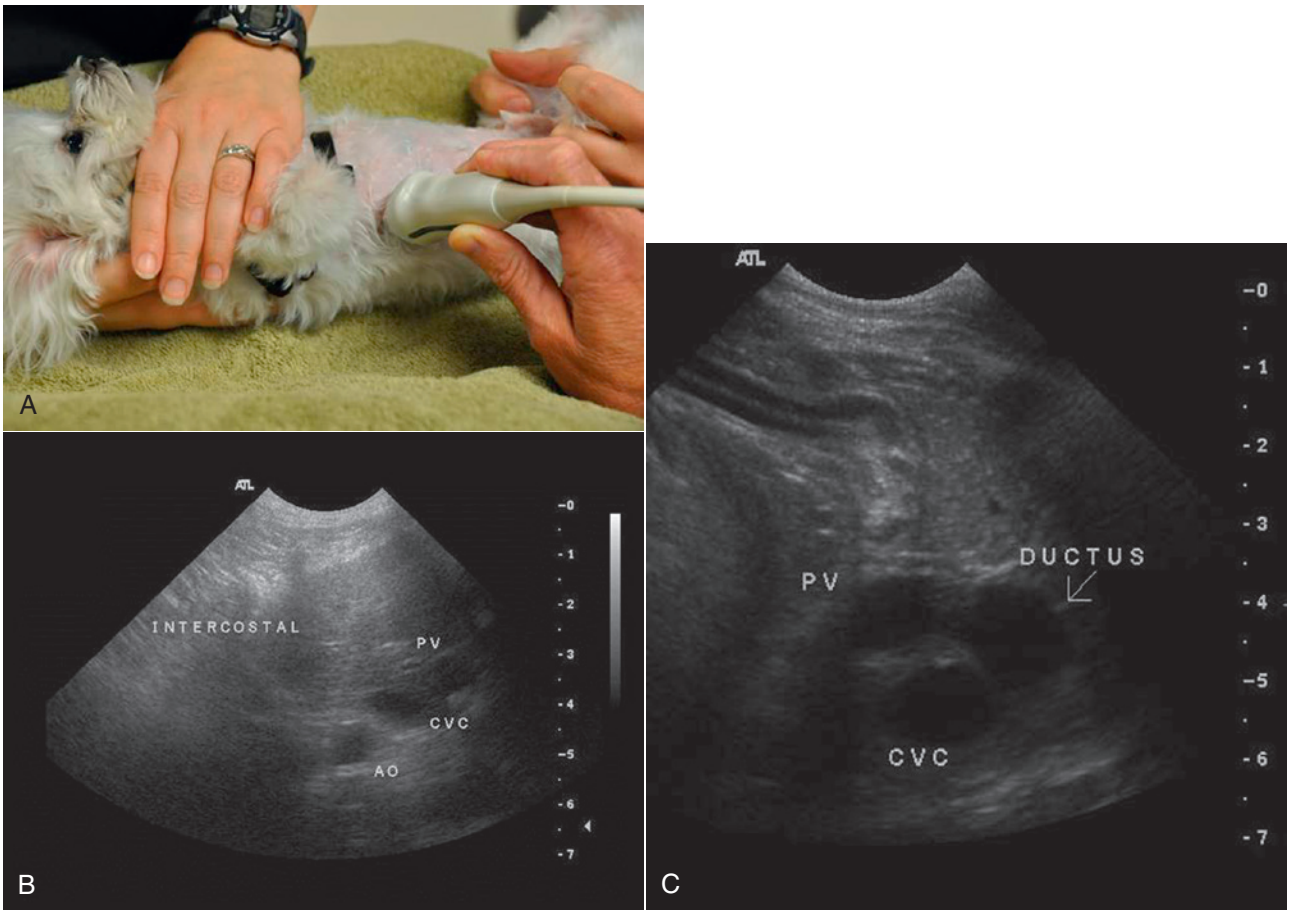


FIG 57.31
(A) Right dorsal intercostal approach to the portal triad, helpful in evaluation of small puppies for portosystemic abnormalities. **(B)** Intercostal ultrasound image showing stacking of vessels; normal anatomy. *AO*, Aorta; *CVC*, caudal vena cava; *PV*, portal vein. **(C)** Intrahepatic portosystemic shunt *(arrow)*. The shunt is identified between the portal vein *(PV)* and caudal vena cava *(CVC)*. *DUCTUS*, Portocaval anomaly. (Image courtesy T.W. Baker.)

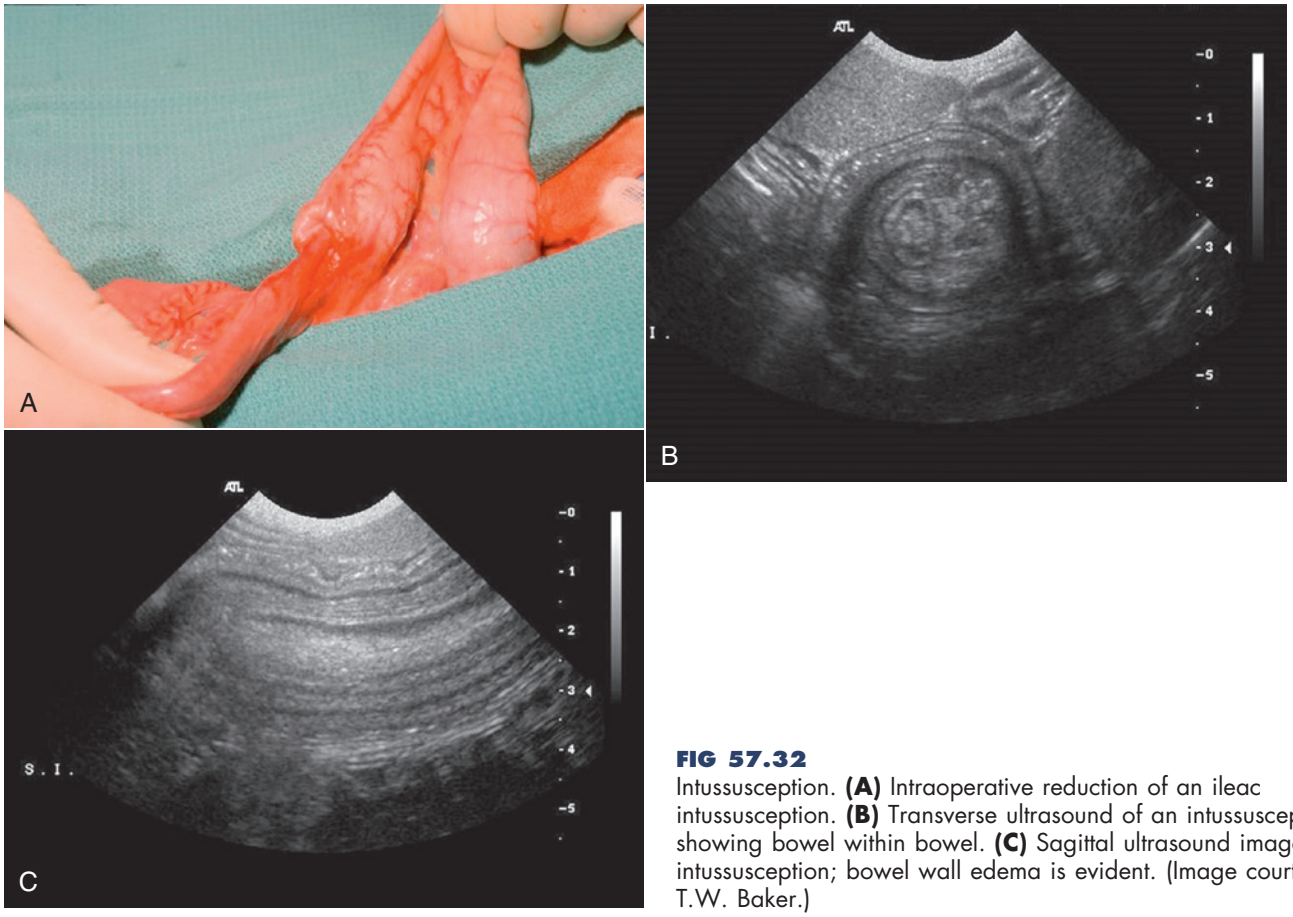


FIG 57.32
Intussusception. **(A)** Intraoperative reduction of an ileac intussusception. **(B)** Transverse ultrasound of an intussusception showing bowel within bowel. **(C)** Sagittal ultrasound image of intussusception; bowel wall edema is evident. (Image courtesy T.W. Baker.)

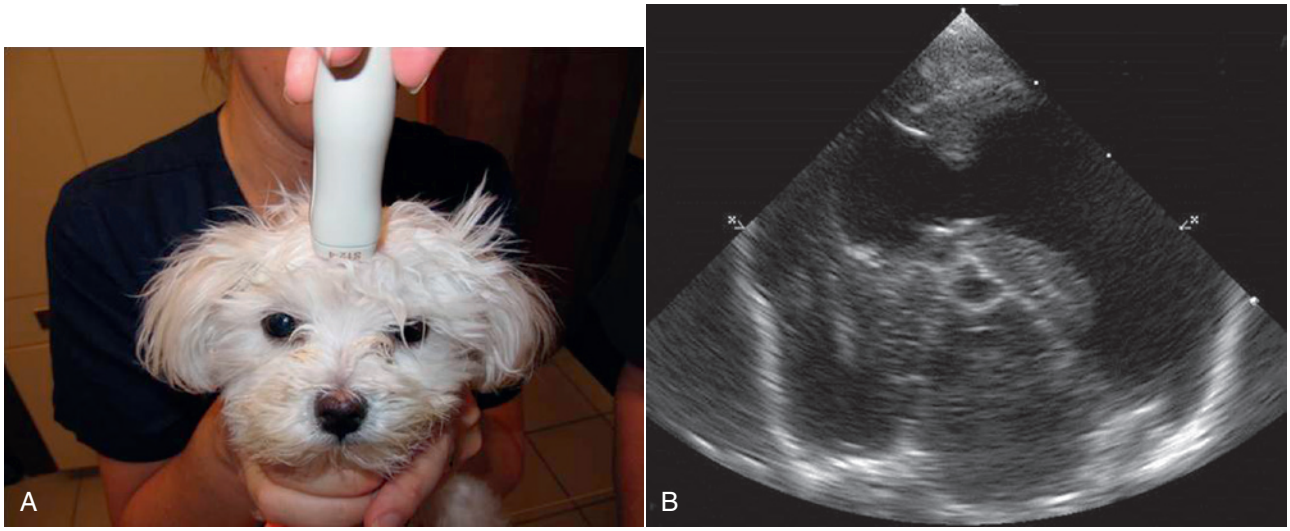


FIG 57.33
(A) Intracranial ultrasound using a trans (open) fontanelle approach. **(B)** Resultant ultrasound image showing an increased amount of cerebrospinal fluid present in the ventricles.

neonatal resuscitation earlier) (Grundy et al., 2009). The normal neurologic examination of the pediatric canine has been reported (Lavely, 2006). Weak or ataxic ambulation can indicate a neurologic or musculoskeletal abnormality. Morphologic neurologic abnormalities occur most frequently. Hydrocephalus has an increased frequency in toy and brachycephalic breeds, and can occur in cats. A domed calvarium, open fontanelle, and prominent suture lines are often present. Aqueduct atresia, birth trauma, or meningoencephalitis can cause the development of hydrocephalus. Clinical signs vary from inapparent to progressively debilitating. Ultrasound, possible through the open fontanelle typical of brachycephalics, can confirm the presence of excessive cerebrospinal fluid within the ventricles (Fig. 57.33, *A*, 57.33, *B*). Cranial and spinal dysraphism occur secondary to embryologic defects in neural tube closure. The presence of resultant neurologic defects generally warrants euthanasia. Vertebral anomalies include hemivertebrae, fused vertebrae, and butterfly vertebrae, and are usually subclinical unless spinal cord compression occurs. Cerebellar hypoplasia and abiotrophy cause truncal ataxia, hypermetria, and intention tremor at the onset of ambulation. Abiotrophy is progressively debilitating and may occur with lissencephaly. Dysmyelination and hypomyelination of the central nervous system cause tremors with onset by 1 to 2 weeks of age.

Ophthalmologic Disorders

Ocular anomalies account for 15% of all congenital defects in puppies and 9% in kittens. Eyelid agenesis occurs most commonly in kittens and is apparent at birth. Neonatal ophthalmia becomes apparent before the eyelids separate at 10 to 14 days of life (see Fig. 57.19). Bacterial infection is most likely in puppies, viral (Herpes, chlamydia) in kittens. Treatment includes gentle manual separation of the lids and topical triple antibiotic ointment (erythromycin in kittens). Microphthalmos, enophthalmos, strabismus, distichiasis, and entropion become apparent after the eyelids separate. Temporary eyelid tacking (puppy <4 months of age) with 2 to 4 vertical mattress sutures can preclude or postpone surgical correction of entropion. Congenital cataracts can be genetic, secondary to in utero conditions (drugs, toxins, nutritional), and amino acid deficiencies in artificial milk products. Epiphora can be secondary to increased lacrimation from ocular irritation or imperforate or stenotic nasolacrimal puncta. Medial canthal trichiasis causes wicking of tears onto the facial folds; this is also recognized with shallow lacrimal space seen in brachycephalic breeds. Keratoconjunctivitis sicca can be congenital in some breeds (Yorkshire Terrier) or secondary to canine distemper virus and herpesvirus in kittens. Prolapse of the third eyelid gland occurs in brachycephalic dogs and the Burmese cat; preservation of tear production is accomplished by anchoring the gland in place rather than excising it. Congenital disorders of metabolism can result in corneal opacities.

Dermatologic Disorders

Juvenile cellulitis is a progressive granulomatous pustular disorder of puppies. Immunosuppression is indicated for resolution and prevention of severe cicatricial lesions. It is most common in dogs younger than 4 months of age but is occasionally reported in dogs up to 4 years old. The eyelids, pinnae, lips, chin, muzzle, paws, abdomen, thorax, vulva, prepuce, and anus can be affected with lesions that fistulate, drain, and crust (Fig. 57.34, *A*, 57.34, *B*). Lymphadenomegaly, most commonly mandibular and superficial cervical, can be distant from the affected skin sites and is often painful

(Fig. 57.34, *C*). Pustules and lymph nodes are usually sterile when cultured. Superficial cutaneous flora can be cultured from open, draining lesions. Pyrexia, anorexia, sterile suppurative painful polyarthritis, and an inflammatory hemogram can occur. The diagnosis is confirmed by histopathologic evaluation but is commonly made on the basis of clinical appearance. Therapy consists of immunosuppression, most commonly with prednisone, which is tapered once lesions are resolved. Inadequate immunosuppression results in persistence of lesions and increased chance of permanent cicatricial lesions (Fig. 57.34, *D*). Griseofulvin (30 mg/kg PO bid) can be used as adjunctive therapy due to its immunomodulatory effects, permitting earlier tapering of corticosteroids (Shibata et al., 2004). Concurrent use of antibiotics effective against cutaneous organisms (Clavamox, cephalexin) is common. Vaccination during immunosuppression is debatable; strict hygiene should be emphasized and immunization is best accomplished once immunosuppressants are discontinued.

Endocrinologic

Congenital hypothyroidism is an uncommon disorder that can be recognized by the physical stature of 3- to 4-week-old puppies who appear as disproportionate dwarfs as compared with normal littermates, resulting from epiphyseal dysgenesis (Fig. 57.35, *A*). Persistence of deciduous dentition beyond expected teething (>12-16 weeks) can also be observed along with macroglossia (Fig. 57.35, *B*). Congenital hypothyroidism results from thyroid gland aplasia, hypoplasia, ectopia, or dyshormonogenesis most commonly. Early diagnosis is confirmed with a complete thyroid panel (TT4, fT4ED, cTSH); note that normal puppies aged 5 to 6 weeks of age have serum total thyroxine concentrations 2 to 3 times higher than adults. cTSH will differentiate between primary (elevated cTSH) and secondary (TSH deficiency) hypothyroidism. Hypercholesterolemia, hypercalcemia, and nonregenerative anemia can be present as a consequence of hypothyroidism. Replacement therapy (L-thyroxine 22-44 µg/kg



FIG 57.34
Juvenile cellulitis. **(A)** Erythemic raised nodules at mucocutaneous junction of the lips and eyelids in a 10-week-old Labrador Retriever. **(B)** Sterile pustules, ventral abdomen. **(C)** Marked mandibular lymphadenomegaly. **(D)** Cicatricial lesions, Labrador Retriever with delayed immunosuppressant therapy.

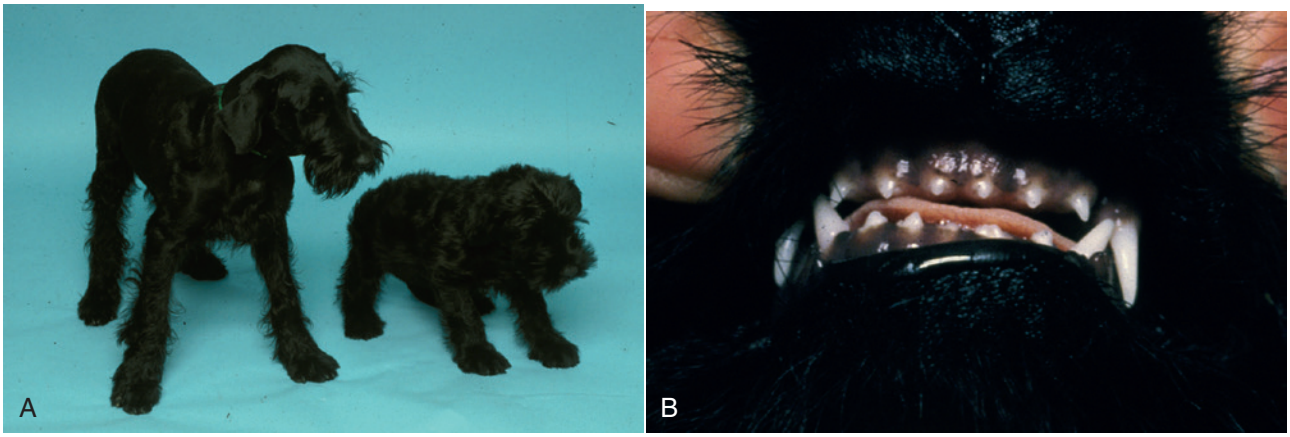


FIG 57.35
Congenital hypothyroidism. **(A)** Giant Schnauzer littermates; the puppy on the right was congenitally hypothyroid. **(B)** Prolonged deciduous dentition in congenital hypothyroidism. Note the increased interdental spaces.

q12-24h) permits these puppies to attain normal size and mental development.

Juvenile diabetes, insulin deficient, is characterized by poor weight gain, polyuria, polydipsia, and polyphagia. Dogs usually present between 3-6 months of age with emaciation, dehydraton, and sometimes decreased vision secondary to cataract formation. A genetic basis is suspected in the Keeshonden; predisposed breeds include Puliks, Cairn Terriers, Miniature Pinschers, Standard Poodles, Miniature Schnauzers, Dachshunds, and Beagles. Insulin therapy is challenging because rapid growth causes changing insulin requirements; a combination of long-acting and regular insulin can be useful. A growth formulated diet should be fed rather than a high-fiber diet. Exocrine pancreatic deficiency can be a comorbidity. Familial in some breeds, it is usually of later juvenile onset, typified by poor weight gain, polyphagia, and abnormal stools. The diagnosis is confirmed with a TLI screen.

Juvenile pituitary disorders include congenital central diabetes insipidus and pituitary dwarfism. Central diabetes insipidus is characterized by profound polyuria and polydipsia (>100 mL/kg/day), poor housebreaking, nocturia, weight loss, and dehydration. Urine is persistently dilute (SG 1.004-1.012). Diagnostics include the modified water deprivation test or preferably (safer) the response to antidiuretic hormone supplementation. Hypoplasia of the pituitary gland causes proportionate dwarfism, infantile genitalia, delayed dental eruption, and mental retardation. The disorder is inherited as a simple recessive trait in the German Shepherd Dog. The diagnosis is made based on somatomedin C (insulin-like growth factor 1) measurement. Concurrent decreased production of other pituitary hormones can exist (thyroid stimulating hormone, adrenocorticotropic hormone, luteinizing hormone, follicle-stimulating hormone).



FIG 57.36
Facial angioedema in a 9-week-old Labrador Retriever puppy; type II hypersensitivity to vaccination.

Pediatric Vaccination

Pediatric dogs and cats should initiate vaccination at 6 to 8 weeks of age (canine DA2P ±P, feline FVRCP/FeLV), with boosters every 3 to 4 weeks until 16+ weeks of age. In dogs, vaccination with leptospirosis serovars should be added at the last two puppy vaccinations if exposure (water activity) warrants it. Pediatric dogs and cats can experience acute (type I) and delayed (type II) hypersensitivity reactions to vaccination (Fig. 57.36). These core vaccinations are repeated a year later, then at 3-year intervals until middle age. Leptospirosis, a bacterin, is an annual booster. Rabies is given at 16+ weeks of age. Additional noncore vaccination for bordetella, borreliosis, and influenza are based on exposure/geography and lifestyle.

Suggested Readings

Baker TW, Davidson AP. Focused or COAST–Pediatrics. In: Lisciandro GR, ed. *Focused ultrasound techniques for the small animal practitioner*. Wiley Blackwell; 2014:222–242.

Casal M. Neonatology: management and critical care of the neonate. In: England G, von Heimendahl A, eds. *BSAVA manual of canine and feline reproduction and neonatology*. 2nd ed. BSAVA; 2010:135–146.

Casal M. Neonatology: clinical approach to neonatal conditions. In: England G, von Heimendahl A, eds. *BSAVA manual of canine and feline reproduction and neonatology*. 2nd ed. BSAVA; 2010:135–146.

Davidson AP, Gregory C, Dedrick P. Successful management permitting delayed operative revision of cleft palate in a Labrador retriever. *Vet Clin North Am Small Anim Pract*. 2014;44(2):325–329. In: Davidson AP, ed. Pediatrics.

Davidson AP, Grundy SA, Foley JE. Successful medical management of neonatal canine herpesvirus: a case report. *Commun Theriogenol*. 2003;3(1):1.

Greco DS. Diagnosis and treatment of juvenile endocrine disorders in puppies and kittens. *Vet Clin North Am Small Anim Pract*. 2001;31(2):401–409. In: Davidson AP, ed. Clinical Theriogenology.

Grundy SA. Clinically relevant physiology of the neonate. *Vet Clin North Am Small Anim Pract*. 2006;36(3):443–459. In: Davidson AP, ed. Pediatrics.

Grundy SA, Liu SM, Davidson AP. Intracranial trauma in a dog due to being "swung" at birth. *Top Companion Anim Med*. 2009;24(2):100–103.

Heinze CR, et al. Comparison of the nutrient composition of commercial dog milk replacers with that of dog milk. *J Am Vet Med Assoc*. 2014;244(12):1413–1422.

Lavely JA. Pediatric neurology of the dog and cat. *Vet Clin North Am Small Anim Pract*. 2006;36(3):475–502. In: Davidson AP, ed. Pediatrics.

Levy JK, et al. Use of adult cat serum to correct failure of passive transfer in kittens. *J Am Vet Med Assoc*. 2001;219(10):1401–1405.

Levy X, England GC. Pregnancy and parturition: pregnancy diagnosis, normal pregnancy and parturition in the queen. In: England G, von Heimendahl A, eds. *BSAVA manual of canine ad feline reproduction and neonatology*. 2nd ed. BSAVA; 2010:98–105.

Linde-Forsberg C. Pregnancy and parturition: pregnancy diagnosis, normal pregnancy and parturition in the bitch. In: England G, von Heimendahl A, eds. *BSAVA manual of canine ad feline reproduction and neonatology*. 2nd ed. BSAVA; 2010:89–97.

Moon PF, et al. Perioperative risk factors for puppies delivered by cesarean section in the United States and Canada. *J Am Anim Hosp Assoc*. 2000;36:359–368.

Payne PA, et al. Efficacy of a combination febantel-praziquantelpyrantel product, with or without vaccination with a commercial Giardia vaccine, for treatment of dogs with naturally occurring giardiasis. *J Am Vet Med Assoc*. 2002;220(3):330–333.

Poffenbarger EM, et al. Use of adult dog serum as a substitute for colostrum in the neonatal dog. *Am J Vet Res*. 1991;52(8):1221–1224.

Reichler IM, et al. The effect of GnRH analogs on urinary incontinence after ablation of the ovaries in dogs. *Theriogenology*. 2003;60(7):1207–1216.

Shibata K, Nagata M. Efficacy of griseofulvin for juvenile cellulites in dogs. *Vet Dermatol*. 2004;15(suppl 1):26.

Sipriani TM, et al. Pulmonary maturation in canine foetuses from early pregnancy to parturition. *Reprod Domest Anim*. 2009;44(s2):137–140.

von Dehn B. Pediatric clinical pathology. *Vet Clin North Am Small Anim Pract*. 2014;44(2):205–219. In: Davidson AP, ed. Pediatrics.

Welborn LV, et al. 2011 AAHA canine vaccination guidelines. *J Am Anim Hosp Assoc*. 2011;47(5):1–42.



Drugs Used in Reproductive Disorders

(*Note:* Many of these drugs are extra-label use in small animals. Many dosages are in micrograms [µg]. Most have various sources, even if only one is listed herein.)

USE	DRUG	TRADE NAME	CANINE DOSE	FELINE DOSE
Abortifacient	Cloprostenol	Estrumate, Schering-Plough	Begin 25 days after LH, 1-3 µg/kg SC q48h to effect (usually 2 doses if in combination with cabergoline) **Plus** cabergoline, 5 µg/kg PO q24h *or* Plus misoprostol 1-3 µg/kg, intravaginally, q24h until abortion complete	1-3 µg/kg SC q24h to effect



Drugs Used in Reproductive Disorders—cont'd

USE	DRUG	TRADE NAME	CANINE DOSE	FELINE DOSE
	Aglepristone	Alizine, Virbac	10 mg/kg SC, twice, 24 hr apart	10 or 15 mg/kg SC, twice, 24 h apart
	Cabergoline	Galastop, Boehringer Ingelheim; Dostinex, Pfizer	5 µg/kg PO q24h, 3-5 days, begin ≥ day 49	
	$PGF_{2\alpha}$	Lutalyse, Zoetis	0.1-0.2 mg/kg SC q8-12h, begin ≥ day 35, until abortion complete Plus misoprostol 1-3 µg/kg, intravaginally, q24h until abortion complete	0.1-0.2 mg/kg SC q12h, begin day 45, until abortion complete
		Dexamethasone	0.2 mg/kg PO, twice daily to effect	
Agalactia	Oxytocin 10 U/mL	Various	0.25-1 U/dog SC, 30 min before nursing for milk letdown *and*	0.25-1 U/queen SC, 30 min before nursing for milk letdown *and*
	Metoclopramide	Reglan, Wyeth-Ayerst	0.1-0.2 mg/kg, PO or SC, q12h for milk production	0.1-0.2 mg/kg, PO or SC, q12h for milk production
Benign prostatic hyperplasia	Finasteride	Proscar and Propecia, Merck	0.1-0.5 mg/kg *or* 5 mg/dog PO q24h	
Dystocia*	Calcium gluconate SC or IM	Various	10% solution 1 mL/4.5 kg SC q4-6h; give in multiple sites if > 6 mL. Give before oxytocin.	10% solution 1 mL/4.5 kg SC q4-6h; give before oxytocin
	Oxytocin SC or IM	Various	0.25-2 U/bitch, SC or IM, q30-60 min to maintain normal labor pattern	0.25-2 U/queen, SC or IM, q30-60 min to maintain normal labor pattern
Estrus induction during anestrus	Cabergoline	Galastop, Boehringer Ingelheim; Dostinex, Pfizer	5 µg/kg PO q24h, until 2 days after onset of cytologic proestrus	
	Deslorelin	Ovuplant, Fort Dodge	1.05 or 2.1 mg, SC implant in vestibular mucosa in ventral commissure of vulva; remove when in proestrus	
				eCG 100 IU IM Followed in 80-84 h with hCG 75-100 IU IM
Estrus suppression	Deslorelin	Ovuplant, Fort Dodge	6-12 mg, SC implant†	6 mg, SC implant
False pregnancy	Cabergoline	Galastop, Boehringer Ingelheim; Dostinex, Pfizer	5 µg/kg PO q24h to effect (usually 3-5 days)	

Continued

Drugs Used in Reproductive Disorders—cont'd

USE	DRUG	TRADE NAME	CANINE DOSE	FELINE DOSE
Follicular ovarian cysts	GnRH hCG	Cystorelin, Abbott; Various	50-100 µg/bitch IM q24h, 3 days 500 IU/kg IM once	
Increase sperm ejaculated	$PGF_{2\alpha}$	Lutalyse, Pfizer	0.1 mg/kg SC, 15 min before collection	
Luteal ovarian cysts	Cloprostenol		1-3 µg/kg SC q24h to effect	
Mammary hyperplasia	Aglepristone‡	Alizine, Virbac	NA	20 mg/kg SC once *or* 10 mg/kg SC, 2 consecutive days
Ovulation induction during estrus	GnRH hCG	Cystorelin, Abbott Various		25 µg/cat IM, once or twice, q24h 75-100 IU/cat IM, once or twice, q24h
Preterm labor	Terbutaline	Brethine, Ciba Geigy	0.03 mg/kg PO q8h	0.03 mg/kg PO q8h
Priapism	Gabapentin Terbutaline Ephedrine		10-20 mg/kg PO q 8-12h to effect 0.03 mg/kg PO q8-12h to effect 2-3 mg/kg PO q8-12h to effect	5-10 mg/kg PO q 8-12h to effect 0.03 mg/kg PO q8-12h to effect 2-3 mg/kg PO q8-12h to effect
Puerperal hypocalcemia	Calcium gluconate 10% IV, followed by Ca gluconate SC and then calcium gluconate, lactate, or carbonate PO	Various Example: Tums	10% solution, slow IV to effect (1-20 mL) 10-30 mg/kg PO q8-12h to effect	10% solution, slow IV to effect (1-2 mL) 500-600 mg PO q24h
Pyometra (open) and postpartum metritis	Cloprostenol		1-3 µg/kg SC q24h to effect and appropriate antibiotics	1-3 µg/kg SC q24h to effect and appropriate antibiotics

GnRH, Gonadotropin-releasing hormone; *IM,* intramuscular; *IV,* intravenous; *LH,* luteinizing hormone; *NA,* not applicable; *PO,* by mouth; *SC,* subcutaneous.

*No obstruction.

†May initially produce proestrus.

‡Will cause abortion if pregnant.

PART NINE · Nervous System and Neuromuscular Disorders

Susan M. Taylor

CHAPTER 58

Lesion Localization and the Neurologic Examination



FUNCTIONAL ANATOMY OF THE NERVOUS SYSTEM AND LESION LOCALIZATION

Understanding nervous system structure and function allows correct interpretation of neurologic examination findings and localization of lesions to clinically significant regions of the brain, spinal cord, or neuromuscular system. Establishing an accurate neuroanatomic diagnosis is an important early step in the diagnostic evaluation of dogs and cats with neurologic signs (Box 58.1).

BRAIN

The brain consists of the cerebrum, the brainstem, and the cerebellum. The brainstem is further subdivided from rostral to caudal into the diencephalon (thalamus and hypothalamus), midbrain, pons, and medulla oblongata (Fig. 58.1). Neurologic abnormalities within the brain can usually be localized on the basis of clinical findings to one of three clinically important regions. These include (1) the forebrain (cerebrum and diencephalon), (2) the pons and medulla, and (3) the cerebellum (Box 58.2).

Forebrain

The forebrain includes the cerebral cortex, cerebral white matter, basal nuclei, and diencephalon. The cerebral cortex is important for behavior, vision, hearing, fine motor activity, and conscious perception of touch, pain, temperature, and body position (proprioception). Cerebral white matter transmits ascending sensory information and descending motor signals, and the basal nuclei are involved in maintaining muscle tone and initiating and controlling voluntary motor activity. Animals with unilateral cerebral cortex lesions usually have a relatively normal gait but mild postural reaction deficits (see discussion of postural reactions, p. 1046) and increased muscle tone in limbs on the contralateral (opposite) side of the body. There may also be contralateral loss of vision and decreased skin sensation (hypalgesia) that is most noticeable on the mucosa of the nasal septum.

The diencephalon includes the thalamus and hypothalamus, and is located deep in the brain underneath the cerebrum and above the pituitary gland, The thalamus is important in the organization and integration of sensory input and maintenance of consciousness and alertness. The hypothalamus is located ventral to the thalamus and controls autonomic and endocrine functions such as appetite, thirst, body temperature, and electrolyte and water balance, linking the nervous system to the endocrine system via the pituitary gland. The olfactory nerve, cranial nerve 1 (CN1), projects onto the hypothalamus, and the optic nerve (CN2) and optic chiasm are on the ventral surface of the hypothalamus so lesions in this region can result in loss of the sense of smell or contralateral visual deficits with normal pupillary light reflexes. Neurologic examination findings associated with forebrain lesions are listed in Box 58.3.

Pons and Medulla

The pons and medulla comprise the portion of the brainstem that contains the regulatory centers for consciousness (ascending reticular activating system) and normal respiration. This area provides a link between the spinal cord and cerebral cortex through ascending sensory and descending motor tracts. These tracts cross in the rostral midbrain, such that although unilateral forebrain lesions result in mild contralateral limb deficits, unilateral lesions of the pons, medulla, or cervical spinal cord cause much more significant ipsilateral (same-sided) spastic paresis, ataxia, and postural reaction deficits. Ten pairs of cranial nerves (3 to 12) also originate in this region, with lesions causing motor or sensory dysfunction of individual nerves. Because vestibular nuclei are located in the medulla as well as in the flocculonodular lobe of the cerebellum, lesions in this region of the brainstem commonly result in head tilt, disequilibrium, and nystagmus (see Chapter 63). Box 58.3 lists

BOX 58.1

Steps in Neurologic Diagnosis

1. Describe the neurologic abnormalities.
2. Localize the lesion.
3. Describe any concurrent nonneurologic disease.
4. Characterize the onset and progression of the neurologic disease.
5. Generate a list of differential diagnoses.
6. Use ancillary tests, if needed, to make a diagnosis and gauge the prognosis.

BOX 58.2

Clinically Important Neuroanatomic Regions

Brain

Forebrain
- Cerebrum
- Diencephalon (thalamus and hypothalamus)

Brainstem
- Midbrain
- Pons
- Medulla oblongata

Cerebellum

Spinal Cord

C1-C5
C6-T2 (cervical intumescence)
T3-L3
L4-S3 (lumbar intumescence)

Neuromuscular System

Peripheral nerves
Neuromuscular junction
Muscle

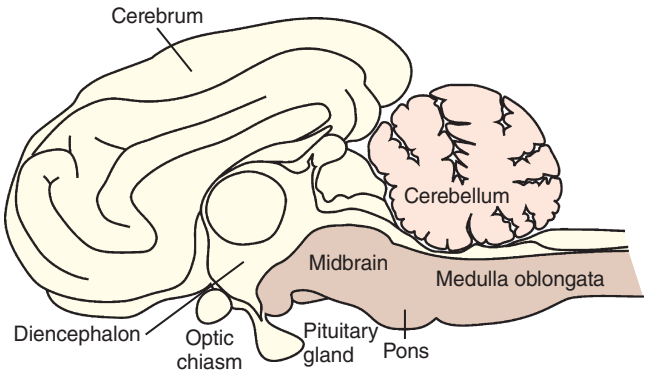


FIG 58.1
Regional anatomy of the brain.

BOX 58.3

Signs Caused by Lesions in the Brain

Forebrain Lesions

Seizures
Altered mentation: depression, stupor, coma
Abnormal behavior: agitation, delirium, aggression, loss of learned behaviors
Contralateral:
- Blindness with normal pupillary light reflexes
- Subtle decrease in skin/facial sensation
- Hemi-inattention syndrome

Normal gait
Circling, pacing towards lesion
±Postural reaction deficits in contralateral limbs
Normal or increased (contralateral) spinal reflexes

Brainstem Lesions

Altered mentation: depression, stupor, coma
Multiple cranial nerve deficits (CN3-CN12, ipsilateral)
Upper motor neuron tetraparesis or hemiparesis (ipsilateral)
Postural reaction deficits in ipsilateral limbs
Normal or increased (ipsilateral) spinal reflexes
Respiratory and cardiac abnormalities

Cerebellar Lesions

Normal mentation
Ipsilateral menace deficit ±
Intention tremor
Hypermetric gait, truncal ataxia with normal strength
Normal knuckling and hopping (hypermetric ipsilateral)
Normal spinal reflexes
Possible paradoxical vestibular syndrome

common neurologic examination abnormalities in patients with lesions of the pons and medulla.

Cerebellum

The cerebellum controls the rate, range, and force of movements. It serves to coordinate muscular activity, regulate fine movement, and modulate muscle tone. Lesions of the cerebellum result in a wide-based stance, ataxia (incoordination) with normal strength and normal postural reactions, and increased muscle tone (spasticity). The gait is hypermetric or exaggerated, with each limb being raised excessively during protraction and then returned more forcefully than normal to weight bearing. Cerebellar lesions may also result in a fine tremor of the head that becomes more pronounced during voluntary movement such as reaching for food (intention tremor). Central vestibular nuclei and pathways are located in the flocculonodular lobe of the cerebellum and in the caudal cerebellar peduncle so that lesions of these regions commonly produce vestibular signs including head tilt, ataxia, and nystagmus. Cerebellar lesions commonly cause paradoxical vestibular syndrome, where the head tilt is

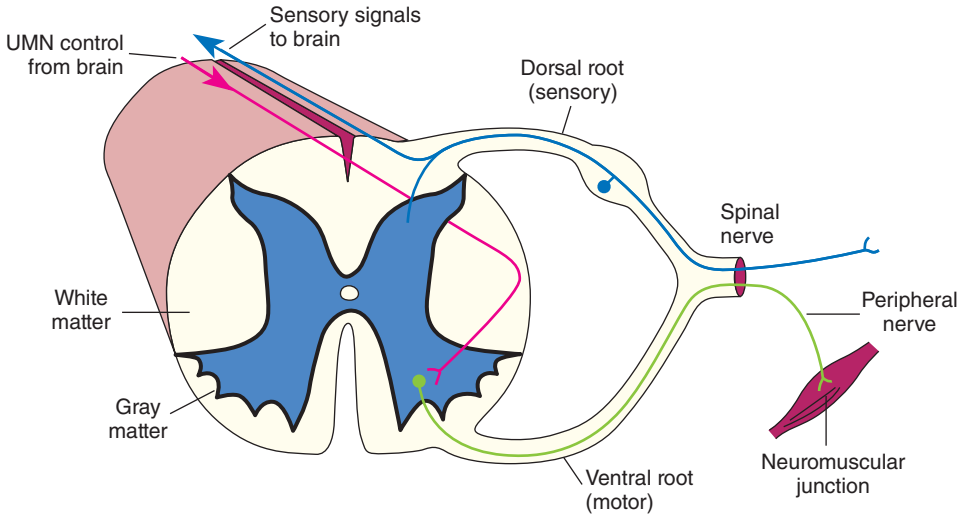


FIG 58.2
A single spinal cord segment.

directed towards the side opposite the lesion (see Vestibular disease, Chapter 63). Severe lesions of the rostral cerebellum may result in opisthotonus with rigid extension of all four limbs with flexed hips (decerebellate posture) (see the discussion of posture, p. 1043). Box 58.3 lists the clinical signs caused by lesions of the cerebellum. Causes of cerebellar dysfunction are discussed with other intracranial disorders in Chapter 60.

SPINAL CORD

The spinal cord resides entirely within the bony vertebral column. It is composed of a central H-shaped core of gray matter surrounded by white matter. Spinal cord gray matter contains the cell bodies of interneurons and lower motor neurons (LMNs). White matter is composed of nerve fibers organized into columns of ascending and descending long tracts. These long tracts transmit ascending sensory information (proprioception, touch, temperature, pressure, and pain) and descending motor signals between higher centers in the brain and spinal cord neurons.

The spinal cord can be functionally divided into segments, with each spinal cord segment giving rise to one pair of spinal nerves (left and right), each of which has a dorsal (sensory) and ventral (motor) root (Fig. 58.2). The cell bodies for the LMNs supplying the thoracic limbs are in the ventral gray matter within a thickened region of the cord called the *cervical intumescence* (segments C6-T2), whereas the LMNs supplying the pelvic limbs originate in the *lumbar intumescence* (segments L4-S3; Fig. 58.3).

Lower Motor Neuron Signs

The LMN is the efferent neuron that directly connects the central nervous system (CNS) to a muscle or gland (Fig. 58.4). Components of LMNs include the nerve cell bodies within the ventral gray matter, the axons leaving the spinal canal as ventral nerve roots and spinal nerves, and the peripheral nerves formed by the spinal nerves that terminate at the neuromuscular junction (NMJ) in the muscle to

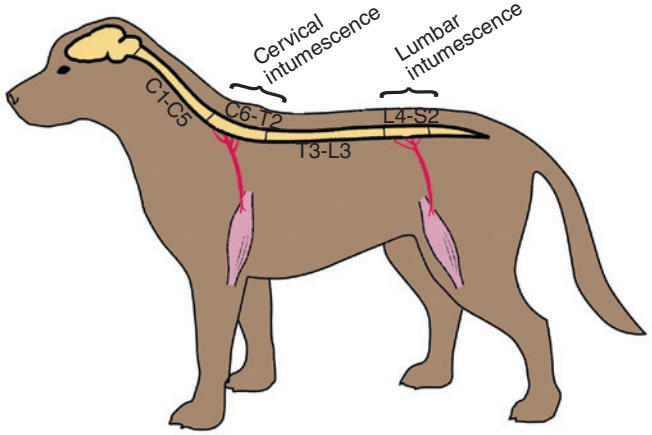


FIG 58.3
Spinal cord segments at the cervical intumescence (C6-T2) and the lumbar intumescence (L4-S3) give rise to the important peripheral nerves of the limbs.

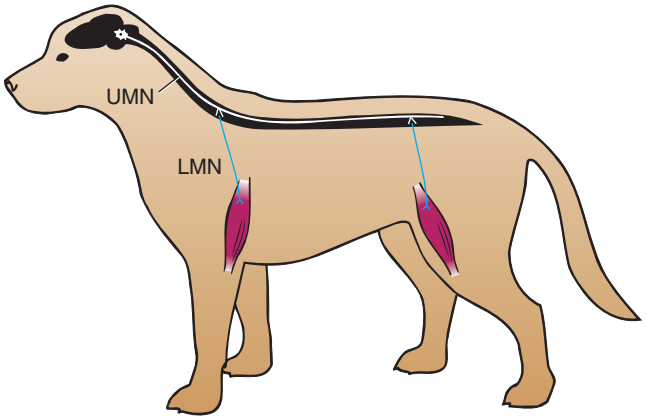


FIG 58.4
The upper motor neuron (UMN) and lower motor neuron (LMN) systems are responsible for mediating normal motor function.

produce contraction (see Fig. 58.2). Damage to any component of the LMN will result in the appearance of abnormalities called *LMN signs* in the muscles normally innervated by that particular LMN. LMN signs include flaccid paresis (weakness) or paralysis (loss of motor function), decreased or absent muscle tone, rapid muscle atrophy, and decreased or absent spinal reflexes (Table 58.1). Animals with LMN signs have a short-strided gait and usually normal postural reactions if their weight is supported. When there is severe damage to the sensory component of the LMN (peripheral nerve, spinal nerve, or dorsal nerve root), there may also be a loss of sensation in the skin and limb directly supplied by that LMN. Spinal cord lesions causing focal LMN signs are discussed in Chapter 65. Disorders affecting peripheral nerves and disorders causing diffuse LMN paralysis are discussed in Chapter 66.

Upper Motor Neuron Signs

Those motor systems originating in the brain to control the LMN are UMNs (see Fig. 58.4). UMNs are responsible for initiating and maintaining normal movement, regulating the muscle tone used to support the body against gravity, and inhibiting myotactic reflexes. Components of the UMN include ascending sensory tracts in the spinal cord and brainstem, nerve cell bodies in the cerebral cortex, basal nuclei, and brainstem as well as the descending motor tracts in the brainstem and spinal cord white matter, which relay information from the higher centers to the LMN. These pathways cross the midline in the rostral brainstem so that forebrain lesions result in contralateral deficits in the limbs, whereas UMN lesions of the spinal cord, pons, or medulla result in ipsilateral deficits in the limbs (Fig. 58.5). Damage to the UMN nuclei or tracts will cause loss of the ability to initiate movement and a release of the inhibitory effect of UMNs on all LMNs caudal to the level of injury. The resultant UMN signs in the limbs caudal to the site of the lesion include loss of voluntary movement (paralysis) or delayed limb movement when trying to walk or hop (UMN paresis), increased extensor muscle tone, and normal to increased spinal reflexes (see Table 58.1). Associated sensory signs such as ataxia (incoordination) and decreased sensation in the skin and limbs caudal to the lesion reflect interruption of the UMN sensory tracts responsible for mediating proprioception (position sense) and pain perception.

Spinal Cord Sensory Pathways

Sensory nerves that detect touch, temperature, and nociception (pain) are distributed to the surface of the body and limbs. There are also sensory nerves responsible for proprioception that originate in the skin, muscles, tendons, and joints. The nerve cell bodies of most of these sensory nerves are located in the ganglia of dorsal nerve roots entering the spinal cord (see Fig. 58.2). Sensory tracts responsible for mediating sensation and proprioception ascend the spinal

TABLE 58.1

Summary of Upper Motor Neuron and Lower Motor Neuron Signs

CHARACTERISTIC	UPPER MOTOR NEURON	LOWER MOTOR NEURON
Motor function	Spastic paresis to paralysis in all limbs caudal to lesion	Flaccid paresis or paralysis at site of lesion
Postural reactions (knuckling)	Often delayed	Normal unless severe lesion
Gait	Wide-based stance, ataxic, long strides, delayed limb protraction	Short strides, limbs maintained under center of gravity
Muscle tone	Normal or increased	Decreased
Muscle atrophy	Late and mild—disuse	Rapid and severe—neurogenic
Spinal reflexes	Normal or increased	Decreased or absent

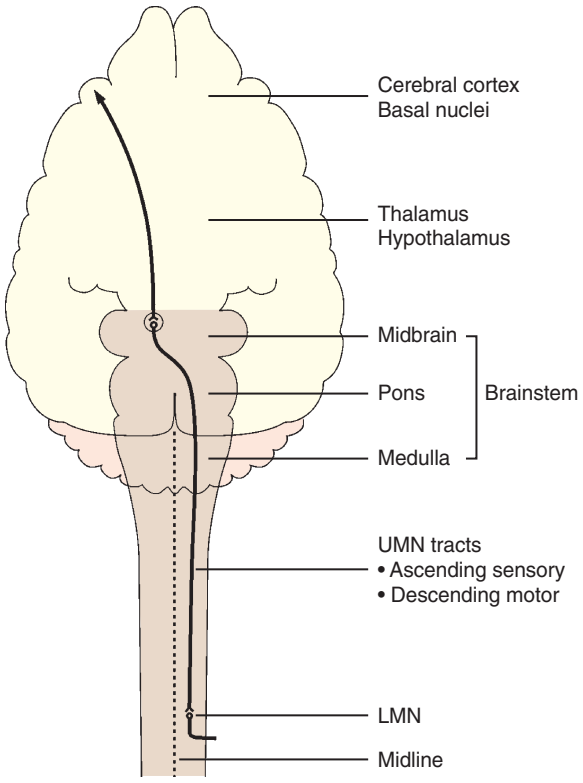


FIG 58.5
Ascending (sensory) and descending (motor) upper motor neuron pathways cross midline in the rostral brainstem.

cord and brainstem to the brain. Most of these tracts ascend the ipsilateral spinal cord and cross over in the rostral brainstem to reach the contralateral cerebrum (see Fig. 58.5). Patients with a unilateral forebrain lesion will typically experience hypalgesia (decreased sensation) in the limbs, trunk, and face on the opposite side. Damage to the sensory tracts in the spinal cord will disrupt the transmission of sensory and proprioceptive information to the brain (UMN), resulting in ataxia and loss of proprioception in all limbs caudal to the site of the lesion. With unilateral spinal cord lesions, the deficits will be ipsilateral. If UMN spinal cord lesions are severe, there may also be some loss of skin sensation caudal to the lesion. In addition to the sensory tracts responsible for relaying information to UMN centers regarding skin sensation and proprioception, there are multisynaptic, small-diameter, bilateral crossing tracts deep in the white matter of the spinal cord that project to the cerebral cortex and are involved in conscious perception of noxious stimuli (nociception, deep pain). The small diameter and deep location of these tracts make them very resistant to compressive injury, so loss of the ability to perceive a noxious stimulus (loss of deep pain perception) in the rear limbs of an animal with a compressive T3-L3 lesion usually indicates a very severe transverse spinal cord injury.

Loss of sensation caused by damage to spinal cord dorsal gray matter, dorsal nerve roots, or the sensory portion of a peripheral nerve allows a LMN lesion to be precisely localized by mapping where skin sensation has been lost. Compressive or irritative lesion of nerve roots or peripheral nerves will sometimes cause severe hyperesthesia (nerve pain) at the site.

Localizing Spinal Cord Lesions

After a neurologic examination, each limb should be characterized as normal or as having upper motor neuron (UMN) or LMN signs. This will allow localization of spinal cord lesions to one of four clinically important functional anatomic regions: spinal cord segments C1-C5, C6-T2, T3-L3, or L4-S3 (Box 58.4). Cervical (C1-C5) spinal cord lesions cause UMN signs in all limbs whereas C6-T2 lesions cause LMN signs in the forelimbs and UMN signs in the pelvic limbs. Animals with thoracolumbar (T3-L3) lesions have normal forelimbs and UMN signs in the pelvic limbs, and lumbosacral lesions cause LMN signs in the pelvic limbs.

Because the ascending and descending tracts to the rear limbs are located more superficially in the cord than the tracts supplying the forelimbs, it is common for dogs and cats with compressive lesions of the cervical (C1-C5) cord to have more pronounced UMN deficits in the rear limbs than in the forelimbs. In contrast, lesions such as hemorrhage, infarcts, or intramedullary neoplasms that preferentially affect the central regions of the spinal cord (*central cord syndrome*) cause unusual signs that can be explained by the location of ascending and descending spinal cord tracts. Lesions of the central spinal cord in the C1-C5 region spare the more superficially located UMN tracts to the pelvic limbs, resulting in UMN deficits only affecting the forelimbs with normal or only mildly affected (UMN) rear limbs. Central cord lesions in the C6-T2 region affect the centrally located LMNs in the intumescence, causing profound LMN deficits in the forelimbs with normal or only mild UMN deficits in the rear limbs.

BOX 58.4

Localization of Spinal Cord Disease

C1-C5

UMN signs forelimbs
UMN rear limbs
UMN bladder ±

C6-T2 (Cervical Intumescence)

L MN signs forelimbs
±Horner syndrome
UMN rear limbs
UMN bladder ±

T3-L3

Normal forelimbs
UMN rear limbs
UMN bladder ±

L4-S3 (Lumbar Intumescence)

Normal forelimbs
L MN rear limbs
Loss of perineal sensation and reflex
Dilated anus, fecal incontinence
L MN bladder ±

L MN, Lower motor neuron; *UMN,* upper motor neuron.

NEUROMUSCULAR SYSTEM

Peripheral Nerves

The peripheral nervous system consists of 12 pairs of cranial nerves originating in the brainstem and 36 pairs of spinal nerves originating in the spinal cord. Nerve fibers from the spinal nerves in the cervical and lumbar intumescences form the peripheral nerves that innervate the muscles of the limbs. Spinal nerve or peripheral nerve lesions result in LMN motor signs in affected muscles and limbs and sometimes decreased, absent, or altered sensation. Box 58.5 lists the clinical signs caused by peripheral nerve lesions. Peripheral nerve disorders are discussed in Chapter 66.

Neuromuscular Junction

At the NMJ, electrical activity is transmitted from nerve axons to muscle fibers, resulting in muscular contraction. This process is mediated through the calcium-dependent release of the neurotransmitter acetylcholine (ACh) from the nerve terminal into the synaptic cleft. ACh diffuses across the synaptic cleft and binds to ACh receptors on the postsynaptic (muscle) membrane, inducing a conformational change and ion flux that result in muscular contraction. ACh

BOX 58.5

Signs Caused by Lesions in the Neuromuscular System

Peripheral Nerve Lesion: Signs Seen in Affected Limb/Muscle

Flaccid paresis/paralysis
Decreased to absent muscle tone
Rapid and severe muscle atrophy
Decreased or absent spinal reflexes
EMG suggests denervation
Skin sensation decreased or absent if sensory portion of nerve is affected
Abnormal proprioception/postural reactions if sensory portion of nerve is affected

Neuromuscular Junction Disorders: Signs Seen in All Limbs

Flaccid paresis/paralysis
Decreased to absent muscle tone
Decreased or absent spinal reflexes
EMG: decreased amplitude of muscle action potential
Normal postural reactions if able to move and weight is supported
Normal sensation
Myasthenia gravis (postsynaptic defect)
- Paresis, often exacerbated by exercise
- Normal postural reactions
- Normal muscle tone and size
- Normal spinal reflexes

Muscle Disorders

Paresis, may be exacerbated by exercise
Muscle atrophy, pain, or swelling ±
Normal postural reactions if weight is supported
Normal spinal reflexes
Normal skin sensation

EMG, Electromyography.

is then rapidly removed from the synapse by acetylcholinesterase (AChE), readying the synapse for the next nerve impulse. Disorders that interfere with ACh release or inactivation and disorders that alter postsynaptic cholinergic receptor function will adversely affect neuromuscular transmission. Presynaptic NMJ disorders causing decreased release of ACh result in flaccid tetraparesis and decreased spinal reflexes (see Box 58.5) similar to diffuse peripheral nerve disorders.

Myasthenia gravis (MG) is a postsynaptic disorder with reduction in the number of functional ACh receptors. The result is partial failure of NMJ transmission. Animals with MG have clinical signs that are more typical of a muscle disorder than an NMJ disorder, including exercise-induced weakness that improves with rest, normal muscle tone, and normal spinal reflexes (see Box 58.5). Disorders that interfere with AChE, the enzyme that normally inactivates ACh in the synapse, typically cause autonomic nervous system overstimulation and excessive muscle depolarization followed by neuromuscular weakness. Disorders of neuromuscular transmission are discussed in Chapter 66.

Muscle

Skeletal muscle functions to maintain body posture and produce movement. Generalized weakness (tetraparesis), a stiff and stilted gait, and exercise intolerance are common clinical features (see Box 58.5). Postural reactions and reflexes are typically normal. Some disorders cause muscle pain and muscle swelling, whereas others cause muscle atrophy and/or fibrosis. Muscle disorders are discussed in Chapter 67.

NEUROLOGIC CONTROL OF MICTURITION

Physiologic control of micturition is complex and integrated centrally. The pelvic nerve originates in sacral segments S1-S3 (in the L5-L6 vertebral bodies) and detects bladder fullness (stretching) and supplies parasympathetic innervation to the bladder, with stimulation causing detrusor muscle contraction, and bladder emptying. The striated skeletal muscle of the external urethral sphincter is under conscious and reflex control and is innervated by the pudendal nerve, also arising from sacral segments S1-S3. Sympathetic innervation to the bladder is supplied through the hypogastric nerves arising in the lumbar segments (L1-L4 segments in L1-3 vertebrae in dogs, L2-L5 segments in L2-4 vertebrae in cats). Sympathetic tone dominates during urine storage, causing detrusor muscle relaxation (β-adrenergic fibers) and contraction of the internal urethral sphincter (α-adrenergic fibers), allowing the bladder to distend with urine. As the bladder enlarges, sensory information from bladder wall stretch receptors is transmitted via the sensory portion of the pelvic nerve through ascending spinal cord pathways to the thalamus and cerebral cortex. When it is appropriate to void, impulses are sent from the cerebral cortex to the pons and then down the reticulospinal tract to the sacral spinal cord segments. Parasympathetic stimulation results in detrusor muscle contraction. There is normally simultaneous inhibition of α-adrenergic sympathetic tone in the internal urethral sphincter and somatic (pudendal) input to the external urethral sphincter, allowing urine to flow. Damage to any component of this complex system or the connection with UMN centers will result in disorders of micturition.

Sacral spinal cord, sacral nerve and nerve root lesions, and pelvic and pudendal nerve lesions result in urinary incontinence and a large bladder that is easily expressed and leaks continuously (LMN bladder). Perineal and bulbocavernosus reflexes are decreased or absent. The spinal nerves arising from the sacral spinal cord segments are most susceptible to compressive or traumatic injury at the lumbosacral junction.

Spinal cord lesions cranial to the sacral segments (cranial to the L5 vertebral body) may cause diminished voluntary control of urination and reflex hyperexcitability of the urethral sphincter. With relatively mild lesions a syndrome of detrusor-urethral dyssynergia may result, wherein

involuntary contraction of the urethral sphincter occurs during detrusor contraction, halting urine flow during voiding. UMN spinal cord lesions causing severe paresis or paralysis typically result in a bladder that is enlarged and very difficult or impossible to express manually (UMN bladder). Occasionally a reflex or automatic bladder will develop 5 to 10 days after acute UMN spinal cord injury, resulting in reflex detrusor contraction and spontaneous partial emptying of the bladder without cortical perception or voluntary control.

SCREENING NEUROLOGIC EXAMINATION

A screening neurologic examination takes only a few minutes (Box 58.6). Abnormalities of mentation, posture, and gait are initially evaluated. Postural reactions are then evaluated. If abnormalities are detected, evaluation of muscle tone, spinal reflexes, urinary tract function, and sensory perception aids in lesion localization. Finally, cranial nerves are evaluated, and if necessary, localization of a lesion within the brain is attempted.

MENTAL STATE

Owners should always be asked if they have noticed any changes in their pet's behavior, because subtle changes are often not apparent to the examiner. A decreased level of consciousness, such as depression or stupor (Table 58.2), may occur with a metabolic disturbance, systemic illness, or damage or disease affecting the cerebrum or brainstem. Coma almost always indicates a brainstem lesion. Delirium, confusion, or agitation suggests either cerebral cortical disease or a metabolic encephalopathy. Seizures occur with forebrain lesions or functional disturbances secondary to metabolic encephalopathies or intoxications. Aggression, compulsive pacing, loss of housebreaking, vocalizing, and head pressing can all be seen with a forebrain lesion. A behavioral syndrome in which animals with a structural unilateral forebrain lesion ignore all sensory input from the contralateral half of their environment has been called *hemiinattention syndrome.*

BOX 58.6

Components of the Neurologic Examination

- Mental state
- Posture
- Gait
  - Paresis/paralysis
  - Ataxia
    - Proprioceptive (UMN)
    - Vestibular
    - Cerebellar
  - Circling
  - Lameness
- Postural reactions
  - Knuckling
  - Hopping
  - Hemiwalking
  - Wheelbarrowing
- Muscle tone and size
- Spinal reflexes
- Perineal reflex/anal tone
- Sensory perception (nociception)
- Cranial nerves

POSTURE

A normal upright posture is maintained through integration of multiple CNS pathways and spinal reflexes. Abnormal postures reflect a disruption of this normal integration. A wide-based stance is common in ataxic animals, particularly those with balance problems due to cerebellar or vestibular disease (Fig. 58.6). A continuous head tilt with resistance to

TABLE 58.2

Disorders of Consciousness

STATE	CHARACTERISTIC
Normal	Alert; responds appropriately to environmental stimuli
Depressed	Quiet or drowsy, responds to environmental stimuli; obtunded
Delirious	Alert; responds inappropriately to stimuli; agitated or confused
Stuporous	Unconscious, except when aroused by strong (often painful) stimuli
Comatose	A state of deep unconsciousness from which the animal cannot be aroused, even with noxious stimuli



FIG 58.6
Wide-based stance and excessive limb abduction indicative of ataxia in a 2-year-old Boxer with *Neospora caninum* meningoencephalomyelitis affecting the cervical spinal cord and cerebellum.

straightening is usually associated with an abnormality of the vestibular system (Fig. 58.7; see Chapter 63). In recumbent animals, posture and other neurologic findings aid in lesion localization.

Schiff-Sherrington Posture

The Schiff-Sherrington posture is observed in dogs when an acute, severe, thoracic, or cranial lumbar spinal cord lesion (usually a fracture/luxation, infarction, or hemorrhage) interferes with the normal ascending inhibition of thoracic limb extensor motor neurons by border cells in the cranial lumbar spinal cord segments (mostly L2-L4). Forelimbs exhibit increased extensor tone with normal voluntary motion, strength, and proprioception (Fig. 58.8). The rear limbs are paralyzed, with normal to increased reflexes (UMN). This posture suggests acute severe spinal cord damage between the T3 and L1 spinal cord segments but does not have prognostic significance.

Decerebrate Rigidity

This posture is observed when there is a severe rostral brainstem (midbrain) lesion. Affected animals are stuporous or comatose, all limbs are rigidly extended, and there is dorsal extension of the head and neck (opisthotonus; Fig. 58.9, *A*).



FIG 58.7
Right-sided head tilt in an adult cat with right-sided peripheral vestibular disease caused by otitis media/interna.



FIG 58.8
Schiff-Sherrington posture in a 9-year-old Lhasa Apso caused by traumatic fracture and luxation of the spine at T11-T12, with damage to the spinal cord at that site. There was a loss of proprioception, loss of voluntary motion, and loss of deep pain in the rear limbs, with increased reflexes. The forelimbs were neurologically normal except for increased extensor tone.

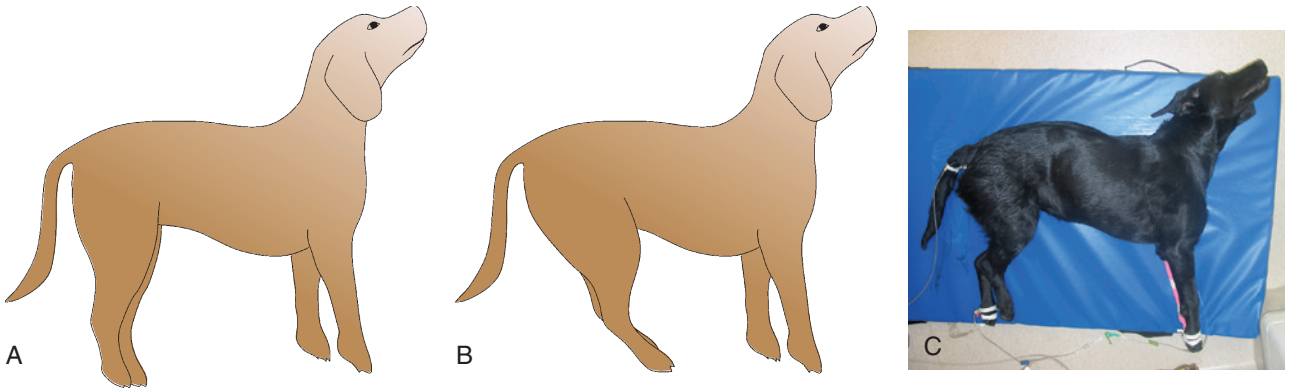


FIG 58.9
Abnormal postures. **(A)** Decerebrate rigidity. **(B)** Decerebellate rigidity. **(C)** Decerebellate rigidity in a 6-month-old Labrador Retriever with intracranial hemorrhage after warfarin intoxication.

Decerebellate Rigidity

The rostral portion of the cerebellum is responsible for inhibition of excessive extensor muscle tone. An acute lesion in this region can result in increased thoracic limb extensor muscle tone and opisthotonus. Mentation is normal, helping to differentiate this posture from decerebrate rigidity. The hips may be flexed forward as a result of increased iliopsoas muscle tone. This posturing can be episodic (see Fig. 58.9, *B* and *C*).

GAIT

Clinical evaluation of gait involves observation of the animal's movements during walking on a flat, nonslippery surface, with frequent turns and circling. If the animal is unable to walk unassisted, it should be supported with a harness or sling so that voluntary movement and gait can be better assessed. Each patient must be evaluated for paresis (weakness), ataxia, lameness, and circling.

Paresis/Paralysis

Paresis is defined as weakness or inability to support weight (LMN paresis) or inability to generate a normal gait (UMN paresis). *Paralysis* is the term used to describe the loss of all voluntary movement (Table 58.3). When animals are still ambulatory, the gait that results from LMN disease is markedly different from the gait that results from a UMN lesion. Animals with LMN disease are usually profoundly weak (paretic), the muscles in affected limbs are relatively flaccid, and they take small steps, attempting to maintain their feet under their center of gravity. Their short-strided, choppy gait is commonly mistaken for an orthopedic lameness, and they may tremble or collapse with minor exertion. Attempts to move quickly may result in a bunny-hopping gait or collapse. Unless they are paralyzed or have significant sensory nerve dysfunction, animals with LMN disease should have normal postural reactions as long as their body weight is supported during placing and hopping.

In contrast, animals with UMN lesions have a delay in the onset of protraction of their limbs (the swing phase of the gait) when trying to walk or hop, and they often have a longer-than-normal stride with a variable degree of spasticity or stiffness of the limbs (spastic paresis). Animals with UMN lesions have abnormal postural reactions and are ataxic as a result of disruption of the general proprioceptive (sensory) tracts that accompany the UMN tracts.

TABLE 58.3

Localizing Lesions Causing Paresis and Paralysis

Tetraparesis/Tetraplegia: Paresis or Paralysis of All Four Limbs	
Normal proprioception and spinal reflexes	Nonneurologic disorders *(cardiac disease, hypoglycemia, electrolyte abnormalities, hypoxemia)* Myasthenia gravis Generalized muscle disorders
LMN fore and rear	Generalized disorders of spinal cord ventral gray matter, ventral nerve roots, peripheral nerves or neuromuscular junction
LMN forelimbs, UMN rear limbs	C6-T2 spinal cord
UMN forelimbs, UMN rear limbs	C1-C5 or brainstem
Paraparesis/Paraplegia: Paresis or Paralysis of Rear Limbs	
Normal forelimbs, LMN rear limbs	L4-S3 spinal cord
Normal forelimbs, UMN rear limbs	T3-L3 spinal cord
Monoparesis/Monoplegia: Paresis or Paralysis of One Limb	
LMN	Lesion of the LMN directly innervating the affected limb *(motor neuron cell body in ventral spinal cord gray matter, ventral nerve roots, spinal nerves, peripheral nerves)*
Rear limb UMN	Ipsilateral T3-L3 spinal cord
Hemiparesis/Hemiplegia: Paresis or Paralysis of Both Limbs on One Side	
LMN fore, UMN rear	C6-T2 ipsilateral spinal cord
UMN fore, UMN rear	C1-C5 ipsilateral spinal cord; ipsilateral brainstem; contralateral forebrain lesion

LMN, Lower motor neuron; *UMN,* upper motor neuron.

Ataxia

Ataxia, or incoordination, is caused by lesions of the cerebellum, vestibular system, or the general proprioceptive (GP) sensory tracts in the spinal cord and caudal brainstem (Box 58.7). Animals with GP ataxia lose awareness of where their limbs are in space (Video 58.1). They have a wide-based stance, long strides, increased extensor tone in the affected limbs, excessive abduction of limbs during turning, exaggerated limb flexion, and a tendency to scuff or knuckle affected limbs while walking. When affected animals are walking, their limbs may cross, and the weight-bearing phase may be prolonged because of delayed protraction of affected limbs. Deficits are often most apparent when animals are walked in tight circles. Postural reactions are most obviously abnormal in animals with GP ataxia due to spinal cord or brainstem lesions.

Vestibular ataxia is manifested primarily as a loss of balance, reflected in a head tilt and a wide-based, crouched stance with a tendency to lean, drift, fall, or roll to the side (Video 58.2). Vestibular ataxia is often accompanied by an

BOX 58.7

Localizing Ataxia

Spinal Cord (General Proprioceptive) Ataxia

Paresis of affected limbs
Inability to recognize limb position
Wide-based stance
Long strides
Increased extensor tone in affected limbs (spastic paresis)
Excessive abduction of limbs during turning
Abnormal postural reactions
Normal mentation and cranial nerves

Vestibular Ataxia

Head tilt
Wide-based, crouched posture
Balance problem
Peripheral: normal postural reactions
Central: abnormal postural reactions

Cerebellar Ataxia

Normal strength
Wide-based stance
Hypermetric limb movements
Truncal sway
Normal postural reactions
Intention tremor of the head

abnormal nystagmus (see Chapter 65). Cerebellar ataxia reflects an inability to control the rate, range, and force of movement (Video 58.3). Affected animals will have a wide-based stance, swaying of the body from side to side (truncal ataxia), and slightly delayed limb protraction followed by exaggerated (hypermetric) limb movements. There is marked overflexion of the limbs during protraction and then forceful return to weight bearing, creating a "bursty" effect to the movement. Animals with cerebellar ataxia have normal strength, increased muscle tone, and usually relatively normal postural reactions (Fig. 58.10). A fine head tremor may be present; when vestibular components of the cerebellum are affected, head tilt, nystagmus, and loss of balance may be evident (see Chapters 60 and 63).

Lameness

Animals are lame when normal movement causes discomfort. If all limbs are equally painful, they may develop a stiff, short-strided gait, as seen in animals with polyarthritis. Animals with lameness affecting one limb have a short weight-bearing phase in the affected limb and a longer-than-normal weight-bearing phase in the contralateral limb. In some cases the painful limb will be elevated or carried. Lameness affecting one limb is common in animals with orthopedic disease but can also be a prominent feature in animals with entrapment (pinching) of a spinal nerve or nerve root by a lateralized disk extrusion or nerve root tumor.



FIG 58.10
Exaggerated (hypermetric) limb movements in a Miniature Poodle with granulomatous meningoencephalitis affecting the cerebellum.



FIG 58.11
Tight circling and head tilt to the right in a 3-year-old Maltese with inflammatory disease affecting the right forebrain and brainstem.

Circling

Circling can be caused by lesions of the forebrain or the vestibular system. Dogs with unilateral forebrain lesions will usually walk or pace in wide circles toward the side of the lesion. Tight circling toward the side of the lesion is more often associated with vestibular disorders (Fig. 58.11). Most animals with vestibular disease also exhibit ataxia, loss of balance, head tilt, and nystagmus.

POSTURAL REACTIONS

The complex series of responses that maintain an animal in an upright position are called *postural reactions.* Postural

reaction testing is used to determine whether animals can recognize the position of their limbs in space (proprioception). Sensory receptors for proprioception originate in the muscles, tendons, and joints, and spinal cord proprioceptive tracts relay this sensory information to the cerebral cortex. Most proprioceptive tracts ascend the ipsilateral spinal cord and cross midline in the rostral brainstem (see Fig. 58.5). Abnormalities detected during the manipulations performed to test postural reactions do not provide precise localizing information but are sensitive indicators that suggest the presence of neurologic dysfunction somewhere along the neurologic pathway. A careful and systematic evaluation of postural reactions may permit the examiner to detect subtle deficits not observed during routine gait examination and to determine whether each limb is neurologically normal or abnormal. Postural reaction testing should include knuckling, hopping, wheelbarrowing, and hemiwalking (Fig. 58.12) (Video 58.4). When performed by an experienced clinician comparing the right and left limbs in an animal that has voluntary movement, hopping is the most sensitive and reliable postural reaction test. The animal is supported bearing weight on one limb, and its body is leaned and hopped laterally so that its center of gravity is no longer adequately supported by that limb. The normal response is to immediately lift the limb and replace it directly under its center of gravity. Any delay in this response is abnormal. In animals with significant weakness, it is important to support most of the body weight during postural reaction testing. Animals with neuromuscular disorders that still have normal sensation and the ability to voluntarily move their limbs will hop quickly (normal) as long as their weight is supported because their proprioception is normal. For the purpose of lesion localization, abnormalities of postural reaction testing are usually interpreted as UMN signs, which must then be confirmed with testing of muscle tone and spinal reflexes (see Box 58.4 and Table 58.1).

MUSCLE SIZE/TONE

Muscle atrophy and muscle tone should be assessed by careful palpation and movement of each limb through a range of motion. Muscle atrophy can occur slowly as a result of disuse or rapidly as a result of a lesion of the LMN supplying a muscle (neurogenic atrophy). If focal muscle atrophy is detected in a limb, this can be used to precisely localize lesions of the peripheral nerve, nerve roots, or spinal cord gray matter because the spinal cord segments and peripheral nerves responsible for innervating each of the individual limb muscles are well known. Muscle swelling or enlargement is a feature of some myopathies. Muscle tone is generally decreased in animals with significant lesions of the LMN, whereas extensor muscle tone is usually increased with UMN lesions (see Table 58.1). Extreme alterations in muscle tone can be seen in animals with Schiff-Sherrington syndrome and with decerebrate and decerebellar rigidity (see Figs. 58.8 and 58.9).

SPINAL REFLEXES

Spinal reflex evaluation helps classify a neurologic disorder as being UMN or LMN. Spinal reflexes and muscle tone will be diminished to absent in limbs affected by LMN disorders and normal to increased in UMN disease. Spinal limb reflexes are best assessed in a relaxed animal restrained in lateral recumbency. Each reflex is judged to be absent (0), decreased (+1), normal (+2), or increased (+3 or +4). LMN lesions severe enough to cause weakness and abnormal gait will reliably cause an absent or decreased reflex. UMN lesions cause an increased reflex that will not always be distinguishable from normal. In the absence of other neurologic deficits, an exaggerated reflex means little and can be observed in an excited or nervous animal. The most useful limb reflexes in dogs and cats include the patellar reflex, sciatic reflex, pelvic limb withdrawal (flexor) reflex, and thoracic limb withdrawal (flexor) reflex. Because other reflexes are found inconsistently in normal animals, they are not routinely evaluated. The spinal reflexes and the spinal cord segments responsible for mediating each reflex are listed in Table 58.4.

Patellar Reflex

With the animal restrained in lateral recumbency, the examiner evaluates the reflex in the upper (nonrecumbent) limb by holding the stifle in partial flexion and striking the patellar ligament with the flat surface of the reflex hammer (pleximeter), stretching the fibers of the quadriceps muscle (Fig. 58.13). The normal response is a reflex contraction of the quadriceps muscle. This is a monosynaptic myotactic (stretch) reflex, with both sensory and motor components contained in the femoral nerve and the L4, L5, and L6 spinal nerves, nerve roots, and spinal cord segments. A weak or absent patellar reflex indicates a lesion of the femoral nerve or the L4-6 spinal cord segments or nerve roots. A lesion cranial to the L4 spinal cord segment will typically cause an exaggerated reflex. Although this is the most reliable tendon reflex for evaluation, it is sometimes difficult to interpret the response. Occasionally a lesion of the sciatic nerve or the L6-S2 spinal cord segments will cause the patellar reflex to appear increased by decreasing tone in the muscles opposing stifle extension (pseudohyperreflexia). The patellar reflex is sometimes difficult to elicit in animals with significant orthopedic disease of the stifle. It is occasionally decreased or absent in normal dogs (especially large-breed puppies) and may be absent in some geriatric dogs, presumably due to an age-related neuropathy affecting the sensory side of the reflex arc. In tense patients, the reflex is sometimes decreased or absent in the upper limb but normal in the relaxed recumbent limb, making it important to check this reflex in both limbs in both recumbencies.

Pelvic Limb Withdrawal (Flexor) Reflex

The examiner squeezes a digit with enough pressure to elicit flexion of the hip, stifle, hock, and digits (Fig. 58.14, *A* and *B*). If manual pressure is inadequate, the examiner squeezes the base of a toenail with a pair of forceps. The pelvic limb withdrawal reflex is complex. Sensory input is through the



FIG 58.12
Postural reaction testing. **(Aa) (Ab)** Proprioception (knuckling) is evaluated by placing the dorsal surface of the animal's paw on the floor while the animal's weight is supported. The normal response is an immediate return to a normal position. **(B)** Forelimb hopping. The animal is supported under the abdomen, and one thoracic limb is lifted from the ground. The animal is leaned and moved laterally toward the limb being evaluated. The normal animal responds by quickly lifting and replacing the limb under its body as it moves laterally. **(C)** Pelvic limb hopping. The animal is supported under the chest, and one pelvic limb is lifted. The animal is leaned and moved laterally toward the limb being evaluated. The normal animal responds by quickly lifting and replacing its limb under the body as it moves laterally. **(D)** Hemiwalking. The front and rear limbs on one side are lifted, and forward and lateral walking movements are evaluated. **(E)** Wheelbarrowing. The animal is supported under the abdomen and moved forward. The head may be elevated to remove visual input and accentuate proprioceptive abnormalities, as shown here.

TABLE 58.4

Spinal Reflexes

REFLEX	STIMULUS	NORMAL RESPONSE	SPINAL CORD SEGMENTS
Thoracic limb withdrawal	Pinch foot of forelimb	Withdraw limb	C6, C7, C8, T1 (T2)
Patellar	Strike patellar ligament	Extend stifle	L4, L5, L6
Pelvic limb withdrawal	Pinch foot of rear limb	Withdraw limb	L6, L7, S1 (S2)
Sciatic	Strike sciatic nerve between greater trochanter and ischium	Flexion of stifle and hock	L6, L7, S1 (S2)
Cranial tibial	Strike belly of cranial tibial muscle just below proximal end of tibia	Flexion of hock	L6, L7 (S1)
Perineal	Stimulate perineum with pinch	Anal sphincter contraction, ventroflex tail	S1, S2, S3, pudendal nerve
Bulbourethral	Compress vulva or bulb of penis	Anal sphincter contraction	S1, S2, S3, pudendal nerve
Cutaneous trunci	Stimulate skin over dorsum just lateral to vertebral column	Twitch of the cutaneous trunci muscle	Response will be absent caudal to a severe spinal cord lesion Used to localize lesions between T3 and L3

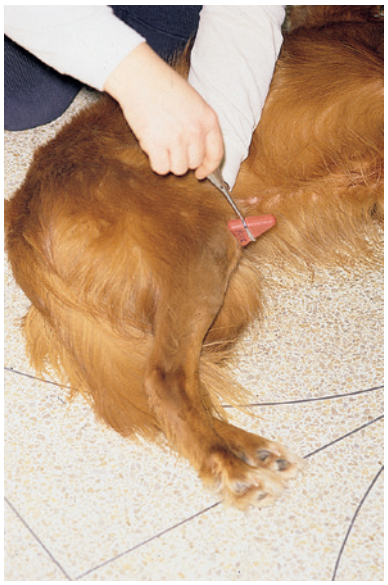


FIG 58.13
Patellar reflex. The straight patellar ligament is struck, resulting in a reflex "kick" extension of the stifle.

peroneal (dorsal, lateral) and tibial (ventral) branches of the sciatic nerve and the saphenous branch of the femoral nerve (medial). Motor output is through the sciatic nerve and its branches, the tibial nerve (digital flexion), and the peroneal nerve (tarsal flexion). Because the femoral nerve and the lumbar spinal nerves mediate hip flexion, this component of the reflex can occur when the medial toe is stimulated even if the sciatic nerve and its branches have been destroyed. A decreased pelvic limb withdrawal response indicates an LMN lesion affecting the sciatic nerve (or branches) or the L6-S1 spinal cord segments or nerve roots (and sometimes S2). A lesion cranial to L6 results in a normal to increased reflex response. The withdrawal response is a segmental reflex that is not dependent on the animal's conscious perception of the noxious stimulus. Functional transection of the spinal cord cranial to L6 will result in a normal to increased reflex (UMN) but no ability to feel the stimulus.

Sciatic Reflex

With the animal in lateral recumbency, the examiner palpates the notch formed by the greater trochanter of the femur and the ischial tuberosity. Using the tapered end of the pleximeter to tap in this notch, the examiner elicits a brief flexion of the hock (see Fig. 58.14, *C*). A normal sciatic reflex requires that the sciatic nerve, spinal cord segments L6-S1, and the peroneal nerve (branch of the sciatic nerve) be intact. The reflex will be decreased with lesions of those components and normal to increased with UMN lesions cranial to L6.

Thoracic Limb Withdrawal (Flexor) Reflex

The only reliable forelimb reflex is the withdrawal reflex. Because multiple nerves are involved, this reflex is used as a crude test of the entire brachial plexus (nerve roots and peripheral nerves) and cervical intumescence (C6-T2). The examiner squeezes a digit to elicit flexion of the shoulder, elbow, carpus, and digits (Fig. 58.15). Lesions involving the peripheral nerves, nerve roots, or spinal cord segments at that site will result in a decreased or absent reflex. Lesions above C6 in the spinal cord will cause a normal to increased (UMN) reflex response.

Crossed Extensor Reflex

When the withdrawal (flexor) reflexes are elicited in an animal in lateral recumbency, a reflex extension of the

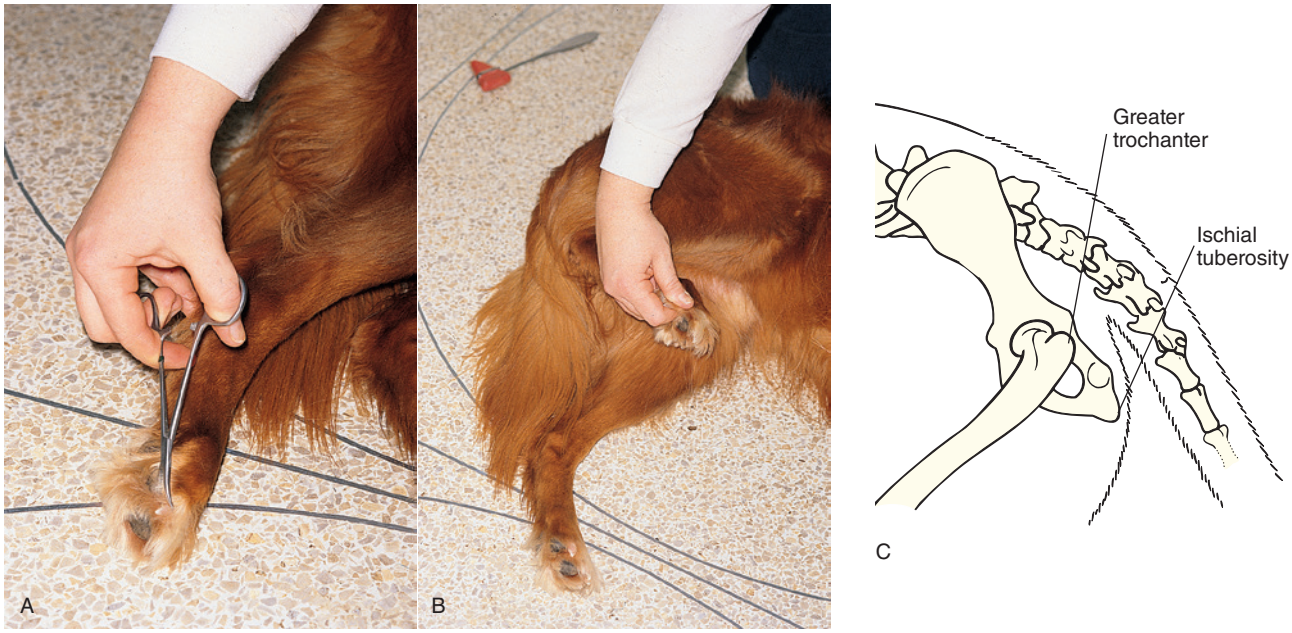


FIG 58.14
Assessing the sciatic nerve and spinal cord segments L6-S2. Pelvic limb withdrawal reflex: pinching the toe **(A)** results in limb flexion **(B).** Assess flexion in all of the joints of the limb. It may be necessary to apply a forceps to the nail base to provide adequate stimulation. **(C)** Sciatic reflex: striking the sciatic nerve in the notch between the greater trochanter of the femur and the ischial tuberosity results in limb flexion.

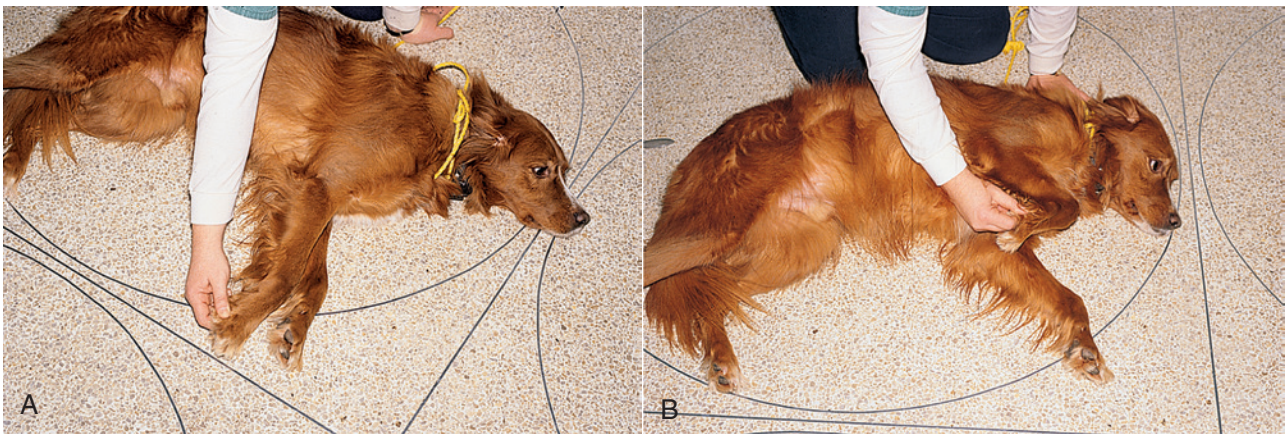


FIG 58.15
Thoracic limb withdrawal reflex. Pinching the toe **(A)** results in limb flexion **(B).** Assess flexion in all the joints of the limb.

limb opposite the one being stimulated is termed a *crossed extensor reflex.* The presence of this reflex in a paralyzed animal or an animal that is not trying to rise or get away suggests that there is a UMN lesion to the limb being evaluated.

Perineal Reflex and Bulbourethral Reflex

The perineal and bulbocavernosus reflexes are used to assess the pudendal nerve (sensory and motor) and sacral spinal cord segments S1-S3. In the perineal reflex the perineal skin is pinched with a hemostat, causing the anal sphincter to contract and the tail to ventroflex (Fig. 58.16). The same response should occur during digital rectal examination. The bulbourethral reflex causes anal sphincter contraction in response to gently squeezing the bulb of the penis or the vulva. LMN damage to the pudendal nerve or the S1-S3 spinal cord segments will cause a loss of both of these reflexes, urinary incontinence (LMN bladder), loss of tone in the internal and external anal sphincters, and resultant anal dilation and fecal incontinence.

Cutaneous Trunci Reflex (Panniculus)

Pinching the skin of the dorsum causes a reflex contraction of the cutaneous trunci muscles bilaterally, producing a



FIG 58.16
Perineal reflex. Stimulate the perineal skin with a hemostat, causing the anal sphincter to contract and the tail to ventroflex.

twitch of the overlying skin. This reflex can be very useful in the evaluation of patients with a severe spinal cord lesion localized to the T3-L3 region. Affected patients will have UMN signs in the rear limbs and normal forelimbs, but unless they have a painful site, it can be difficult to localize the lesion more precisely. When skin along the dorsum is pinched, the stimulated sensory nerve from that site enters the spinal cord and afferent sensory information ascends the spinal cord in sensory tracts. If the spinal cord is intact between the site of stimulation and the C8-T1 segments, a synapse occurs bilaterally at the C8-T1 spinal cord segments, stimulating motor neurons of the lateral thoracic nerve, which causes the cutaneous trunci muscle to contract. In T3-L3 spinal cord lesions causing paralysis, the ascending pathway is often disrupted such that no panniculus reflex is elicited when the skin is pinched caudal to the level of the lesion, but stimulation of the skin cranial to the lesion elicits a response (Fig. 58.17). Testing is started at the level of the iliac wings, although in many normal animals the reflex cannot be elicited until stimulation is applied cranial to the midlumbar region. If a twitch occurs at the most caudal aspect, then the entire pathway is intact. If there is no response, systematic stimulation of the skin just lateral to each vertebral body should be performed, progressing anteriorly until a twitch is observed. Because the sensory nerves that supply the skin enter the spinal cord one or two vertebrae cranial to the dermatome stimulated, the cord lesion is predictably slightly cranial to the site where the panniculus reflex is lost. The cutaneous trunci reflex can be lost unilaterally when there is a lesion of the ipsilateral brachial plexus or C8-T1 spinal cord segments, ventral nerve roots, or spinal nerves. In rare cases this reflex cannot be elicited in a normal dog.

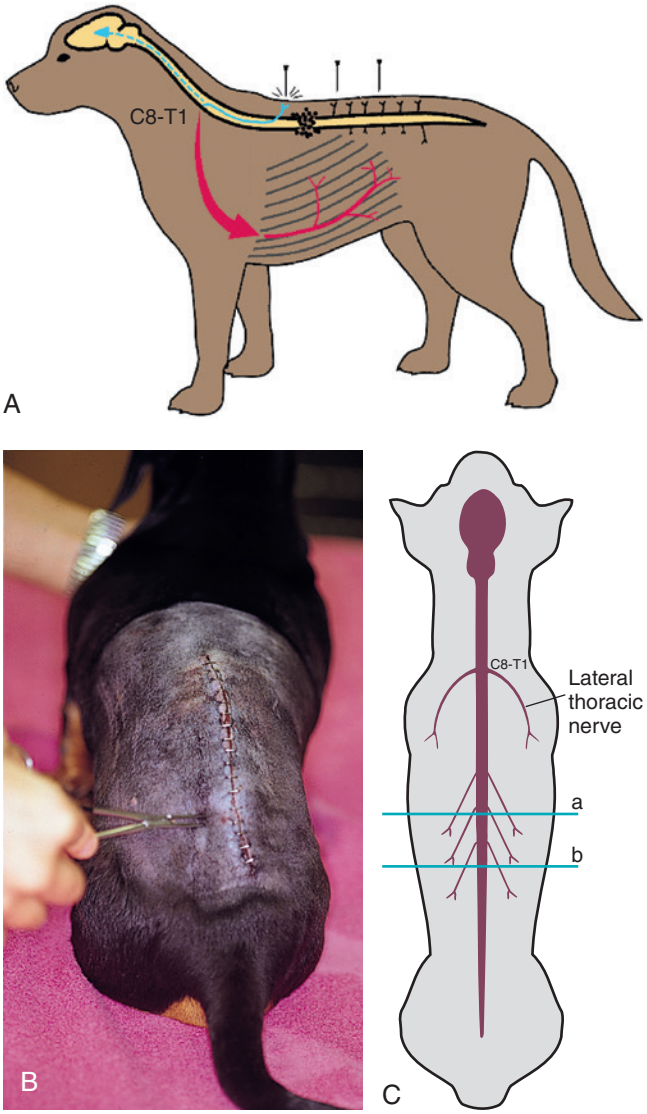


FIG 58.17
Cutaneous trunci reflex. **(A-B)** Pinch the dorsal skin with a hemostat just lateral to the spine. If the spinal cord is not injured between the site of stimulation and the C8-T1 spinal cord segments, this will lead to a bilateral twitch of the cutaneous trunci muscle. The reflex may be absent caudal to a severe spinal cord lesion. **(C)** The spinal sensory nerves course caudally, so the dermatomes for skin sensation lateral to the vertebral column are caudal to their own vertebral bodies. A spinal cord lesion at site *a* will therefore result in loss of the panniculus response caudal to site *b*.

SENSORY EVALUATION

Evaluation of an animal's ability to feel a noxious stimulus such as a pinch (nociception) can be helpful in localizing UMN and LMN lesions. When there is a severe transverse UMN spinal cord lesion in the T3-L3 region, the animal's ability to feel a painful stimulus (skin or toe pinch with fingers or hemostat) may be decreased in the pelvic limbs and in the skin of the trunk caudal to the lesion because the ascending sensory tracts are disrupted in the damaged spinal

cord. If minor stimulation in a paralyzed animal does not elicit a behavioral response such as turning the head, vocalizing, or trying to bite, then the animal's ability to perceive a more severe noxious stimulus such as a hemostat applied to the nail base (deep pain) should be tested. The spinal tracts that carry deep pain sensation are small, bilateral, and multisynaptic and located deep in the spinal cord white matter, so only a very severe bilateral spinal cord lesion will completely disrupt these tracts, making the ability to perceive deep pain an important prognostic indicator in animals with severe compressive T3-L3 spinal cord injury (Fig. 58.18). It is important to remember that withdrawal of the limb indicates only an intact reflex arc (peripheral nerve and spinal cord segments), whereas a behavioral response requires that the sensory spinal cord tracts ascending to the brain also be intact.

When LMN paralysis of a limb is evident, mapping the boundaries of normal and diminished sensation can aid in lesion localization to specific peripheral nerves, dorsal nerve roots, or spinal cord segments. The skin should be pinched with a hemostat and regions of local anesthesia or decreased sensation identified (Fig. 58.19). These results can be compared with established maps of cutaneous regions deriving sensory innervation from individual nerves (dermatomes), allowing the LMN neurologic defect to be precisely localized (see Chapters 65 and 66).

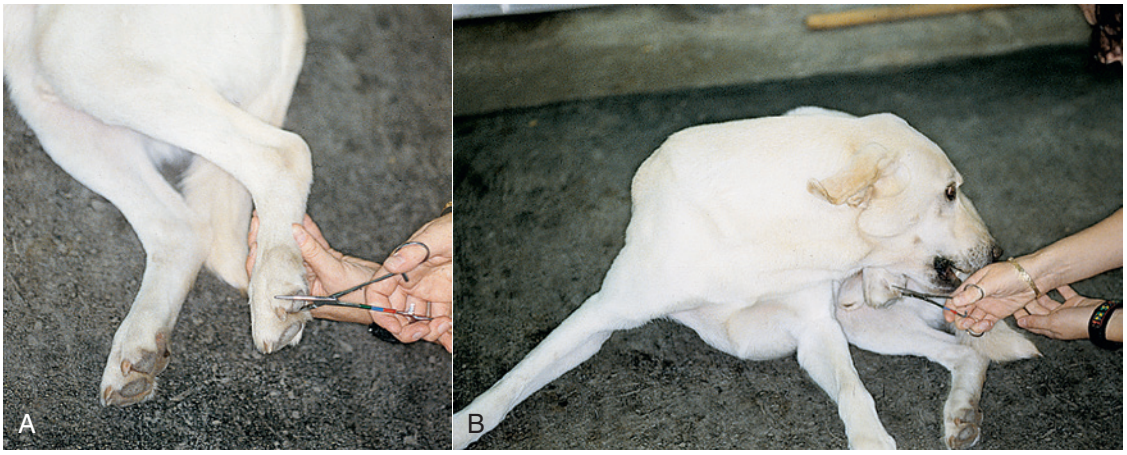


FIG 58.18
Evaluation of deep pain. Pinch the toe **(A)** to assess whether this elicits a behavioral response **(B).** The absence of deep pain sensation indicates the presence of severe spinal cord damage.

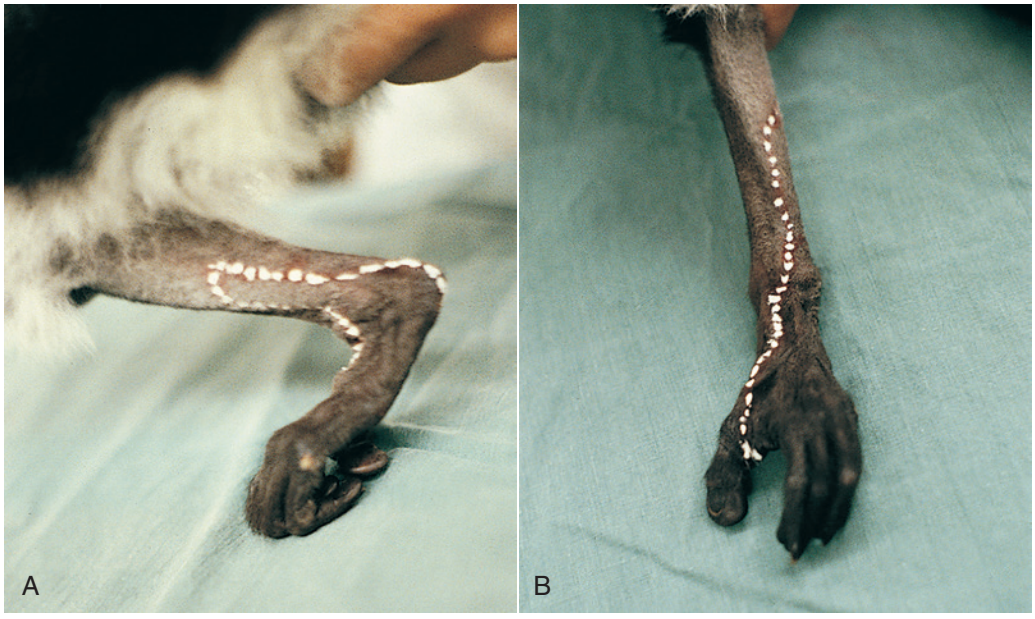


FIG 58.19
Sensory loss in the dorsolateral foot **(A)** and distal rear limb **(B)** in a lemur after damage to the peroneal nerve by an intramuscular injection.

PAIN/HYPERPATHIA

The neck, spine, limbs, muscles, bones, and joints should be palpated and manipulated to detect painful areas or restricted mobility (Video 58.5). Pain is usually most intense directly over a lesion, making this part of the neurologic examination important in lesion localization. Traumatic and inflammatory conditions are most likely to be painful, whereas degenerative and congenital conditions are rarely painful. Neoplastic conditions causing distortion of tissues (meninges, nerve roots, or bone) may also cause discomfort.

The animal's posture and gait should be observed. Animals with neck pain maintain a low head carriage with their head and neck extended, and they are unwilling to turn their neck to look to the side; they will instead pivot their entire body. Animals with pain of the thoracic or lumbar spine stand with an arched back (Fig. 58.20). Animals with painful bones, joints, or muscles typically have a short-strided, stiff gait and are reluctant to exercise.

Neck pain is a sign commonly associated with compressive or inflammatory diseases of the cervical spinal cord, cervical spinal roots, or meninges. The neck should be gently manipulated in dorsal, lateral, and ventral flexion and resistance to movement or pain assessed. Deep palpation of the vertebrae and cervical spinal epaxial muscles may also be performed (Fig. 58.21). Anatomic structures that can cause neck pain include the meninges, nerve roots, facetal joints, bones, and muscles (Box 58.8). Neck pain has also been recognized as a clinical symptom of intracranial disease, particularly of forebrain mass lesions.



FIG 58.20
This 1-year-old Boxer stands with an arched back because of pain associated with diskospondylitis.



FIG 58.21
Testing for cervical and spinal pain by **(A-D)** manipulating the neck through a full range of motion, **(E)** applying pressure through deep palpation of the vertebral bodies and spinal epaxial muscles, **(F)** applying direct pressure over the lumbosacral junction, and **(G)** applying dorsal traction to the tail.

Continued



FIG 58.21, cont'd

Pain when pressure is applied to other regions of the vertebral column may help localize lesions caused by trauma, intervertebral disk disease, diskospondylitis, or neoplasia. Because animals with thoracolumbar spinal pain may also resist abdominal palpation, vertebral or spinal hyperpathia is often misinterpreted as abdominal pain. Cauda equina compression that is caused by a tumor, disk, or ligamentous proliferation typically causes pain in the lumbosacral region (see Chapter 65). This can be demonstrated in affected dogs by applying direct pressure over the lumbosacral junction or applying dorsal traction to the tail (see Fig. 65.20).

Muscular pain should be assessed by manipulating the limbs and palpating individual muscle groups. During palpation, it is important to attempt to differentiate pain that originates within the muscle from that due to bone or joint abnormalities. Muscle disorders that are associated with pain are primarily the inflammatory diseases, such as immune-mediated polymyositis, masticatory myositis, and infectious myositis caused by the protozoal organisms *Toxoplasma* and *Neospora*. Ischemic myopathy, as occurs in animals with thrombosis affecting the arterial blood supply to a muscle group, can also result in severe muscular cramping and pain on palpation.

URINARY TRACT FUNCTION

Severe lesions of the spinal cord are often associated with urinary tract dysfunction. Bladder function should be assessed on the basis of the owner's or clinician's observations of micturition, palpation of the bladder, and attempts to express urine. A flaccid, easily expressed bladder with absent or diminished perineal and bulbocavernosus reflexes and reduced anal tone are expected with lesions of the LMN (S1-S3 spinal cord segments, pudendal nerve, pelvic nerve). UMN lesions cranial to the sacral segments cause diminished voluntary control of urination and reflex hyperexcitability of the urethral sphincter. There can be incomplete voiding or detrusor-urethral dyssynergia. Severe UMN lesions will result in a tense, distended bladder that is difficult to express.

CRANIAL NERVES

Cranial nerve dysfunction may result from a disorder affecting a single nerve, a diffuse polyneuropathy affecting multiple nerves, or a cluster of abnormalities, as is commonly seen in animals with a disease affecting the middle and inner ear or brainstem. Animals with brainstem disease causing cranial nerve dysfunction usually have additional signs such as postural reaction deficits, hemiparesis, quadriparesis, or altered mentation.

Cranial nerve examination is not difficult. The cranial nerves most often affected can be evaluated quickly with a rapid regional neurologic examination (Table 58.5, Video 58.6). If findings yielded by the preliminary examination indicate the presence of an abnormality, a more thorough

BOX 58.8

Causes of Neck Pain

Muscle

Polymyositis (immune, infectious)
Muscle injury

Bone

Fracture/luxation
Atlantoaxial instability/subluxation
Diskospondylitis/osteomyelitis
Wobbler syndrome
Neoplasia

Joint (Facetal Joints)

Polyarthritis (immune, infectious)
Degenerative joint disease (osteoarthritis)

Nerve Root

Neoplasia
Compression (by disk, tumor, fibrous tissue, arachnoid cysts)

Meninges

Neoplasia
Infectious meningitis/meningomyelitis
Meningoencephalitis of unknown etiology (MUE)
Granulomatous meningoencephalitis (GME)
Steroid responsive meningitis arteritis (aseptic meningitis)
Hemorrhage-induced inflammation

Brain

Mass lesion (neoplasia, inflammatory)
Chiari malformation with syringomyelia

examination of each individual cranial nerve can be undertaken (Table 58.6; also see Suggested Readings).

Evaluation of Menace Response, Vision, and Pupils

The optic nerve (CN2) is an important component of the afferent pathways for the menace response, vision, and the pupillary light reflex. To test the menace response, the examiner covers one of the animal's eyes and advances the hand in a menacing way toward the opposite eye, taking care to avoid touching the eyelid or whiskers or generating an air current that will stimulate the cornea, which is innervated by the sensory portion of the trigeminal nerve (CN5). (Fig. 58.22, *A*) It is a good idea to lightly stimulate the face before assessing the menace response to get the animal's attention and make certain there is an intact palpebral reflex (CN7) and the animal is able to blink. The menace response is a cortically mediated learned response and will not be present until 10 to 12 weeks of age in puppies and kittens. In addition to the menace response, vision can be assessed by observing the animal's response to its environment by making sudden movements and dropping cotton balls to see if the animal follows the movement. It may be necessary to set up a maze of objects to assess vision in each eye.

The parasympathetic axons of the oculomotor nerve (CN3) are responsible for pupil constriction. Pupil size should be examined at rest in a well-lit room and then in a dimly lit room and the two eyes compared. The examiner evaluates the ability of each pupil to constrict (parasympathetic function) and dilate (sympathetic function) by shining a bright light in one eye, then swinging the light into the other eye to observe the response, and then swinging it back again (Fig. 58.22, *B*). Loss of vision and pupillary abnormalities are discussed in Chapter 61.

Examine for Strabismus, Nystagmus, and Head Tilt

To check for strabismus and nystagmus, the examiner must determine whether the eyes are normally positioned in the orbits and whether there is any spontaneous nystagmus when the head is stationary. Spontaneous nystagmus at rest is always abnormal and indicates a central vestibular (medullary) lesion, a lesion of the vestibular portion of CN8, or a lesion of the cerebellum. A head tilt is common with a lesion in any of these locations. Abnormal eye position (strabismus) may occur when there is a vestibular disorder or damage to the innervation of the extraocular muscles (innervated by CN3, 4, 6) (Figs. 58.23 and 58.24). Oculomotor nerve (CN3) dysfunction can result in a ventrolateral strabismus and an inability to rotate the eye dorsally, ventrally, or medially. Lesions of the abducent (CN6) nerve cause a medial strabismus and an inability to look laterally, and lesions of the trochlear nerve (CN4) cause a dorsolateral rotation of the eye. Lesions of these nerves (CN3, 4, 6) often occur together, producing complete external ophthalmoplegia, usually due to a mass in the region of the paired cavernous sinuses on the floor of the calvarium (cavernous sinus syndrome).

Vestibular disorders may cause a ventral strabismus (eye drop) on the side of the lesion that is only evident during head and neck extension (positional strabismus). A quick assessment of the function of all these nerves can be accomplished by moving the head from side to side and eliciting the vestibulo-ocular reflex (Fig. 58.25). As the head is turned slowly to the right, the gaze of both eyes should slowly drift left before jerking to the right to resume a central position. The examiner assesses these normal vestibular eye movements (physiologic nystagmus, oculocephalic reflex) while moving the head in each direction.

In addition to moving the head from side to side to determine whether the eye movements are normal, the examiner should hold the animal's head still in each lateral position to determine whether an abnormal (positional) nystagmus develops. The head and neck should then be extended and held in that position while the eyes are evaluated for a ventral strabismus and development of nystagmus. When the head of a normal animal is held still in any position, there should be no nystagmus. In most animals with severe or acute central or peripheral vestibular lesions, a resting

TABLE 58.5

Regional Assessment of Cranial Nerves

CRANIAL NERVE TEST	ACTION	SENSORY INPUT	MOTOR FUNCTION
Menace response	Threatening gesture towards eye; results in a blink	CN2—optic nerve	CN7—facial nerve
Palpebral reflex	Touching medial or lateral canthus of eye results in blink	CN5—trigeminal nerve *medial: ophthalmic branch lateral: maxillary branch*	CN7—facial nerve
Pupillary light reflex	Shining a light in the eye elicits pupillary constriction	CN2—optic nerve	CN3—oculomotor nerve (parasympathetic)
Examine for head tilt	Evaluate head position	CN8—vestibulocochlear	—
Vestibulo-ocular reflex	Move head from side to side and dorsoventrally, evaluating for normal eye movements and strabismus	CN8—vestibulocochlear	CN3—oculomotor nerve CN4—trochlear nerve CN6—abducent nerve
Positional nystagmus Facial sensation	Flip animal on back and observe eyes for nystagmus Palpebral response Pinch lip Insert hemostat in nose to stimulate nasal septal mucosa	CN8—vestibulocochlear CN5—trigeminal nerve	— —
Jaw tone	Assess jaw tone and ability to close the mouth	CN5—trigeminal nerve *(mandibular branch)*	CN5—trigeminal nerve
Facial symmetry	Examine for facial symmetry, ability to blink, twitch lip, and move ears	CN2—optic nerve *(menace)* CN5—trigeminal nerve *(palpebral, corneal reflex, lip pinch)*	CN7—facial nerve
Gag reflex Eat, drink	Manual stimulation of the pharynx induces contraction Observe swallowing	CN9—glossopharyngeal CN10—vagus nerve	CN9—glossopharyngeal nerve CN10—vagus nerve
Tongue evaluation	Inspect the tongue for symmetry, observe tongue movements during eating and drinking	CN5—trigeminal nerve CN7—facial nerve CN12—hypoglossal nerve	CN12—hypoglossal nerve

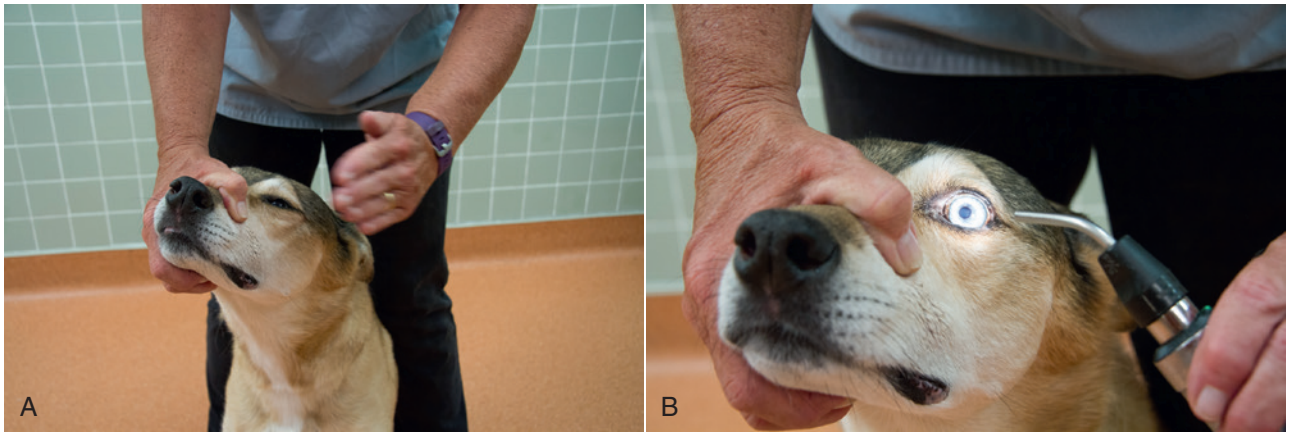


FIG 58.22
Evaluating the menace response, vision, and pupils. **(A)** Assess the menace response by making a menacing gesture toward the eye. **(B)** Shine a light in the eye to assess pupillary light reflexes.

TABLE 58.6

Cranial Nerve Function

CRANIAL NERVE	SIGNS OF LOSS OF FUNCTION
I (olfactory)	Loss of ability to smell
II (optic)	Loss of vision, dilated pupil, loss of pupillary light reflex (direct and consensual when light shone in affected eye)
III (oculomotor)	Loss of pupillary light reflex on affected side (even if light shone in opposite eye), dilated pupil, ventrolateral strabismus
IV (trochlear)	Slight dorsomedial eye rotation
V (trigeminal)	Atrophy of temporalis and masseter muscles, loss of jaw tone and strength, dropped jaw (if bilateral), analgesia of innervated areas (face, eyelids, cornea, nasal mucosa)
VI (abducent)	Medial strabismus, impaired lateral gaze, poor retraction of globe
VII (facial)	Lip, eyelid, and ear droop; loss of ability to blink; loss of ability to retract lip; possibly decreased tear production
VIII (vestibulocochlear)	Ataxia, head tilt, nystagmus, deafness
IX (glossopharyngeal)	Loss of gag reflex, dysphagia
X (vagus)	Loss of gag reflex, laryngeal paralysis, dysphagia
XI (accessory)	Atrophy of trapezius, sternocephalicus, and brachiocephalicus muscles
XII (hypoglossal)	Loss of tongue strength

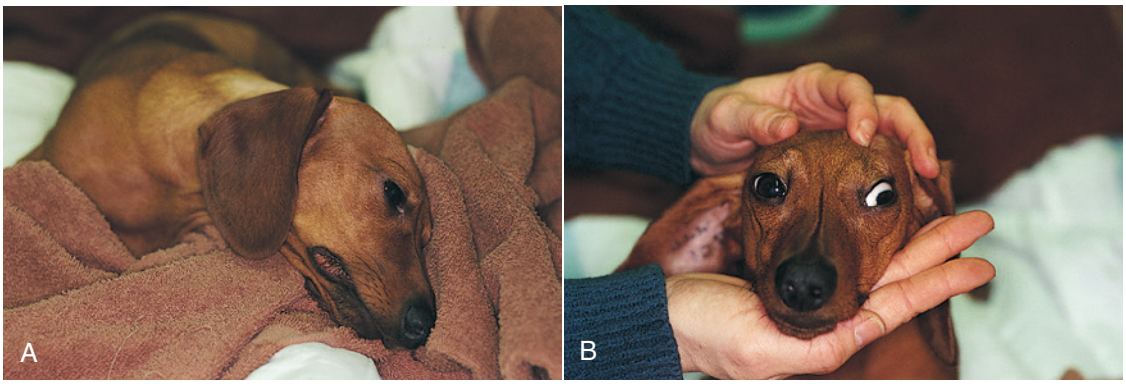


FIG 58.23
Head tilt **(A)** and ventrolateral strabismus **(B)** in a 2-year-old Dachshund after needle trauma to the brainstem during cervical myelography.

(spontaneous) nystagmus will be detected. In less severe or compensated vestibular disorders the examiner will only be able to elicit a few beats of abnormal nystagmus when the animal's head is held in a certain position; this is called *positional nystagmus*, and it is abnormal. Positional nystagmus is most likely to become evident when the animal is suddenly placed in dorsal recumbency with the head and neck extended (Fig. 58.26). The direction of nystagmus is defined as the direction of the fast phase of eye movements.

Evaluation of Trigeminal (CN5) Nerves

The trigeminal nerve supplies sensory innervation to the skin of the ipsilateral face, the cornea, the mucosa of the nasal septum, the nasopharyngeal mucous membranes, and the teeth and gingiva of the upper and lower jaw while providing motor function to the muscles of mastication. Sensory function is tested by assessing the ipsilateral palpebral reflexes (sensory CN5, motor CN7) sensation in the skin of the face, and response to stimulation of the nasal septal mucosa (Fig. 58.27, *A, B, C*). The behavioral response is mediated by the contralateral forebrain so both sides should be carefully assessed. Occasionally decreased facial sensation (hypoalgesia) can be observed in animals with contralateral forebrain lesions. Motor function is assessed by evaluating the masticatory muscles for atrophy and testing the resistance of the jaw when opening the mouth. Bilateral trigeminal motor paralysis results in a dropped jaw and inability to close the mouth (Fig. 58.28). Loss of corneal sensation in

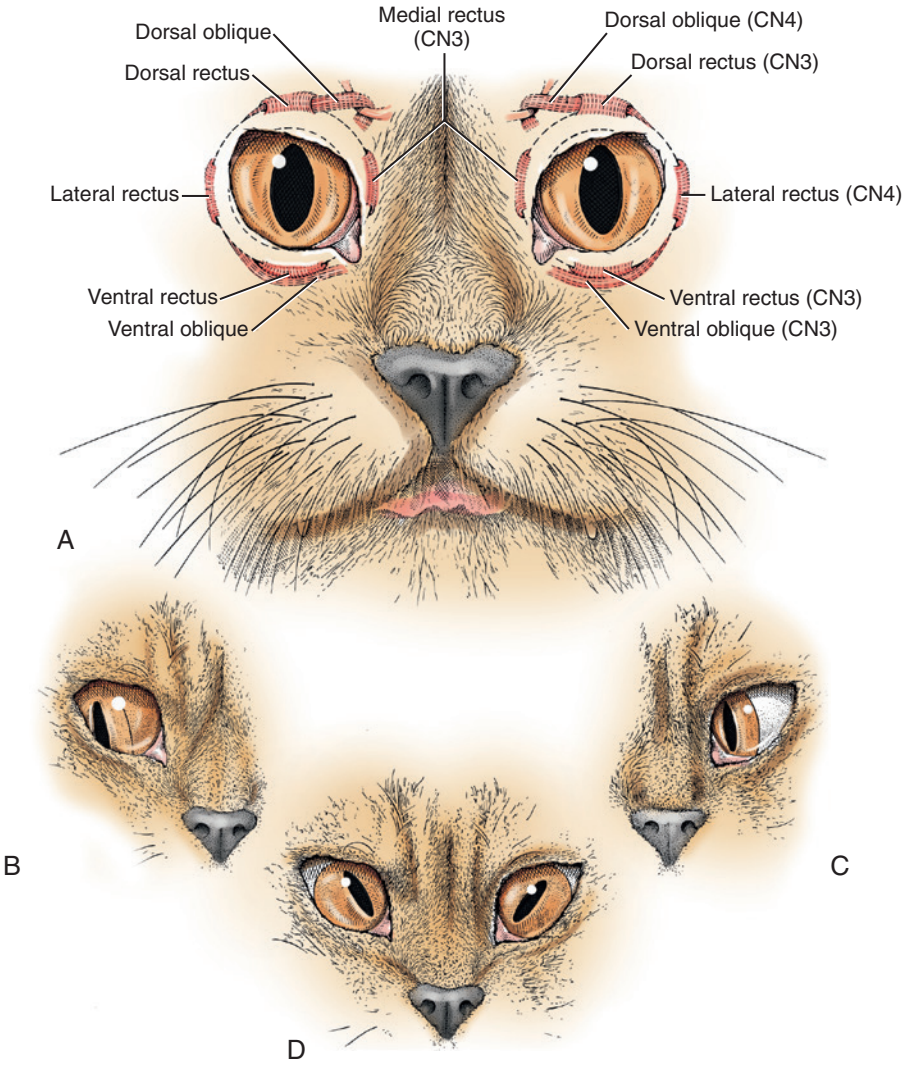


FIG 58.24
(A) Functional anatomy of the extraocular muscles. Directions of strabismus after paralysis of the oculomotor neurons **(B),** paralysis of the abducent neurons **(C),** and paralysis of the trochlear neurons **(D).** CN3, oculomotor nerve; CN4, trochlear nerve; CN6, abducent nerve. (From DeLahunta A, Glass E: *Veterinary neuroanatomy and clinical neurology*, ed 3, St Louis, 2009, Elsevier.)



FIG 58.25
Evaluate eye position and movement as the head is moved into different positions. (From Taylor S: *Small animal clinical techniques*, ed 2, St Louis, 2016, Elsevier.)

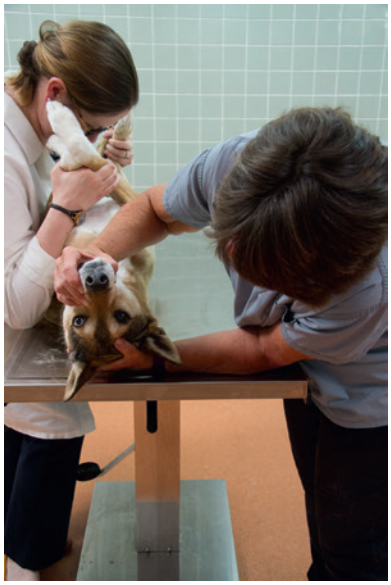


FIG 58.26
Placing an animal in dorsal recumbency can reveal positional nystagmus or strabismus.

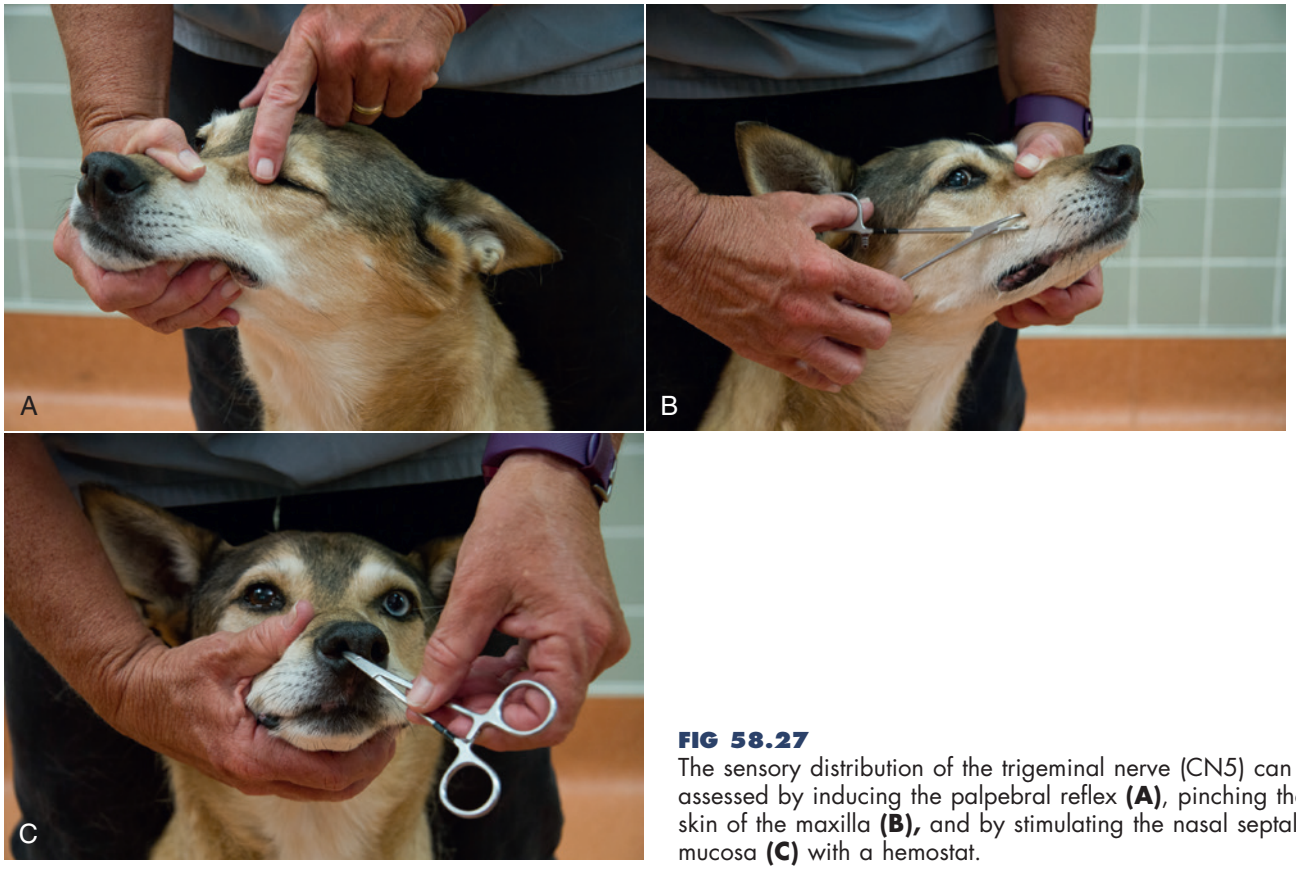


FIG 58.27
The sensory distribution of the trigeminal nerve (CN5) can be assessed by inducing the palpebral reflex **(A)**, pinching the skin of the maxilla **(B),** and by stimulating the nasal septal mucosa **(C)** with a hemostat.



FIG 58.28
Bilateral motor paralysis of the trigeminal nerve results in an inability of this 6-year-old Labrador Retriever to close its mouth.

dogs with trigeminal paralysis may decrease reflex release of tears and trophic factors, leading to keratitis (neurotrophic keratitis) and corneal ulceration in some dogs.

Evaluation of the Facial (CN7) Nerves

The facial nerve provides motor innervation to the muscles of the face and sensory innervation to the rostral two thirds of the tongue (for taste) and palate. Parasympathetic fibers innervate the lacrimal glands and the mandibular and sublingual salivary glands. Motor function is assessed by examining the face for symmetry and observing spontaneous blinking and ear movements, as well as by eliciting the palpebral reflex, the blink induced by the menace response, and the ability to twitch the face in response to a pinch (sensory CN5, motor CN7) (Fig. 58.29, *A, B, C*). Because the facial nerve courses through the middle ear before distribution to the muscles of the face, middle ear lesions can cause facial nerve dysfunction. The Schirmer tear test should be used to evaluate tear production in animals with facial paresis or paralysis.

Evaluation of the Glossopharyngeal (CN9), Vagus (CN10), and Hypoglossal (CN12) Nerves

The glossopharyngeal, vagus, and hypoglossal nerves are usually evaluated together as components of the gag reflex and normal eating and drinking. The glossopharyngeal nerve (CN9) provides motor innervation to the pharynx and palate and sensory innervation to the caudal third of the tongue and pharynx (providing the sense of taste). It also provides parasympathetic stimulation to the parotid and zygomatic salivary glands. The vagus nerve (CN10) provides motor and sensory innervation to the larynx, pharynx, and esophagus and sensory innervation to the thoracic and abdominal viscera. The parasympathetic portion of the



FIG 58.29
Motor function of the muscles of facial expression can be checked by inducing the palpebral reflex **(A)** and evaluating the ability of the lip to twitch in response to a pinch **(B)**. This dog **(C)** has right-sided facial paralysis causing a lip droop and inability to blink the right eye.

vagus provides motor innervation to most thoracic and abdominal viscera. The hypoglossal nerve (CN12) provides motor innervation to the tongue.

The swallowing or gag reflex (CN9 and CN10) can be evaluated by applying external pressure in the hyoid region to induce swallowing or by stimulating the pharynx with a finger to induce the gag reflex. It may be more practical to simply watch the animal eat and drink. The parasympathetic portion of CN10 can be tested by measuring the reflex bradycardia that normally occurs when digital pressure is applied to both eyeballs (oculocardiac reflex). The hypoglossal nerve (CN12) can be evaluated by inspecting the tongue for atrophy or asymmetry (Fig. 58.30) and observing tongue movement during eating and drinking or when licking food paste placed on the nose. Acute unilateral lesions of CN12 can result in deviation of the tongue to either direction, but chronic unilateral lesions result in ipsilateral atrophy and protrusion of the tongue towards the side of the lesion.

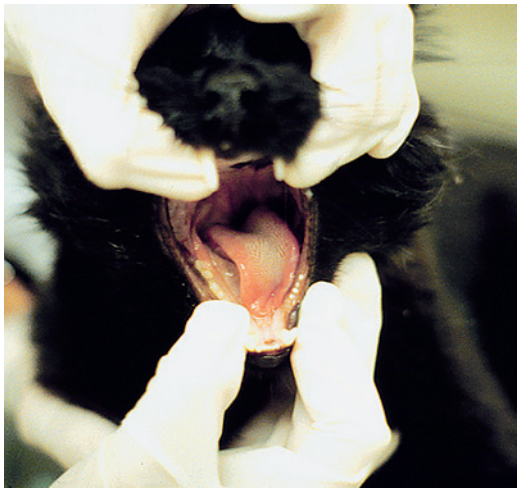


FIG 58.30
Deviation and atrophy of the tongue caused by left-sided hypoglossal nerve (CN12) paralysis.

LESION LOCALIZATION

After the neurologic examination is completed, an animal's mentation, cranial nerves, posture, gait, forelimbs, rear limbs, perineum, anus, and bladder can be characterized as normal or abnormal. If disease above the foramen magnum is present, clinical findings should allow a lesion to be localized to a specific region of the brain. In patients with spinal cord disease, determining whether the neurologic abnormality in each limb is UMN or LMN in origin allows localization to a region of the spinal cord or specific spinal cord segments (see Box 58.4). When LMN signs are present in a single limb, the lesion can often be even more precisely localized by determining the muscles affected and, if sensory nerves are also affected, by testing sensation in dermatomes. Focal hyperpathia may also help to precisely localize a lesion. Whenever possible, the clinician should be able to explain all detected neurologic abnormalities on the basis of a single lesion. Occasionally, however, this will be impossible because the animal has multiple foci of disease or a diffuse disorder.

DIAGNOSTIC APPROACH

Once a neurologic lesion has been localized, it is necessary to generate a list of likely differential diagnoses. This list should take into account the signalment, historical data, the neuroanatomic location of the lesion, and the nature of the onset and progression of neurologic signs. It is important to consider all possible mechanisms or causes of disease that can affect the nervous system (Box 58.9). Once a list of likely differential diagnoses has been developed, diagnostic tests can be performed to confirm or exclude each.

ANIMAL HISTORY

Patient age, gender, breed, and lifestyle may provide clues regarding the underlying disease. Young animals are most likely to be seen because of congenital or hereditary disorders; they are also at highest risk for intoxications and most infectious diseases. Older animals are more susceptible to neoplastic diseases and many of the known degenerative disorders. Certain breeds are predisposed to particular disorders, and there are many congenital and inherited disorders that have been seen in only one or a few breeds. Dogs engaging in particular competitive or working activities (e.g., hunting, herding, racing, jumping) may be at increased risk for specific activity-related injuries. Potential exposure to trauma, toxins, and infectious disorders should be ascertained through careful history taking.

BOX 58.9

DAMNIT-VP Scheme: Mechanisms of Disease

D	Degenerative
A	Anomalous
M	Metabolic, malformation
N	Neoplastic, nutritional
I	Infectious, inflammatory, immune, iatrogenic, idiopathic
T	Traumatic, toxic
V	Vascular
P	Parasitic

DISEASE ONSET AND PROGRESSION

Evaluation of the onset and progression of neurologic signs is of primary importance in prioritizing the list of differential diagnoses (Box 58.10). The signs may be peracute and nonprogressive, or they may become progressively more severe with time. In peracute disorders, the time of onset of the neurologic signs can be pinpointed exactly, with the animal going from being normal to abnormal within minutes or hours. Signs reach maximal intensity very rapidly and then remain static or improve over time. Examples include external trauma, internal trauma from intervertebral disk extrusion, vascular disorders such as infarcts or hemorrhage, and some rapid-acting intoxications such as strychnine. Rarely, animals with a typically slow progressive disorder (e.g., tumor) present with a peracute exacerbation of their signs as a result of hemorrhage or fracture at the site of the tumor. A thorough history will often reveal that these animals were not entirely normal before the acute deterioration.

Neurologic disorders with fairly rapid deterioration over days to weeks are classified as subacute and progressive. Infectious and noninfectious inflammatory diseases and some of the more rapidly progressive neoplasms (e.g., lymphomas, metastatic malignancies) usually fall into this category. Metabolic and nutritional disorders and some intoxications can also cause subacute progressive signs. Animals with chronic progressive signs that develop very slowly over many weeks or months are most likely to have neoplastic or degenerative disease.

BOX 58.10

Characterization of Disease Processes Based on Onset and Progression

Peracute (Minutes to Hours)

External trauma
Hemorrhage
Infarct
Internal trauma (disk extrusion, fracture)
Some intoxications

Subacute Progressive (Days to Weeks)

Infectious disease
Noninfectious inflammatory disease
Rapidly growing tumors (lymphoma, metastatic neoplasia)
Metabolic disorders
Some intoxications

Chronic Progressive (Months)

Most tumors
Degenerative disorders

Suggested Readings

DeLahunta A, Glass E, Kent M. *Veterinary anatomy and clinical neurology*. ed 4. Philadelphia: WB Saunders; 2014.

Garosi L, Lowrie M. Neurological examination. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Garosi L. Neurological examination of the cat. *J Feline Med Surg*. 2009;11:340.

Sharp NJH, Wheeler SJ. *Small animal spinal disorders*. Philadelphia: Elsevier; 2005.

Taylor SM. Neurological examination. In: Taylor SM, ed. *Small animal clinical techniques*. 2nd ed. St. Louis: Elsevier; 2016.

Thomas WB. Evaluation of veterinary patients with brain disease. *Vet Clin North Am Small Anim Pract*. 2010;40:1.

CHAPTER 59

Diagnostic Tests for Nervous System and Neuromuscular Disorders



NEUROLOGIC EXAMINATION

A complete neurologic examination (Chapter 58) will enable the clinician to localize disease to a clinically relevant region of the nervous system. The neuroanatomic location of the lesion and the onset and progression of neurologic signs are important when developing a prioritized list of reasonable differential diagnoses. Once a list of likely differential diagnoses has been developed, diagnostic tests can be performed to confirm or exclude each.

SEARCH FOR SYSTEMIC ABNORMALITIES

Identification of concurrent systemic abnormalities may aid in the diagnosis of neoplastic, metabolic, or inflammatory disorders affecting the nervous system. A complete physical examination should be performed with particular attention to structures that have the potential to directly contact the nervous system such as eyes, ears, and bones of the spine and skull. Organs commonly affected by cancers with a high potential for nervous system metastasis such as skin, lymph nodes, mammary chain, prostate, and spleen should be carefully assessed whenever metastatic cancer to the nervous system is considered. A complete ophthalmologic evaluation including a funduscopic examination can identify abnormalities suggesting infectious or neoplastic disease.

Whenever metastatic neoplasia is being considered as a differential diagnosis for brain or spinal cord signs, a systemic cancer search should be performed, including thoracic and abdominal radiographs, abdominal ultrasound, and cytologic examination of fine-needle aspirates from lymph nodes and any cutaneous or internal masses. Imaging modalities and laboratory tests that allow diagnosis of specific nervous system disorders are limited, so identification and characterization of associated abnormalities in other tissues can facilitate diagnosis. More specific targeted diagnostic tests can then be performed to further evaluate animals with neurologic disease and thereby arrive at a specific diagnosis.

ROUTINE LABORATORY EVALUATION

Laboratory evaluation is used to search for a metabolic cause of encephalopathy in animals with seizures or other signs suggesting diffuse forebrain dysfunction, to characterize systemic disease, or to identify clinicopathologic abnormalities associated with some primary neurologic disorders. Routine testing including a complete blood count (CBC), serum biochemistry profile, and urinalysis is recommended in all patients with nervous system disease.

Hematologic findings are rarely specific, but a leukocytosis may suggest inflammatory disease. Dogs with acute canine distemper infection may be lymphopenic, and rarely inclusion bodies are identified within red blood cells (RBCs) and lymphocytes. Morulae are sometimes seen within neutrophils from dogs with granulocytic ehrlichiosis. Microcytosis with or without thrombocytopenia is common in dogs with portosystemic shunts. Rarely, atypical lymphocytes are identified in the blood from an animal with brain or spinal cord lymphoma.

A serum biochemical profile is most useful in identifying metabolic disorders causing neuropathies, encephalopathies, or seizures. A normal biochemistry profile can be used to eliminate diabetes mellitus, hypoglycemia, hypocalcemia, hypokalemia, uremia, and serum electrolyte disorders from the list of differential diagnoses. Serum creatine kinase is elevated in dogs and cats with muscle inflammation or necrosis. Urine specific gravity can be used to differentiate primary renal from prerenal azotemia. Ammonium biurate crystals are occasionally found in the urine of dogs and cats with portosystemic shunts (see Chapter 34).

Additional biochemical tests are frequently performed during the diagnostic evaluation of patients with neurologic disorders. Preprandial and postprandial bile acids are routinely measured to rule out hepatic encephalopathy in animals with forebrain signs and to monitor liver

function in animals being chronically treated with some anticonvulsants. Alternatively, provocative ammonia tolerance testing can be used to assess hepatic function in nonencephalopathic patients, and resting ammonia concentration can be measured in encephalopathic patients. Serum concentrations of anti-epileptic drugs are routinely monitored so that dosages can be adjusted to maximize efficacy and minimize toxicity (see Chapter 62). Several endocrine disorders can cause neurologic signs so specific testing is warranted whenever thyroid disease, adrenal gland dysfunction, or abnormalities of calcium or glucose metabolism could be responsible for an animal's neurologic signs.

IMMUNOLOGY, SEROLOGY, AND MICROBIOLOGY

A number of special diagnostic tests can be performed in patients with neurologic disorders when infectious or immune-mediated diagnoses are being considered. Clinicians should routinely perform bacterial culture of the cerebrospinal fluid (CSF), urine, and potentially blood in patients with inflammatory disease of the brain, spinal cord, or meninges. Concurrent systemic illness, potential for exposure, and vaccination status will determine what additional infectious disease testing is warranted. When lesions outside the CNS are identified (e.g., pneumonia, dermatitis), the most direct route to a diagnosis is usually by sampling those extraneural sites. Serum antibody or antigen tests are available for many of the infectious agents that can affect the CNS. An increased titer of a specific antibody in CSF relative to that in serum may be required to make a definitive diagnosis. Alternatively, immunohistochemical staining can be used to identify organisms in tissue (brain, spinal cord, muscle). In some cases, polymerase chain reaction (PCR) analysis is available for diagnosis of active infection by a specific organism.

Immune-mediated CNS disorders such as steroid-responsive meningitis-arteritis (SRMA), meningoencephalitis of unknown etiology (MUE), and granulomatous meningoencephalomyelitis (GME) are relatively common in dogs. Diagnosis requires finding typical clinical and clinicopathologic abnormalities and eliminating the possibility of infectious disorders, as previously discussed. Dogs with SRMA commonly have elevated serum and CSF immunoglobulin (IgA) levels, and some have concurrent immune-mediated polyarthritis that contributes to the diagnosis. In dogs with polyneuropathies, polymyositis, or apparent multisystemic immune-mediated disease, it may be useful to measure antinuclear antibody (ANA) titers to support a diagnosis of systemic lupus erythematosus (SLE). Most dogs with acquired myasthenia gravis have detectable circulating antibodies against acetylcholine receptors, and some dogs with masticatory muscle myositis have circulating serum antibodies directed against type 2M myofibers (see Chapter 67).

ROUTINE SYSTEMIC DIAGNOSTIC IMAGING

RADIOGRAPHS

Radiographs of the thorax are a useful screening test for metastatic neoplasia, some infectious disorders affecting the lung, and megaesophagus. Abdominal radiographs are useful for assessing liver size and organomegaly. Radiographs are noninvasive tests that should be performed routinely in animals with nervous system signs.

ULTRASOUND

Abdominal ultrasound is recommended to search for a primary tumor whenever metastatic neoplasia is considered as a possible cause of neurologic signs. Fine-needle aspirates of masses and enlarged organs should be submitted for cytologic evaluation. Ultrasound can also be used to identify portosystemic shunts in dogs and cats with forebrain signs.

DIAGNOSTIC IMAGING OF THE NERVOUS SYSTEM

SPINAL RADIOGRAPHS

Spinal radiographs are useful in the diagnosis of congenital malformations, fractures and luxations, disk disease, degenerative disease of the vertebrae or articular facets, diskospondylitis, and primary or metastatic vertebral neoplasia. Radiographs should be centered on the region of clinical interest established by the neurologic examination. General anesthesia is required to obtain lateral and ventrodorsal radiographs of sufficient quality to permit the detection of subtle abnormalities, but more obvious changes can often be identified with simple sedation. Radiographs are a useful first-line test but are not a very sensitive test for spinal disease. Vertebral bone lysis will not be detected radiographically until more than 50% of the cancellous bone is lost. Neoplasia affecting the soft tissues of the brain or spinal cord rarely causes abnormalities on plain radiographs.

MYELOGRAPHY

Myelography involves the intrathecal injection of a nonionic contrast medium followed by acquisition of lateral, ventrodorsal, and oblique radiographs to visualize the distribution of contrast material within the subarachnoid space. Historically, myelography has been most useful in identifying and localizing spinal cord compressive lesions such as herniated disks or tumors. During the last two decades, computed tomography (CT) and magnetic resonance imaging (MRI) have become more readily available and have largely replaced myelography for characterizing spinal lesions. Myelography is still a useful imaging study for patients with spinal cord disease when CT and MRI are unavailable.

CSF should always be collected before performing a myelogram, and it should be either analyzed or preserved for analysis. Injection of contrast will cause mild inflammation,

making diagnostic interpretation of CSF cytology difficult for at least 1 week after myelography.

Myelography can be technically difficult to perform and is associated with some risk of complications. The animal is anesthetized, CSF is collected for analysis, and survey radiographs are performed. Contrast material is introduced into the subarachnoid space at the atlanto-occipital (AO) or lumbar (L5/6) space. Lumbar injections are technically more difficult but associated with decreased risk of iatrogenic spinal cord trauma and improved delineation of thoracic and lumbar compressive spinal cord lesions, because the contrast material can be injected under increased pressure and forced around a site of severe compression. The techniques for cervical and lumbar myelography are described in detail elsewhere (see Suggested Readings).

Seizures occur in 10% to 20% of animals recovering from anesthesia after myelography and are most likely to occur in dogs larger than 29 kg requiring a large volume of contrast medium and when cisternal myelography is performed. These seizures can usually be controlled with diazepam (5-20 mg, administered intravenously). Neurologic deterioration occurs in some animals after myelography. Large-breed dogs with cervical spondylomyelopathy (Wobbler syndrome), dogs and cats with inflammatory CNS disease or extradural tumors, and dogs with degenerative myelopathy are most often affected. Fortunately this deterioration is usually transient.

A normal myelogram will show contrast material filling the subarachnoid space. This appears as a column of contrast agent on each side of the cord on ventrodorsal views and in the ventral and dorsal columns on lateral views (Fig. 59.1). In normal myelograms, a slight elevation and thinning of the ventral column of the contrast agent can be seen as it passes over each intervertebral disk space; however, a wide dorsal column remains, indicating that spinal cord compression is not present. Based on the features of the myelogram, a spinal cord lesion can be characterized as extradural compression, intradural extramedullary compression, or intramedullary swelling (Fig. 59.2). When available, the use of CT after myelography enhances visualization of small amounts of contrast in the subarachnoid space, allowing more precise lesion localization and diagnosis. This can be very helpful in determining location and laterality in the emergency evaluation of patients with acute nonmineralized disk extrusions. A much lower dose of contrast medium is required for CT myelography than for conventional myelograms (25% of contrast medium dose), decreasing the risk of myelogram-associated complications.

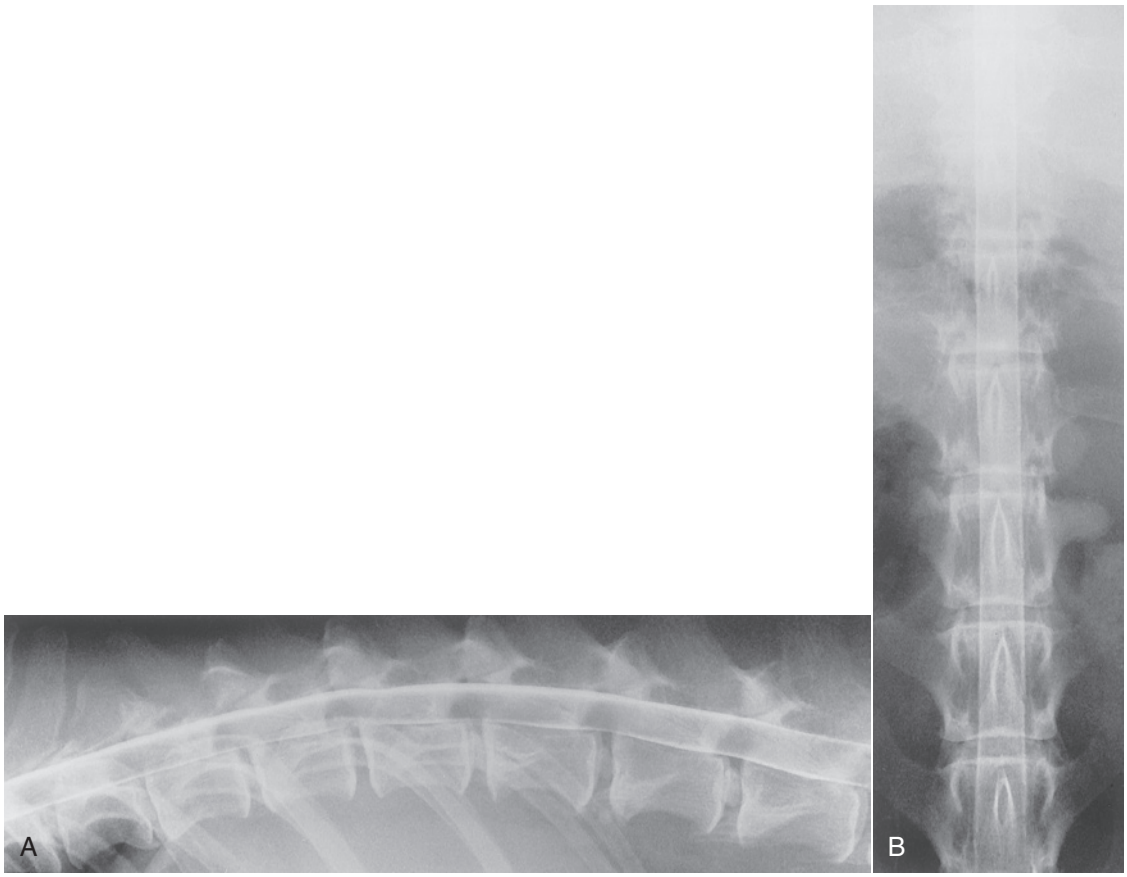


FIG 59.1
Lateral **(A)** and ventrodorsal **(B)** views of a normal myelogram of the thoracolumbar region in a dog. Multiple calcified intervertebral disks can be seen, but no spinal cord compression is evident. (Courtesy Dr. John Pharr, University of Saskatchewan.)

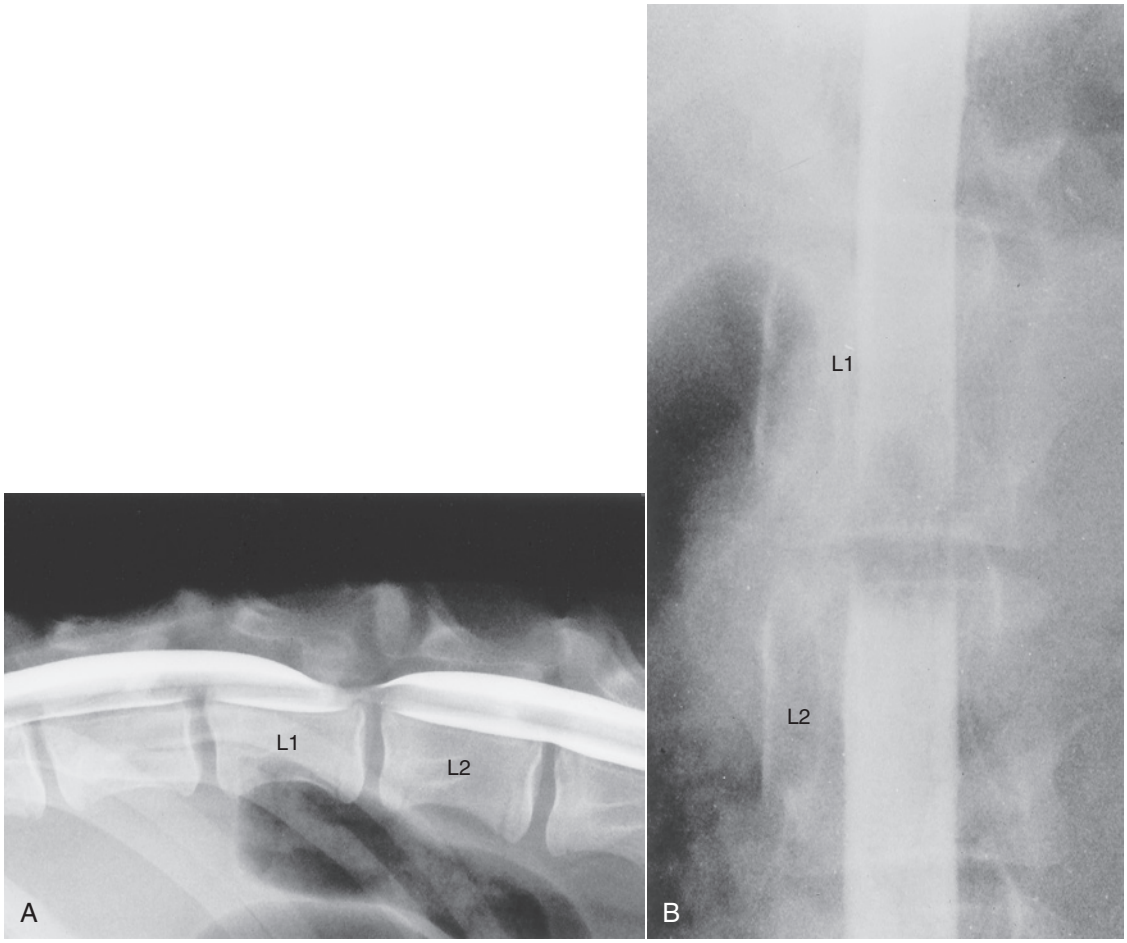


FIG 59.2
Lateral **(A)** and ventrodorsal **(B)** views of a myelogram in a 5-month-old German Shepherd Dog with a 3-week history of progressive ataxia. A dorsally located extradural compression of the spinal cord within the caudal portion of the L1 vertebra can be seen. At necropsy, the dog was found to have a single focal cartilaginous exostosis of the roof of the L1 vertebra.

COMPUTED TOMOGRAPHY

CT is most useful for identifying and characterizing bony abnormalities of the vertebral bodies and skull, particularly in patients with vertebral fractures/luxations, acute mineralized disk extrusions, vertebral tumors, bony lesions of cervical spondylomyelopathy, otitis media/interna, and fungal or neoplastic disease involving the nasal cavity or sinuses. Visualization and determining the laterality of nonmineralized disk extrusions using CT can be improved by administering nonionic water soluble iodinated contrast material into the subarachnoid space (CT-myelogram) or intravenously (CT-IV contrast). Although intraparenchymal detail of the brain and spinal cord is generally poor using CT alone, gross distortions and asymmetry can often be visualized. Precontrast and postcontrast images can be compared with highlight lesions that have increased vascularity or leaky vessels like many tumors or inflammatory lesions (Fig. 59.3)

During CT image acquisition an X-ray tube moves in a circular direction around the animal, and detectors measure X-rays projected through the animal. Images are reconstructed from this data, generating transverse and sagittal image slices and the potential for construction of images in other planes and 3-D volume renderings. This process is very rapid, resulting in very short scan times. CT scans are less expensive and more readily available than MRI, and can be performed under sedation rather than general anesthesia in stable patients.

MAGNETIC RESONANCE IMAGING

MRI, when available, is the imaging modality of choice for all lesions involving brain or spinal cord parenchyma, and peripheral nerves. MR images provide excellent soft tissue contrast resolution, displaying excellent neuroanatomical detail while providing insight into tissue composition and response to injury. The appearance of brain lesions using different MRI sequences not only localizes lesions precisely but helps distinguish inflammatory, neoplastic, and hemorrhagic lesions and infarcts. In animals with brain tumors,

anatomic location together with MRI characteristics can be used to predict tumor type in many cases (Figs. 59.4 and 59.5). Spinal MRI has been shown to be superior to CT and myelography in the imaging of dogs with cervical spondylomyelopathy, intervertebral disk herniation, synovial cysts, lumbosacral stenosis, spinal cord neoplasia, diskospondylitis, and vascular events such as bleeds, infarcts, and fibrocartilaginous emboli (Fig. 59.6). In addition to identifying sites of spinal cord compression, MRI allows evaluation of the response of neural tissues to compression, helping differentiate lesions causing acute clinical signs from older, more chronic lesions and scars.

MR images are generated by the effect of transiently applied radiofrequency currents on protons that are aligned by the strong magnetic field of the MRI scanner. When the radiofrequency pulse is halted, the protons realign and generate their own radiofrequency signal, which is measured by a coil. The combination of magnetic fields and radiofrequency pulses used to create an MRI image are called a pulse sequence. Different MRI sequences provide different information about tissues. The most common MR images used in veterinary neurology are T1-weighted and T2-weighted spin-echo images. Free fluid and most fluid within tissues (CSF, edema), appear black (low signal, hypointense compared with normal CNS parenchyma) on T1-weighted images and white (high signal, hyperintense compared with normal CNS parenchyma) on T2-weighted images.

Many tumors and inflammatory disorders result in increased fluid in tissues so have regions of increased T2-weighted signal intensity (bright regions). Wispy regions of high signal around lesions on T2-weighted images may represent edema. (Table 59.1) T1-weighted sequences are good for evaluating anatomy but are poor at detecting most lesions until MR imaging contrast material (gadolinium) is administered. In the regions where contrast leaks into the parenchyma due to a disrupted blood-brain barrier, there will be increased signal intensity (brightness on T1-contrast) representing the regions of the lesion that have a strong blood supply (see Fig. 59.4). In addition to the T1- and T2-weighted images obtained using routine spin-echo sequences, inversion recovery sequences can be used to suppress the high signal from fat using a short tau inversion recovery (STIR) sequence or the signal from free fluid using a fluid attenuated inversion recovery (FLAIR) sequence. Suppression of the signal from free fluid with a FLAIR sequence (making it hypointense) makes it possible to distinguish between cystic lesions and tissue edema within brain parenchyma and also improves visualization of subtle lesions adjacent to ventricular or subarachnoid CSF (see Table 59.1) It is important that MR images of the brain and spinal cord be evaluated and interpreted by specialists who are able to distinguish artifacts from actual lesions and are familiar with the rapidly expanding literature regarding the MRI characteristics of neurologic lesions. More details can be found in the recommended readings.



FIG 59.3
Computed tomography (CT) scan of the head of an 11-year-old Golden Retriever with a 5-month history of seizures and a progressive right head tilt. There is a large cystic, contrast-enhancing mass in the left cerebrum and cerebellum, most consistent with a cystic meningioma.

CEREBROSPINAL FLUID COLLECTION AND ANALYSIS

INDICATIONS

Analysis of CSF can be useful in the diagnostic evaluation of patients with CNS disease. Typical alterations in CSF

TABLE 59.1

The Appearance of CSF, Tissue Edema, and Fat With MR Imaging Sequences

SEQUENCE	CSF	TISSUE EDEMA	FAT	VASCULAR LESION
T1-weighted spin-echo	hypointense	hypointense	hyperintense	— — —
T1-weighted with contrast	hypointense	hypointense	hyperintense	hyperintense
T2-weighted spin-echo	hyperintense	hyperintense	hyperintense	— — —
T2 FLAIR	hypointense	hyperintense	hyperintense	— — —
T2 STIR	hyperintense	hyperintense	hypointense	— — —

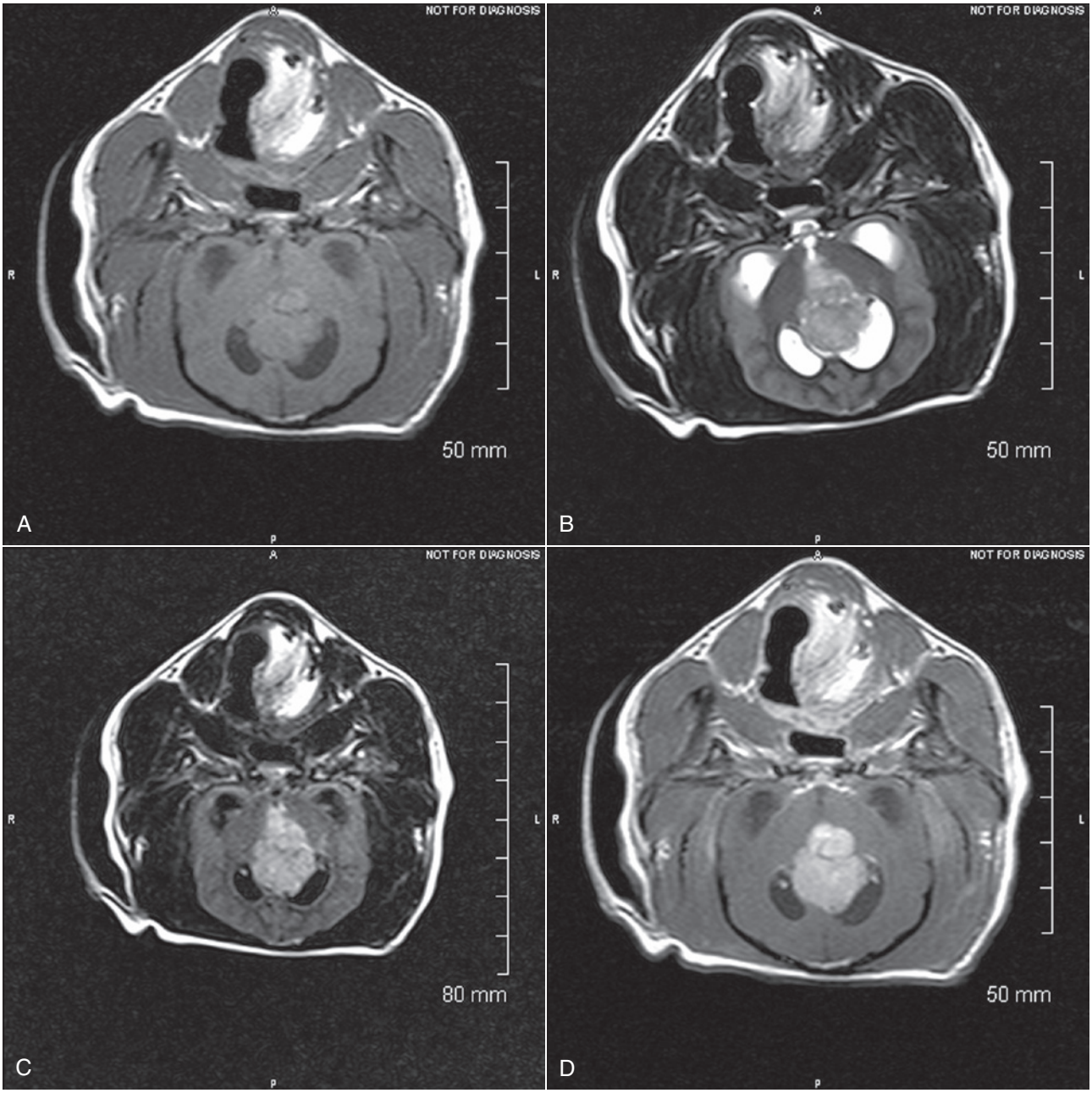


FIG 59.4
MR images from a 7-year-old Shih Tzu with a 2-month history of seizures. There is a large mass originating from the axial margin of the left lateral ventricle. The lesion is isointense on T1W **(A)**, hyperintense on T2W **(B)** and FLAIR **(C),** and strongly contrast enhancing on T1W-C **(D)**. (Courtesy Dr. Sally Sukut, University of Saskatchewan.)

cytology and protein concentration aid diagnosis in many conditions. Bacterial culture, PCR, and antibody determination in CSF can occasionally lead to a definitive diagnosis in patients with infectious CNS disease. CSF examination should be performed in most animals with certain or suspected brain or spinal cord disease in which a diagnosis is not readily apparent based on historical features, systemic abnormalities, and results of imaging. Analysis of CSF is most likely to contribute to diagnosis in dogs and cats with inflammatory CNS disease; patients with progressive forebrain signs and animals with fever and neck pain have the highest likelihood of CSF cytology being diagnostic.

CONTRAINDICATIONS

If proper technique is followed, the procedure for obtaining CSF is safe and simple. The animal is first placed under general anesthesia, and the puncture site is prepared in a sterile fashion. Spinal puncture should not be performed in

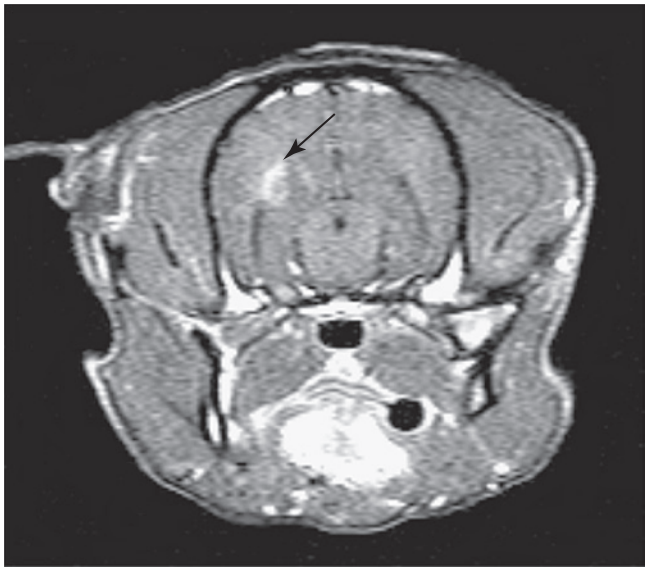


FIG 59.5
Magnetic resonance imaging (MRI) scan (transverse T1 image) of the brain of a 2-year-old Boston Terrier with a 2-week history of behavior change and difficulty walking. There is a 1-cm lesion within the right cerebrum that enhances with contrast *(arrow)*. This dog had granulomatous meningoencephalitis (GME) in his brain and cervical spinal cord.

BOX 59.1

Signs Suggesting Increased Intracranial Pressure

Depressed mentation or abnormal behavior
Constricted, dilated, or unresponsive pupils
Bradycardia
Increased arterial blood pressure
Altered breathing pattern

BOX 59.2

Treatment Steps to Decrease Intracranial Pressure

Oxygenate
Administer 20% mannitol: 1 g/kg, administered intravenously over 15 minutes
Furosemide: 1 mg/kg, administered intravenously
If anesthesia is necessary:
Rapid induction, intubate, and ventilate to maintain $Paco_2$ 30-40 mm Hg

an animal that is an obvious anesthetic risk or that has a severe coagulopathy. General anesthesia and collection of CSF should not be performed in any patient with suspected increased intracranial pressure (Box 59.1) without first taking steps to lower the intracranial pressure; this decreases the risk of brain herniation (Box 59.2).

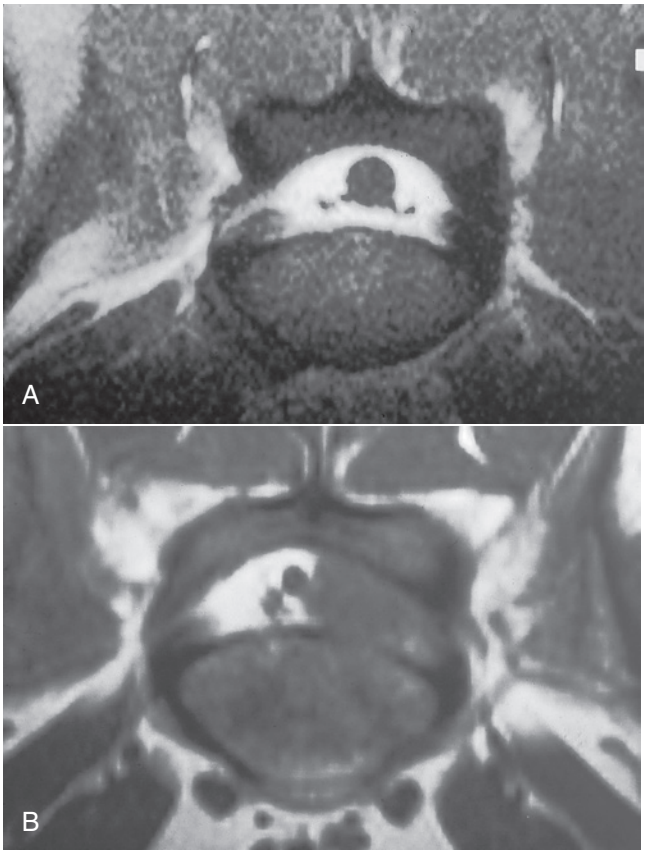


FIG 59.6
Magnetic resonance imaging (MRI) scans (transverse T1 images) of the caudal lumbar region of **(A)** a normal dog and **(B)** a Golden Retriever with prolapsed disk material within the vertebral canal. (Courtesy Dr. John Pharr, University of Saskatchewan.)

TECHNIQUE

In dogs and cats the most reliable source of CSF for analysis is the cerebellomedullary cistern (CMC), also termed the AO site. Lumbar CSF collection from the L5-L6 site may also be used, but it is more difficult to obtain a large volume of uncontaminated fluid from this site. CSF is produced by the choroid plexi within the ventricular system of the brain and flows from cranial to caudal, so when there is focal disease, CSF samples are most likely to be abnormal when collected caudal to the lesion. It is recommended to collect both lumbar and CMC CSF in animals with spinal cord disease.

Cisternal Puncture

With the animal under general anesthesia, clip and scrub the back of its neck between the ears from 2 cm rostral to the occipital protuberance to C2. If the clinician is right handed, the animal should be placed in right lateral recumbency with its neck flexed so that the median axis of the head is perpendicular to the spine. The nose should be elevated slightly so that its midline is parallel to the surface of the table. With the thumb and third finger of the left hand, the clinician should palpate the cranial edges of the wings of the atlas and

draw an imaginary line at their most cranial aspect. If that imaginary line is not perpendicular to the table, then padding should be placed under the animal's shoulder to bring the wings into alignment.

The examiner can then use the left index finger to palpate the external occipital protuberance and draw a second imaginary line caudally from that site along the dorsal midline. The needle should be inserted where the two imaginary lines intersect (Fig. 59.7) (Video 59.1).

A 1½ or 3-inch-long (3.75-7.5 cm) styletted spinal needle is then directed straight in through the skin (perpendicular to the spine) and into the underlying tissues, with the bevel directed cranially. The needle is advanced 1 to 2 mm at a time, and the stylette is removed so that the clinician can look for CSF. While the right hand is used to remove the stylette, the thumb and first finger of the left hand, which is rested against the spine for support, should grasp and stabilize the hub of the needle. A "pop" may be felt as the dorsal AO membrane and the dura mater and arachnoid mater are penetrated simultaneously (Fig. 59.8). This is not a reliable sign, however, and the level at which the subarachnoid space is reached varies greatly with the breed and individual animal. It is often very close to the skin surface in toy breeds and some cats.

If the needle strikes bone, it should be withdrawn, the patient position and landmarks reassessed, and the procedure repeated. If whole blood appears in the spinal needle, the needle should be withdrawn and the procedure repeated with another sterile needle. When CSF is observed, the fluid should be allowed to drip directly from the needle into a test tube. The clinician should check with the laboratory to determine the type of tube preferred for collection of CSF. Plastic tubes are preferred because cells may adhere to glass tubes. Grossly hemorrhagic CSF should be collected into a tube containing ethylenediaminetetraacetic acid (EDTA) to prevent clotting but samples for bacterial culture should be free of anticoagulant. The amount of CSF collected ranges from 0.5 to 3 mL depending on the size of the animal (no more than 1 mL/5 kg body weight). Simultaneous jugular vein compression may hasten flow but will transiently increase intracranial pressure. Blood in the CSF may be the result of the disease or the tap. If it is caused by the procedure, the amount of blood should decrease as the CSF drips from the needle. If this occurs, some of the less contaminated fluid should be collected in a second tube for cytologic evaluation. Mild CSF contamination with hemorrhage (<500 RBCs/μL) does not alter the CSF protein and leukocyte determinations.

Lumbar Puncture

The animal is placed in lateral recumbency with its trunk flexed. Foam cushions are placed between its limbs and beneath the lumbar region to achieve true lateral positioning. The spines of the lumbar vertebrae are palpated; the first dorsal spinous process that can be palpated cranial to the ilial crests is L6. Lumbar puncture should be performed at the L4-L5 or the L5-L6 space (ideal) in dogs and the L6-L7 space in cats. To access the L5-L6 space, a 3½-inch (8.75-cm) spinal needle is inserted on midline at the cranial edge of the dorsal spinal process of L6 and directed ventrally into the ligamentum flavum (Fig. 59.9). The needle is passed in a smooth motion through or alongside the caudal spinal cord and cauda equina into the ventral subarachnoid space. The animal's tail and pelvic limbs may twitch when the cord is penetrated. Because CSF flow is slower from this site and more likely to be contaminated by blood, cerebellomedullary collection is usually preferred for diagnostic purposes.

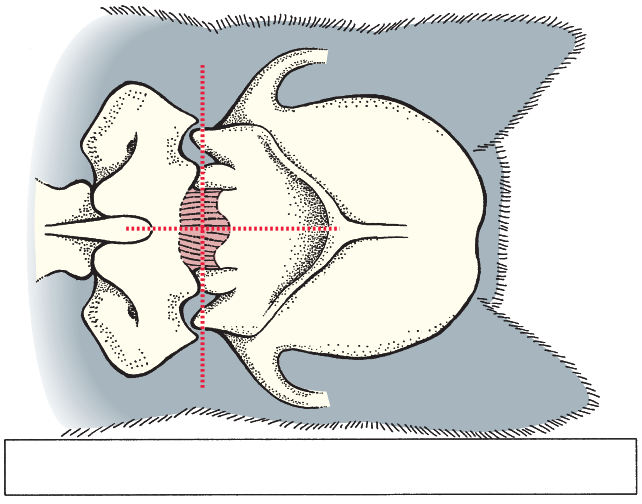


FIG 59.7
Landmarks for cerebrospinal fluid (CSF) collection at the cerebellomedullary cistern. The site of needle entry is at the intersection of the dorsal midline and the most cranial aspect of the wings of the atlas.

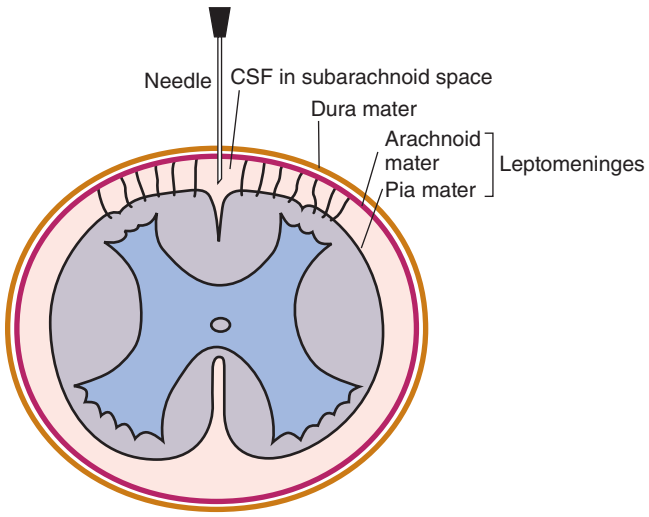


FIG 59.8
Transverse section showing the relationship among the meninges, cerebrospinal fluid (CSF), and spinal cord. Needle tip is in the subarachnoid space, as it would be for CSF collection or myelography.

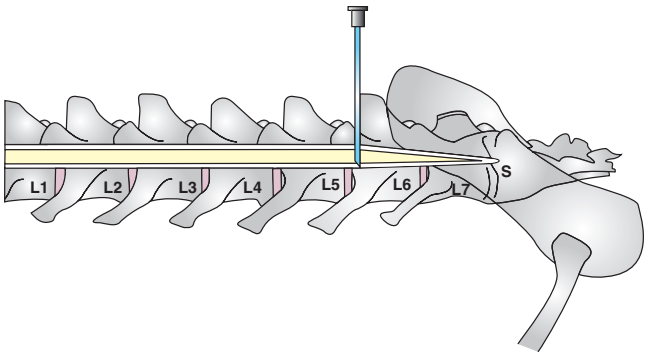


FIG 59.9
Landmarks for cerebrospinal fluid (CSF) collection from a lumbar site. The needle is inserted at the cranial edge of the dorsal spinal process of the L6 vertebra and directed into the ventral subarachnoid space. (From Taylor SM: *Small animal clinical techniques,* St Louis, 2010, Elsevier.)

ANALYSIS

Normal CSF is clear and colorless. A cell count should be performed and a cytologic preparation made for examination as soon as possible because white blood cells (WBCs) in the CSF deteriorate rapidly. If the sample must be stored for longer than 1 hour before analysis, the specimen should be refrigerated to slow cellular degeneration. Abnormal CSF with high protein and cell count can be refrigerated for up to 8 hours without changing diagnostic interpretation, but cellular degeneration is rapid in samples with normal protein concentration. The addition of autologous serum (10% by volume of the sample or 3 drops of serum/0.25 mL CSF) will preserve CSF so that cytologic analysis 24 to 48 hours after collection will yield reliable results, but a separate sample should be saved for protein analysis. Alternatively, hetastarch (6% hydroxyethyl starch in 0.9% NaCl [Abbott Laboratories, North Chicago, Ill]) can be added to CSF in equal volume (1:1) to preserve cytologic features without affecting the protein measurement (but diluting it by half) when CSF must be stored for longer than 1 hour before analysis.

Once the fluid is collected, a total cell count is performed and the concentration of RBCs and WBCs is determined. The normal range of values varies with each laboratory, but in general there should be fewer than 3 to 5 WBCs/μL. An increased number of CSF WBCs is referred to as *pleocytosis.* A pleocytosis should be further characterized by microscopic examination and differential cell count to determine the predominant leukocyte present. Cytologic analysis of CSF is necessary even if the WBC count is normal, because there may be abnormal cell types or organisms present.

A concentration procedure is usually required to obtain sufficient cells for cytologic assessment. Cytocentrifuge concentration of CSF is available in most institutions and commercial laboratories, and results are best if samples are processed within 60 minutes of collection or if samples are preserved as described earlier.

Most of the cells in the CSF of normal dogs and cats are small, well-differentiated lymphocytes (60%-70%). Minimally vacuolated large mononuclear phagocytes comprise most of the additional cells. Occasional neutrophils and eosinophils are present, but these cells should not normally make up more than 2% of the cell population. The typical CSF findings in some specific disorders in dogs and cats are summarized in Box 59.3. It is important to realize, however, that CSF cytologic findings must always be interpreted in relation to the signalment, history, and clinical findings.

If blood contamination is severe, it can influence the cytologic findings, but even grossly apparent iatrogenic contamination with peripheral blood will have only a minor impact on WBC count and protein analysis. To approximate the maximum effect blood contamination will have on the WBC count in CSF, 1 WBC/μL can be expected for every 500 RBCs/μL. Iatrogenic blood contamination can be distinguished from pathologic hemorrhage by the presence of platelets and/or the absence of cytologic evidence of erythrophagia or erythrocyte breakdown pigments in the sample.

The protein content of the collected CSF should be determined. The protein concentration in samples collected from the lumbar site (<40 mg protein/dL) is normally higher than the protein content of CSF collected from the CMC (<25 mg protein/dL). An increase in the CSF protein content can occur in diseases that disrupt the blood-brain barrier, cause local necrosis, interrupt normal CSF flow and absorption, or result in intrathecal globulin production. Whenever the CSF is cellular, it should be submitted for Gram staining and anaerobic and aerobic bacterial culture. If infectious disorders are considered likely (see discussion of meningitis, Chapter 64), specific culture techniques can be applied or, when available, PCR can be used to identify infectious agents in CSF. Antibody titers to a variety of infectious organisms can also be measured in CSF, but blood contamination and leakage of antibodies from the serum to the CSF can be problematic.

ELECTRODIAGNOSTIC TESTING

Electrophysiologic studies can be used to record electrical activity from muscle or neural tissue and aid in lesion localization and characterization. These tests are minimally invasive but usually require sedation or general anesthesia. Equipment costs and the experience needed to conduct the studies limit their use to academic and referral clinics.

ELECTROMYOGRAPHY

Normal muscle is electrically silent. As a needle is inserted into normal muscle, a short burst of electrical activity is elicited, which stops when the needle insertion is stopped. Severance, destruction, or demyelination of the peripheral nerve supplying the muscle results in the development of spontaneous fibrillations and positive sharp waves (i.e., denervation potentials) and prolonged insertional activity in affected muscles 5 to 7 days after denervation. These changes

BOX 59.3

Interpreting Cerebrospinal Fluid Cytology

Normal: Cell Count <5 White Blood Cells/μL; Protein <25 mg/dL

Normal Cell Count and Differential; Slightly Increased Protein
- Extradural spinal cord compression (disk, tumor, malformation, synovial cyst)
- Intramedullary spinal cord mass or dilation
- Brain neoplasia
- Degenerative myelopathy
- Fibrocartilaginous embolism
- Trauma
- Polyradiculoneuritis

Lymphocytic Pleocytosis (>50% lymphocytes)
- Viral meningitis/encephalitis (rabies, distemper)
- Necrotizing meningoencephalitis (Pugs, Malteses, Yorkshire Terriers, Chihuahuas)
- Feline polioencephalomyelitis
- Central nervous system lymphoma

Mixed Cell Pleocytosis (Lymphocytes, Mononuclear Phagocytes, Neutrophils, Plasma Cells)
- Canine granulomatous meningoencephalitis (GME)
- Meningoencephalitis of unknown etiology (MUE)
- Protozoal infection (neosporosis, toxoplasmosis)
- Rickettsial infection (ehrlichiosis, *Rocky Mountain spotted fever*)
- *Feline infectious peritonitis meningoencephalitis*
- *Lyme neuroborreliosis*
- *Fungal meningoencephalitis (blastomycosis, cryptococcosis, aspergillosis)*

Neutrophilic Pleocytosis
- Bacterial meningoencephalitis
- Fungal meningoencephalitis (blastomycosis, cryptococcosis, aspergillosis)
- Steroid-responsive meningitis arteritis
- Rocky Mountain spotted fever
- Feline infectious peritonitis meningoencephalitis
- Lyme neuroborreliosis
- Postmyelographic irritant meningitis

Eosinophilic Pleocytosis
- Steroid-responsive eosinophilic meningitis (especially Golden Retrievers)
- Parasite migration
- *Protozoal infection*
- *Fungal meningoencephalitis*
- *Neoplasia*

Italics signify unusual presentation.

may also be seen in some primary muscle disorders. Electromyography (EMG) is most useful to confirm a suspected diagnosis of a muscle or peripheral nerve disorder and to identify abnormal muscles for subsequent biopsy.

NERVE CONDUCTION VELOCITIES

The conduction velocity of motor nerves can be determined by stimulating a nerve at two separate sites and recording the time it takes for an evoked compound muscle action potential to occur in a target muscle. The motor nerve conduction velocity in the segment of nerve between the two stimulation sites can be determined by measuring the distance between the two sites and the difference in the time it takes for the evoked potentials to appear. Variations on this technique are used to determine conduction in motor nerve roots (F waves) and in sensory (or mixed motor/sensory) nerves. Slow conduction times are seen in demyelinating disorders, allowing the diagnosis of peripheral neuropathies. Nerves that have been injured or avulsed and that have degenerated (onset typically 4-5 days after injury) do not conduct an impulse, so nerve conduction velocity testing can also be used to diagnose and localize peripheral nerve injuries.

ELECTRORETINOGRAPHY

An electroretinogram (ERG) is a recording of the electrical response of the retina to a flashing light stimulus. It is an objective way to evaluate retinal function, assessing both rod and cone receptors. The ERG is most useful for evaluating blind animals in which the retina appears normal on ophthalmic examination (e.g., diagnosing sudden acquired retinal degeneration) or in which the retina cannot be visualized (e.g., determining whether animals with cataracts have concurrent retinal degeneration). The ERG is abnormal with degenerative disorders of the retina, but it is normal if the lesion causing visual dysfunction is located caudal to the retina (in the optic nerves, optic chiasm, optic tract, or cerebral cortex). The ERG can be performed under general anesthesia or under sedation if the patient is uncooperative.

BRAINSTEM AUDITORY EVOKED RESPONSE

The brainstem auditory evoked response (BAER) depicts the response of nervous tissues to an auditory stimulus (a click). The response is a series of waveforms representing activity beginning in the cochlea and being relayed up the auditory pathway in the brainstem. Lesions of the outer, middle, or inner ear; the peripheral vestibulocochlear nerve; and the brainstem caudal to the midbrain cause characteristic changes in the response, aiding in lesion localization. This test has been most widely used for detecting unilateral and bilateral congenital deafness in dogs.

ELECTROENCEPHALOGRAPHY

Electroencephalography provides a graphic record of the spontaneous electrical activity of the cerebral cortex. Results may help determine whether a cerebral disorder is focal or diffuse. Some dogs with epilepsy will have abnormal electroencephalograms (EEGs) between seizures.

BIOPSY OF MUSCLE AND NERVE

MUSCLE BIOPSY

Muscle biopsy specimens should be evaluated when there is clinical and electrophysiologic evidence of muscular disease. A biopsy may provide a definitive diagnosis or indicate the nature of the disease process. For best results, muscle that is affected should be biopsied, and in generalized disorders two different muscles should be sampled. For investigation of myopathic disorders, proximal limb muscles such as the vastus lateralis or triceps should be biopsied, whereas neuropathies are more evident in distal limb muscles such as the cranial tibial or extensor carpi radialis. Because complete histopathologic examination of muscle requires fresh-frozen tissue, most laboratories request that fresh muscle samples be wrapped in a saline-moistened gauze and shipped overnight under refrigeration. Whenever formalin-fixed samples are submitted, the sample should be attached to a splint, such as a tongue depressor, to prevent contraction during fixation. Routine histologic studies may reveal inflammatory or neoplastic changes and the etiologic agent if the disease is infectious.

When fresh-frozen tissue is evaluated using a full range of enzymatic and immunohistochemical techniques, many characteristics of the muscle can be determined. Based on enzymatic staining characteristics, muscle fibers can be classified according to type and the proportion and distribution of myofiber types described. Some myopathies result in a selective loss of one fiber type. Denervation with reinnervation, as occurs in many neuropathies, results in "type grouping," wherein the normal checkerboard pattern disappears and large clusters of fibers of the same type appear. Muscle fiber shape and size, the presence of degeneration or necrosis, the location of nuclei, the presence of vacuoles or inclusions, and the presence of cellular infiltrates are all evaluated. Immunostains are also available to identify some parasites *(Neospora)* and evaluate muscles for normal structural components. Muscle samples should be sent to a laboratory with a special interest and expertise in muscle disorders to ensure that optimal results are obtained and accurately interpreted. Clinicians should consult the laboratory that will process the biopsy to learn the proper technique of obtaining, preparing, and submitting specimens and the other procedures to be followed.

NERVE BIOPSY

It may be useful to obtain nerve biopsy specimens in an effort to evaluate peripheral nerve disorders. Nerves are biopsied by transecting approximately one third of the width of the nerve and removing fascicles about 1 cm in length, leaving most of the nerve trunk intact. It is important to biopsy nerves that are affected. The common peroneal nerve and the ulnar nerve are the mixed (i.e., motor and sensory) nerves most commonly biopsied. As with muscle biopsy specimens, nerve biopsy specimens require special handling to ensure that maximal information is obtained. Samples should be laid out on a piece of wooden tongue depressor and pinned at each end to keep them oriented longitudinally, but they should not be stretched. They should then be fixed in 2.5% glutaraldehyde or buffered 10% formalin for light microscopy. Fresh nerve samples can be frozen in liquid nitrogen and stored for biochemical analysis.

Suggested Readings

Bohn A, et al. Cerebrospinal fluid analysis and magnetic resonance imaging in the diagnosis of neurologic diseases in dogs: a retrospective study. *Vet Clin Pathol*. 2006;35:315.

da Costa RC, Samii VF. Advanced imaging of the spine in small animals. *Vet Clin North Am Small Anim Pract*. 2010;40:765.

Dickinson PJ, LeCouter RA. Muscle and nerve biopsy. *Vet Clin North Am Small Anim Pract*. 2002;32:63.

Fry MM, Vernau W, Kass PH. Effects of time, initial composition and stabilizing agents on the results of canine cerebrospinal fluid analysis. *Vet Clin Pathol*. 2006;35:72.

Hecht S, Adams WH. MRI of brain disease in veterinary patients: part 1: basic principles and congenital brain disorders. *Vet Clin North Am Small Anim Pract*. 2010;40:21.

Olby NJ, Thrall DE. Neuroimaging. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. 4th ed. Gloucester: BSAVA; 2013.

Sharp NJH, Wheeler SJ. Diagnostic aids. In: Sharp NJH, Wheeler SJ, eds. *Small animal spinal disorders: diagnosis and surgery*. 2nd ed. St Louis: Mosby; 2005.

Taylor SM. Cerebrospinal fluid collection. In: Taylor SM, eds. *Small animal clinical techniques*. 2nd ed. Philadelphia: Elsevier; 2016.

Wamsley H, Alleman AR. Clinical pathology. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2004.

CHAPTER 60

Intracranial Disorders



GENERAL CONSIDERATIONS

When the neurologic examination suggests a lesion is located above the foramen magnum, a variety of disorders should be considered as differential diagnoses. Some disorders typically affect only one particular region of the brain (e.g., forebrain, cerebellum, or brainstem), whereas others can affect any location or multiple locations within the brain simultaneously. Localization of intracranial disease will help to determine a reasonable list of differential diagnoses and guide your diagnostic plan.

Altered mentation or seizures with a relatively normal gait are the most pronounced abnormalities in animals with forebrain disease, whereas dull mentation, proprioceptive ataxia, and multiple cranial nerve deficits suggest brainstem disease. Hypermetria and ataxia are common in cerebellar disorders, and lesions of the central vestibular system within the brainstem or cerebellum usually cause a head tilt, loss of balance, and nystagmus (see Chapter 63).

ABNORMAL MENTATION

Abnormal behavior, delirium, compulsive behavior, and seizures can be seen in dogs and cats with lesions of the cerebral cortex and with intoxications or metabolic encephalopathies. Disorders affecting the brainstem can also cause severe depression, stupor, and coma.

When presented with a dog or cat with abnormal mentation, the clinician must first ascertain whether the problem is purely behavioral, the result of systemic illness, or an indication of an intracranial lesion. The history obtained from the owner regarding the animal's normal behavior, systemic signs, and the circumstances preceding the onset of altered mentation may help identify a neurologic problem. Defined neurologic deficits confirm the existence of an abnormality within the nervous system. With some unilateral forebrain lesions, animals turn or circle toward the side of the lesion and ignore all sensory input (touch, seeing, hearing) on the side opposite the lesion (hemiinattention syndrome). Although their gait will usually be normal, animals with forebrain lesions may exhibit postural reaction deficits on the side opposite the lesion. Brainstem lesions more reliably cause altered consciousness, multiple cranial nerve deficits, and ipsilateral upper motor neuron (UMN) paresis, ataxia, and postural reaction deficits.

INTOXICATIONS

Intoxication with household toxins, insecticides, rodenticides, and prescription or illicit drugs must be considered in any dog or cat with an acute onset of abnormal mentation. Anxiety and delirium may precede severe depression, seizures, and other neurologic and systemic signs. Common toxic agents causing mentation changes and seizures in dogs and cats are discussed in Chapter 62. The clinical signs of intoxication are usually acute and severe, with rapid deterioration. A history of potential ingestion or exposure to a toxin and the finding of characteristic progressive clinical signs lead to the diagnosis. Treatment must be initiated to remove the toxin, prevent further absorption, and expedite its elimination. Intoxications resulting in seizures also require emergency treatment for seizures, as described for status epilepticus (see Box 62.7).

METABOLIC ENCEPHALOPATHIES

Animals with abnormal mentation, diminished consciousness, or seizures should always be evaluated for metabolic disturbances such as hepatic encephalopathy, hypoglycemia, severe uremia, electrolyte disturbances, and hyperosmolality (e.g., untreated diabetes mellitus). Severely depressed mentation can also be a manifestation of severe systemic illness, sepsis, hypoadrenocorticism, or hypothyroid myxedema coma. Detailed information on diagnosis and management of these metabolic disorders can be found elsewhere in this text.

HYPERMETRIA

A hypermetric gait, with each limb raised excessively during protraction and then returned more forcefully than normal to weight bearing, suggests that there has been a loss of the

normal cerebellar regulation of the rate, range, and force of movement. Animals with disease limited to the cerebellum are ataxic but strong, with normal postural reactions and spinal reflexes. They are unable to judge distances or control the range of movements and will make a series of jerking and bobbing movements (intention tremor) when attempting to perform precise movements. A fine tremor of the head and body may also be present at rest.

DIAGNOSTIC APPROACH TO ANIMALS WITH INTRACRANIAL DISEASE

Intracranial disorders that commonly cause neurologic signs include external trauma, vascular disorders (e.g., hemorrhage and infarction), congenital anomalies (e.g., hydrocephalus, lissencephaly, cerebellar hypoplasia), infectious and noninfectious inflammatory diseases (e.g., encephalitis), degenerative disorders, and primary or metastatic brain tumors (Box 60.1). Evaluation should always include a complete physical and neurologic examination as well as an ophthalmologic examination. When the cause of the neurologic signs is not readily apparent, animals should be screened for metabolic disorders and systemic manifestations of infectious or neoplastic disease using clinicopathologic tests, cytologic examination of aspirates from lymph nodes and masses, thoracic and abdominal radiographs, and abdominal ultrasound. Approximately 10% of dogs with intracranial neoplasia have abnormalities on these staging tests that make further diagnostic evaluation unnecessary. Advanced neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and cerebrospinal fluid (CSF) collection and analysis will be required for diagnosis when disease is restricted to an intracranial site. MRI provides much better soft tissue resolution than CT and is the preferred imaging method whenever brain lesions are suspected, but CT is faster, less expensive, and more readily available in emergency situations, and it provides adequate images when bony lesions are present (Box 60.2).

BOX 60.1

Disorders Causing Intracranial Disease

- External trauma
- Vascular disorders
  - Hemorrhage
  - Infarcts
    - Ischemic infarcts—many causes
    - Feline ischemic encephalopathy (FIE)
    - Hippocampal necrosis
  - Hypertensive encephalopathy
- Congenital anomalies
  - Hydrocephalus
  - Lissencephaly
  - Cerebellar hypoplasia
  - Others
- Inflammatory disease
  - Infectious encephalitis
  - Meningoencephalitis of unknown etiology (MUE)
    - Granulomatous meningoencephalitis (GME)
    - Necrotizing meningoencephalitis
    - Leukoencephalitis
    - Others
- Degenerative disorders
  - Metabolic storage diseases
  - Spongy degeneration
  - Neuroaxonal dystrophy
  - Hereditary cerebellar ataxia
    - Cerebellar cortical degeneration
    - Spinocerebellar degeneration
    - Others
  - Many other disorders
- Neoplasia
  - Primary brain tumors
  - Tumors extending into brain (skull, nose, sinus, ear, eye)
  - Secondary brain tumors (metastatic from nonneural site)

INTRACRANIAL DISORDERS

HEAD TRAUMA

The outcome for animals with head trauma depends largely on the location and severity of the initial injury. Common causes of head injuries in dogs and cats include motor vehicle accidents and kicks and bites from larger animals. The initial trauma to the brain parenchyma is followed by secondary damage resulting from hemorrhage, ischemia, and edema. Because the brain is enclosed within the bones of the skull,

BOX 60.2

Diagnostic Approach to Animals With Suspected Intracranial Disease

1. Perform a complete history, physical examination, and neurologic assessment.
   - Focal or asymmetric deficits suggest intracranial disease.
2. Rule out metabolic encephalopathies.
   - Hematology, serum chemistry profile, urinalysis
   - Blood glucose: fasting, symptomatic, postprandial
   - Liver function test
3. Evaluate for systemic inflammatory or neoplastic disease.
   - Complete ophthalmic examination
   - Thoracic and abdominal radiographs
   - Abdominal ultrasound
   - Aspirates of lymph nodes (± spleen, liver, bone marrow, masses)
   - Serology when appropriate
4. Perform an intracranial examination.
   - Neuroimaging (computed tomography, magnetic resonance imaging)
   - Cerebrospinal fluid collection and analysis

as brain volume increases with edema or hemorrhage, there is an increase in intracranial pressure, leading to decreased cerebral perfusion and further brain damage.

Initial management of a patient with brain injury should focus on recognizing and treating systemic injuries and maintaining adequate circulation and respiration. Systemic hypotension decreases cerebral perfusion, so fluids should be administered to maintain blood volume (Box 60.3). Administration of synthetic colloids such as Pentaspan (10% Pentastarch in 0.9% NaCL [Bristol-Myers Squibb]) or administration of hypertonic saline solution (7.2%) allows rapid restoration of blood volume and pressure without the large volume of fluid required when crystalloids alone are administered. Oxygen should be administered by mask or via nasal or transtracheal catheter. If the animal is unconscious, immediate intubation and ventilation may be required. Hyperventilation reduces intracranial pressure but causes cerebral vasoconstriction and decreased cerebral perfusion, so it must be used with caution. Whenever possible, a $Paco_2$ of 30 to 35 mm Hg should be maintained. If seizures are evident, aggressive anticonvulsant therapy should be initiated as for status epilepticus (see Chapter 62) because seizure activity greatly increases intracranial pressure. Measures to lower intracranial pressure include elevating the head at a 30-degree angle from horizontal, administration of an osmotic diuretic such as intravenous mannitol (1 to 1.5 g/kg over 15 minutes) or hypertonic saline solution (4-5 mL/kg of 7.2% NaCl over 2-5 minutes), and administration of narcotic analgesic medications as required. Administration of high doses of methylprednisolone sodium succinate (SoluMedrol) during the first 6 hours after presentation has been shown to be beneficial in patients with spinal cord injury but may actually be detrimental in patients with serious brain injury.

Systemic and neurologic assessment should be repeated every 30 minutes. Although a scoring system (modified Glasgow Coma Scale) has been developed to allow grading and serial monitoring of neurologic status, it is only useful in dogs with such severe brainstem and cerebral injury that they are unlikely to recover.



BOX 60.3

Management of Intracranial Injury

All Patients

Establish patent airway, administer oxygen.
Examine, assess, and treat concurrent injuries.
Treat shock, maintain blood pressure (intravenous fluids, colloids).
- Isotonic crystalloids: ¼ of shock dose (90 mL/kg dog, 60 mL/kg cat), reassess q15min
- Pentaspan: ¼ of the 20 mL/kg shock dose
- Hypertonic saline: 4-5 mL/kg of 7.2% NaCl over 2-5 minutes

Maintain mean arterial blood pressure 80-120 mm Hg.
Monitor neurologic status every 30 minutes.

If Severe Initial Injury or Deterioration

Elevate head 30 degrees.
Treat seizures if present (see Box 62.7).
Administer hyperosmolar therapy.
- 20% mannitol: 1-1.5 g/kg, administered intravenously over 15 minutes (can repeat in 3 hours) ***or***
- Hypertonic saline: 4-5 mL/kg of 7.2% NaCl over 2-5 minutes

If intubated, maintain $Paco_2$ at 30-35 mm Hg.

VASCULAR ACCIDENTS

Vascular accidents, also called *strokes,* occasionally occur in the central nervous systems (CNS) of dogs and cats, and cause a peracute onset of neurologic abnormalities. Ischemic strokes result from occlusion of an intracranial blood vessel by a thrombus or embolus. Hemorrhagic strokes result from bleeding into the brain parenchyma.

Ischemic strokes occur when cells or clots enter the circulation from septic foci (endocarditis), primary or metastatic neoplasia, vasculitis, heartworm disease, or cardiac disease. Atherosclerosis, a common cause of thromboembolic stroke in humans, has also been associated with stroke due to intravascular clot formation in dogs with hypothyroidism, and less commonly in dogs with diabetes mellitus, hyperadrenocorticism, or hereditary hyperlipidemia. Chronic hypertension also promotes vascular changes predisposing to ischemic or hemorrhagic stroke. Animals with peracute neurologic signs should always have their blood pressure measured, and if they are hypertensive they should be evaluated for potential causes such as renal failure, hyperadrenocorticism (dogs), and hyperthyroidism (cats). Despite thorough investigations, an underlying cause is only identified in approximately half of all dogs with ischemic stroke.

Spontaneous intracranial hemorrhage can occur without an obvious underlying cause or can be the result of a coagulopathy, a bleeding primary or metastatic brain tumor (especially hemangiosarcoma), or hypertension. Screening for thrombocytopenia, inherited or acquired coagulopathies, disseminated intravascular coagulation, systemic neoplasia, and disorders associated with hypertension is indicated when intracranial bleeding is suspected.

In ischemic or hemorrhagic stroke, the abruptness with which neurologic deficits develop is highly suggestive of a vascular disorder. There may be some progression of signs due to edema in the first 24 to 72 hours, but most animals with nonfatal ischemic strokes begin to recover quickly. Hemorrhagic strokes are more likely than ischemic strokes to cause rapidly progressive neurologic deficits, increased intracranial pressure, and death.

Neurologic deficits reflect the location of the vascular insult, with forebrain and cerebellar strokes most common in dogs. In cats, forebrain and brainstem infarcts are more common. A predisposition for cerebellar infarcts is present in hypothyroid hyperlipidemic Labrador Retrievers and in Cavalier King Charles Spaniels. Results of physical

examination, clinicopathologic evaluation, and thoracic radiography may be unremarkable aside from the neurologic abnormalities or may reflect the underlying disease process. Systemic blood pressure should be measured and an ocular examination performed to search for hypertension-related hemorrhage or retinal detachment. Platelet numbers and coagulation should be assessed, and screening for systemic neoplasia is warranted. CT is an excellent imaging tool for identifying acute hemorrhagic stroke but is rarely diagnostic for ischemic disease. MRI can detect large ischemic strokes within 12 to 24 hours of the onset of signs and can distinguish hemorrhagic lesions from infarction. Although infarcts can be difficult to distinguish from inflammatory or neoplastic brain lesions, the conformity of a lesion to a wedge-shaped vascular territory with sharp demarcation from the surrounding normal brain and no mass effect is highly suggestive of an infarct. It is common for imaging to be normal or to show focal edema in animals with very small infarcts or vascular leaks. A more complete discussion of the imaging findings expected in animals with intracranial hemorrhage and ischemia can be found in the Suggested Readings.

Short-term aggressive therapy to lower intracranial pressure as described for head trauma (see Box 60.3) may be indicated in animals with suspected ischemic or hemorrhagic stroke. Underlying disorders such as hypertension and coagulopathy should be managed. Most mildly or moderately affected animals show dramatic improvement during the first 3 to 10 days after the onset of signs, although some never return to normal functional status.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy has been recognized in dogs and cats with an acute rise in blood pressure (increase >30 mm Hg from resting) or a sustained elevation in systolic arterial blood pressure (>180 mm Hg). Signs may result from vasogenic and interstitial cerebral edema caused by hyperperfusion. Clinical signs include altered mentation, anxiety, blindness, seizures, and occasionally vestibulocerebellar signs such as head tilt, loss of balance, and nystagmus. Signs usually rapidly resolve within hours to days of correcting the hypertension. Long-term treatment is usually required to prevent recurrence of signs.

FELINE ISCHEMIC ENCEPHALOPATHY

Feline ischemic encephalopathy (FIE) is a syndrome of acute cerebral cortical dysfunction caused by cerebral infarction in cats. The portion of the cortex supplied by the middle cerebral artery is most commonly affected. Most cases of FIE are diagnosed during the summer months in cats living in the northeastern United States with access to the outdoors. Cats with FIE are presented because of a peracute onset of asymmetric neurologic abnormalities including aggression, circling to the side of the lesion, and seizures. There may be a loss of proprioception and hyperactive reflexes (UMN signs) in the limbs opposite the side of the lesion, and the cat may be blind but have normal pupillary light reflexes (cortical blindness) on the side opposite the lesion. FIE should be suspected in any cat with a sudden onset of nonprogressive unilateral cerebral cortical dysfunction and no history of trauma or evidence of systemic illness or hypertension. The primary differential diagnosis is a vascular accident. Physical examination typically reveals no abnormalities other than the neurologic signs. Ophthalmologic examination, clinicopathologic evaluation, and blood pressure measurements are also normal. CSF is normal cytologically, with a normal or only slightly increased protein content, making inflammatory disease unlikely. MRI is the best method of documenting the infarcted region.

Cats with FIE that have died or been euthanized have extensive acute necrosis and edema of the cerebral cortex caused by acute infarction of the middle cerebral artery. Moreover, many cats show histopathologic features compatible with aberrant migration of *Cuterebra* fly larvae. The larvae apparently enter the brain through the nasal cavity and the cribriform plate, and once within the CNS they elaborate a toxic factor that causes neurologic damage and vasospasm, leading to brain infarction. Acutely, mannitol should be administered intravenously to decrease the edema associated with the vascular lesion (see Box 60.3). If seizures occur, anticonvulsants should be administered (see Box 64.7). Specific treatment of the migrating parasite is possible and may be warranted in young and middle-aged cats from endemic areas presenting with acute lateralizing cerebral cortical signs in the summer. Treatment is with diphenhydramine (4 mg/kg, administered intramuscularly), followed 2 hours later with dexamethasone (0.1 mg/kg, administered intravenously) and ivermectin (400 µg/kg, administered subcutaneously). This treatment is repeated 48 hours later. Most cats show marked improvement in 2 to 7 days whether or not the ivermectin treatment is initiated. Complete recovery occurs in approximately 50% of cats. Permanent neurologic sequelae may include aggressive behavior or recurrent seizures, often resulting in euthanasia.

FELINE HIPPOCAMPAL NECROSIS

Feline hippocampal necrosis (FHN) is a severe structural abnormality in the brain that has been associated with seizures in cats. It is uncertain whether this hippocampal pathology serves as a primary epileptogenic focus to cause seizures or if the FHN occurs secondary to ischemic damage during severe seizure activity. Most cats with FHN are presented because of a rapidly progressive cluster of seizures together with interictal abnormalities suggesting a forebrain lesion. Complex partial seizures with orofacial involvement are most common, including salivation, facial twitching, lip smacking, chewing, licking, and swallowing. Behavior changes that may persist between seizures include staring into space, disorientation, aggression, rapid running, hyperexcitablility, and fearfulness. MRI shows moderate T2 hyperintensity within the hippocampus and the piriform lobe that is often bilaterally symmetrical with signal alterations most apparent on fluid attenuated recovery sequences (FLAIR). Contrast enhancement is variable.

Early reports suggested that FHN had a poor prognosis, as all cats died or were euthanized when initial anticonvulsant therapy was ineffective, neurologic and behavioral abnormalities persisted, or recurrent seizures were difficult to control. There have, however, been reports of a few cats with FHN that gradually returned nearly to normal with few neurologic deficits and well-controlled seizures, suggesting that the long-term outcome can occasionally be good to excellent. There is some speculation that FHN could be a manifestation of autoimmune limbic encephalitis following reports that many cats with FHN experienced full remission (seizure-free) after antiepileptic, supportive, and corticosteroid treatment.

THIAMINE DEFICIENCY

Thiamine (vitamin B1) is a water-soluble vitamin that is important in normal carbohydrate metabolism and synthesis of neurotransmitters. Cats require more thiamine than dogs and can develop thiamine deficiency due to prolonged anorexia, maldigestion /malabsorption disorders, inadequate dietary intake, or ingestion of thiaminase in raw fish. Most cases of thiamine deficiency in dogs have been in groups of dogs eating raw fish. Thiamine deficiency results in a progressive encephalopathy and polioencephalomalacia of the oculomotor and vestibular nuclei and caudal colliculus. Neurologic signs may include impaired vision, mydriasis, ataxia, ventroflexion of the head and neck, vestibular signs, seizures, coma, and even death. Magnetic resonance (MR) imaging can be normal or can reveal bilaterally symmetrical hyperintense foci on T2-weighted and FLAIR (fluid attenuation recovery) in grey matter regions of the brainstem, cerebrum, and cerebellum. Supplementation with parenteral and oral thiamine, and changing the diet to include adequate thiamine will usually result in a rapid recovery and resolution of all neurologic signs, including seizures. Thiamine (12.5-30 mg/cat IM or SC q24h) is often administered to cats with undiagnosed progressive neurologic signs suggesting an intracranial lesion, particularly those with vestibular signs or seizures.

HYDROCEPHALUS

Hydrocephalus is a condition in which the cerebral ventricular system is enlarged secondary to obstruction of CSF flow toward its point of absorption into the systemic circulation via the arachnoid villi. Obstruction can occur secondary to inflammation, neoplasia, or prior hemorrhage, but most cases are congenital. Dog breeds at risk for congenital hydrocephalus include the Maltese, Yorkshire Terrier, English Bulldog, Chihuahua, Lhasa Apso, Pomeranian, Toy Poodle, Cairn Terrier, Boston Terrier, Pug, Chow Chow, and Pekingese. Cats are occasionally affected.

Many animals with congenital hydrocephalus have an obviously enlarged head, persistent fontanelles, and palpably open cranial sutures (Fig. 60.1). Care must be taken not to overinterpret these findings, however, because domed heads and small open fontanelles (<5 mm) are very common in some toy breeds. Although most dogs with large fontanelles

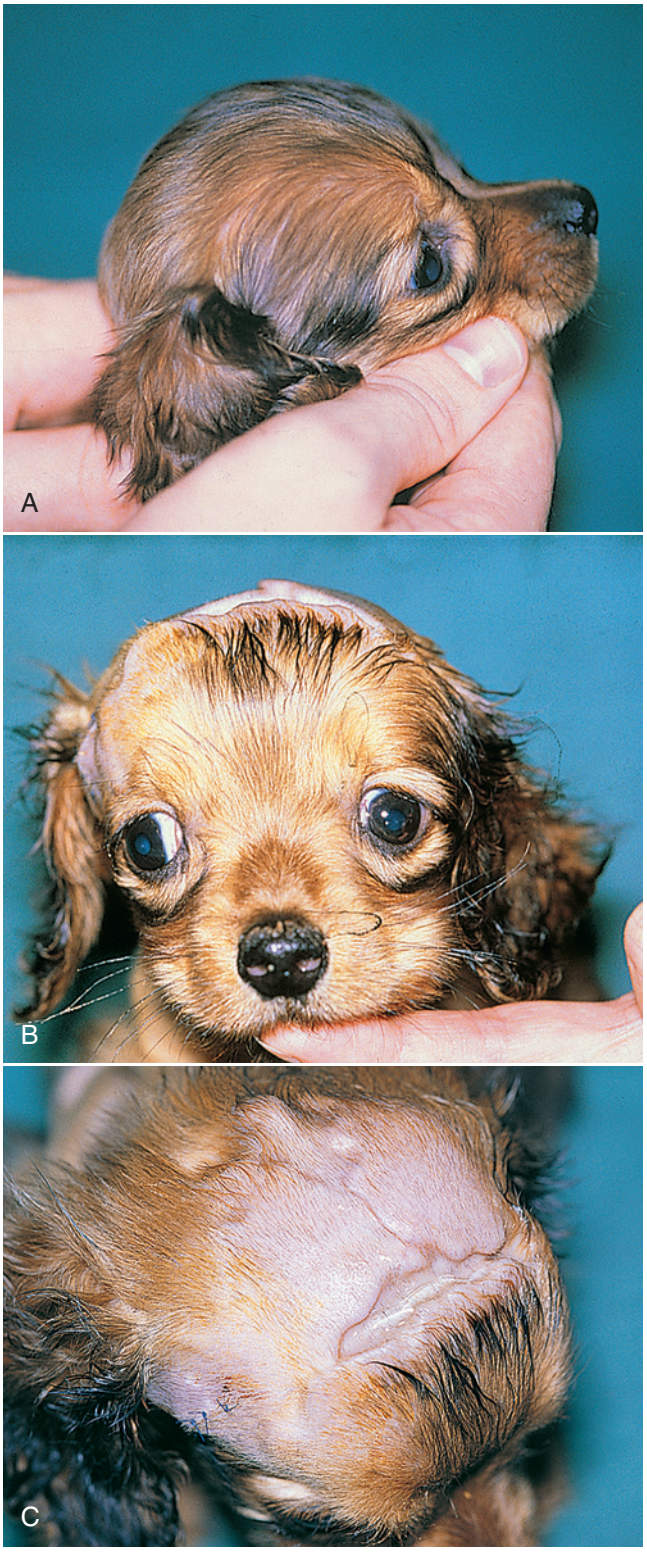


FIG 60.1
(A) and **(B)** Hydrocephalus in a Chihuahua puppy. Note the greatly enlarged, domed skull and the divergent strabismus. **(C)** The open skull sutures (fontanelles) are visible in this puppy after surgical drainage of the lateral ventricles with a ventriculoperitoneal shunt.

or fontanelles that remain open at 9 weeks of age do have some ventricular dilation, many will never develop clinical signs of hydrocephalus.

Animals with symptomatic hydrocephalus can be slow learners and may be difficult to housetrain. They may seem dull or depressed. They may have episodic or constant abnormal behavior, circling, and cortical blindness. Seizures may occur. Severely affected animals may exhibit tetraparesis, slow postural reactions, head tilt, or nystagmus. Some animals will develop a ventrolateral strabismus (see Fig. 60.1) due either to malformation of the orbit or brainstem dysfunction. Neurologic signs have an unpredictable course; deficits can progress over time, remain static, and even improve after 1 to 2 years of age. Signs can worsen coincident with other diseases or minor head trauma. About 30% of dogs with congenital hydrocephalus are not overtly symptomatic until 2 years of age.

Hydrocephalus is suspected on the basis of characteristic signs and physical examination findings in a young animal of a typical breed. If fontanelles are open, ultrasound examination of the brain can be performed through the openings, and this can determine the size of the lateral ventricles and confirm the diagnosis (Fig. 60.2). If the fontanelles are small or closed, ultrasound scanning is more difficult but may still be attempted through the temporal bone in young animals. Alternatively, CT or MRI can be performed to detect ventricular enlargement. Although historical studies have shown very little correlation between ventricular size and clinical signs, one report showed that ventricular enlargement (ventricle/brain [VB] ratio) was correlated with severity of clinical signs in small-breed dogs and that all asymptomatic puppies with a VB ratio of over 60% went on to develop neurologic signs related to their hydrocephalus.

Long-term medical management of animals with neurologic signs is directed at limiting CSF production and reducing intracranial pressure. Acetazolamide (10 mg/kg orally q8h), alone or in combination with oral furosemide (1 mg/kg/day) is the most commonly used drug therapy. Omeprazole may also decrease CSF production and aid control. Some animals improve with glucocorticoid treatment (prednisone, 0.5 mg/kg, administered orally daily, tapered weekly until 0.1 mg/kg q48h). Seizures may be controlled with antiepileptic drug therapy as described for epilepsy (see Chapter 62). The prognosis for a normal life is poor if neurologic signs are present. Surgical drainage and placement of a permanent ventriculoperitoneal shunt is an aggressive treatment option

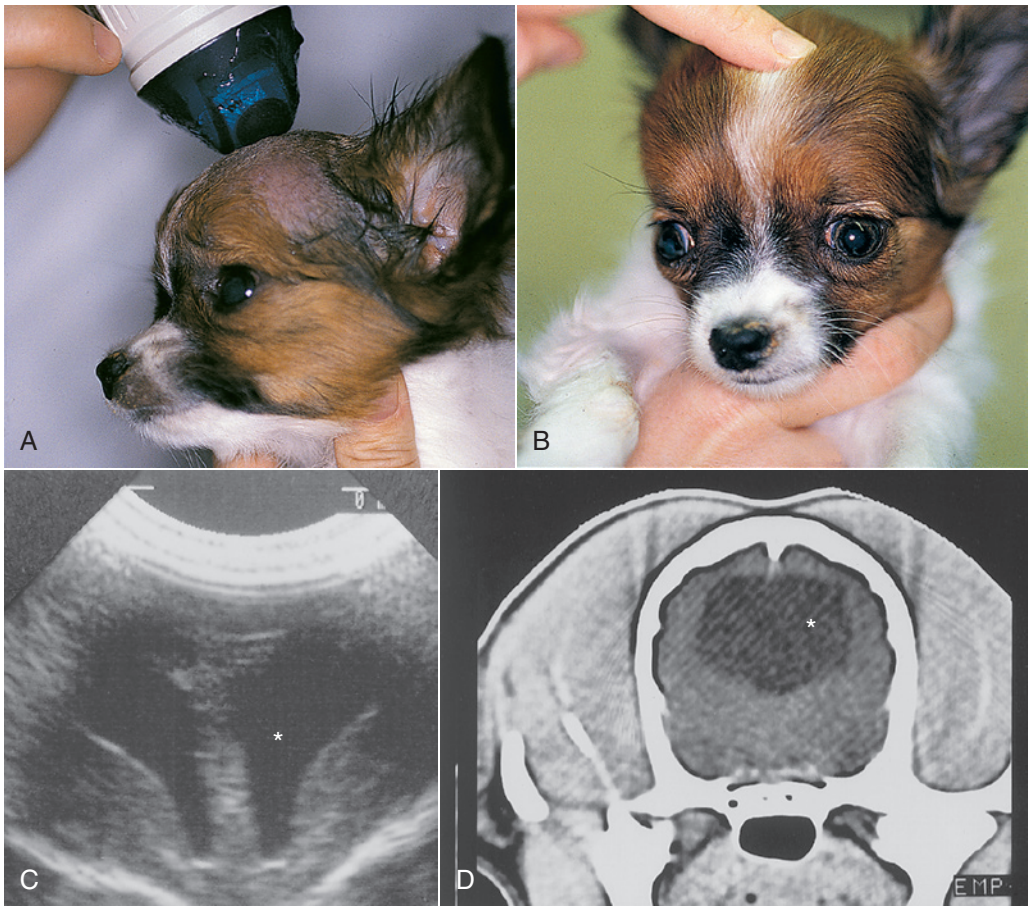


FIG 60.2
(A) and **(B)** Young Papillon with hydrocephalus and open fontanelles. **(C)** Ultrasound image. **(D)** Computed tomography (CT) scan of the head of a dog with hydrocephalus. *, Dilated lateral ventricles. (**D** Courtesy Dr. Greg Daniel, University of Tennessee.)

with many potential complications but is associated with a sustained positive outcome in greater than 50% of patients.

Acute, severe, and progressive neurologic signs occasionally occur in dogs and cats with hydrocephalus, probably as a result of a sudden increase in intracranial pressure. Therefore it is important to rapidly lower intracranial pressure in these animals, as described for animals with head trauma (see Box 60.3). If fontanelles are open, a ventricular tap can be performed and a small volume of CSF (0.1-0.2 mL/kg) removed.

LISSENCEPHALY

Lissencephaly is a rare condition in which the sulci and gyri fail to develop normally, resulting in a smooth cerebral cortex. Lissencephaly has been recognized primarily in the Lhasa Apso, Wire Fox Terrier, and Irish Setter. Behavioral abnormalities, seizures, and visual deficits are common. These animals are also very difficult to train and may not be housebroken. If seizures occur, they often are not prominent until the end of the first year of life. Definitive diagnosis requires MRI, brain biopsy, or necropsy.

CEREBELLAR HYPOPLASIA

Congenital hypoplasia of the cerebellum has been described in Chow Chows, Irish Setters, Wire Fox Terriers, and Siberian Huskies and sporadically in many breeds of dogs and in cats. Feline cerebellar hypoplasia is most often caused by naturally acquired in utero infection with panleukopenia virus (feline parvovirus) or when a pregnant queen is inoculated with modified-live panleukopenia virus vaccine. Clinical signs of cerebellar hypoplasia become noticeable when the animal first starts to walk, with hypermetria, ataxia, truncal sway, and tremor most apparent (*see* Video 58.3). Some cases are mild and others are very severe, making walking and eating difficult. Because signs do not progress, mildly affected animals can function as pets. Cerebellar hypoplasia that is not panleukopenia-related may actually reflect an early onset neurodegenerative disorder.

INFLAMMATORY DISEASE (ENCEPHALITIS)

Inflammatory disease (encephalitis) is an important differential diagnosis in all dogs and cats with progressive intracranial disease. Most of the infectious and noninfectious inflammatory disorders discussed in Chapter 66 have the potential to cause encephalitis, with neurologic signs reflecting the site and severity of the inflammation and parenchymal damage. A subacute onset with progression over a few days to weeks is typical of inflammatory disease. See Chapter 64 for more information regarding the clinical manifestations, diagnosis, and therapy for intracranial inflammatory disorders.

INHERITED DEGENERATIVE DISORDERS AFFECTING THE BRAIN

There are many inherited neurodegenerative disorders resulting from genetically programmed errors in cell metabolism and function. Some of these cause deficiencies of specific enzymes resulting in the accumulation of metabolites within cells (storage diseases), yet others alter cell function, neurotransmission, or brain development leading to degeneration. Signs of inherited neurodegeneration typically develop in young animals and are progressive, but some disorders are not evident until maturity. Some disorders cause widespread neuronal degeneration in the brain and spinal cord while others only cause focal degeneration of the cerebral cortex or cerebellum or spinocerebellar tracts. Diagnosis of these disorders is suspected when an animal of a susceptible breed develops a progressive symmetrical neurologic disorder with characteristic features as described in that breed. Identification of littermates or other related animals with similar signs raises the suspicion for an inherited neurodegenerative disorder and should prompt a search of the current veterinary literature and breed websites for descriptions of breed-specific diseases and available genetic tests. In many cases a presumptive diagnosis is only possible after doing extensive testing to rule out metabolic diseases, infectious and noninfectious inflammatory disorders, and neoplastic disease. Definitive diagnosis usually requires brain biopsy, but occasionally histopathologic examination of biopsy specimens from other affected organs or enzyme assays will provide a diagnosis. Genetic tests are increasingly available. Descriptions of the breed predispositions and clinical features of many inherited degenerative brain disorders can be found in the Suggested Readings, but this is a rapidly expanding field requiring constant updating. Two of the most common inherited neurodegenerative disorders recognized in multiple breeds of dogs are neuroaxonal dystrophy and the hereditary ataxia known as cerebellar cortical degeneration. No treatment is currently available for these conditions.

NEUROAXONAL DYSTROPHY

Neuroaxonal dystrophy is a slowly progressive degenerative disorder affecting sensory axons and nerve cell bodies throughout much of the CNS, with most severe lesions within the spinocerebellar tracts and the Purkinje cells of the cerebellum resulting in cerebellar ataxia. Young adult Rottweilers (typically 1-2 years old) are initially presented for a hypermetric gait and ataxia, and signs progress slowly over 2 to 4 years. Affected dogs develop an intention tremor, a constant fine tremor, spontaneous or positional nystagmus, and menace deficits. Postural reactions (knuckling and hopping) and strength remain normal. A similar disorder has been documented in young (2- to 4-month-old) Border Collies, Chihuahuas, Jack Russell Terriers, and Papillons, and tricolor kittens (5-6 weeks old). Diagnosis requires biopsy or postmortem, and there is no effective treatment.

CEREBELLAR CORTICAL DEGENERATION (ABIOTROPHY)

Historically called cerebellar abiotrophy based on the incorrect presumption that degeneration was secondary to the lack of a vital nutritive factor, the hereditary ataxia now known as cerebellar cortical degeneration is defined by postnatal

degeneration of cells within the cerebellar cortex. Clinical signs are usually rapidly progressive and include cerebellar ataxia, a hypermetric gait, limb spasticity, truncal sway, intention tremor, and sometimes spontaneous nystagmus. Rarely the degeneration occurs in neonates (Beagle), with signs evident at first ambulation and progressively worsening over weeks to months. In most breeds, clinical signs begin between 2 and 12 months of age and progress rapidly, but slow progression over several years has been described in Gordon Setters and Old English Sheepdogs. Scottish Terriers and Old English Sheepdogs occasionally have a late onset of signs at 3 to 8 years of age with slow progression. Testing to eliminate inflammatory and neoplastic disease is warranted. Imaging can be unremarkable or can reveal cerebellar atrophy. Genetic testing is available for a cerebellar cortical degeneration in few breeds. No treatment is effective.

NEOPLASIA

Primary brain tumors are common in dogs and cats, typically resulting in a gradual onset of slowly progressive neurologic signs. Signs may be more rapidly progressive when there are metastases to the brain parenchyma from an extraneural neoplasm or when an intracranial neoplasm bleeds. With the exception of brain lymphoma, which can occur at any age, most primary and metastatic brain tumors occur in middle-aged and older animals. The most commonly affected breeds include Golden Retrievers, Labrador Retrievers, mixed-breed dogs, and Boxers.

Brain tumors cause signs by destroying adjacent tissue, increasing intracranial pressure, or causing intraparenchymal hemorrhage or obstructive hydrocephalus. Seizures and mentation changes are the most common reason for presentation. Circling, ataxia, and head tilt are less common. As intracranial tumors enlarge, they may cause an increase in intracranial pressure with progressive loss of alertness and altered mentation; the owner may report that the dog or cat has recently become dull, depressed, and "old." Progressive subtle neurologic signs are sometimes present for weeks or months before the owner notices them.

Some animals with brain tumors are neurologically normal between seizures, but careful neurologic examination may reveal evidence of asymmetric neurologic dysfunction. Compulsive circling toward the side of the lesion and abnormal postural reactions, vision, and facial sensation on the side opposite the lesion are common with forebrain lesions, whereas positional nystagmus and subtle cranial nerve deficits are common with brainstem tumors.

Intracranial tumors may be primary (arising from the brain), or they may invade the brain from an adjacent site (e.g., skull, nose, sinus, ear, eye) or metastasize to the brain from a distant site. Secondary (metastatic) intracranial neoplasia occurs more often than primary neoplasia in dogs, with metastases from hemangiosarcoma, lymphoma, carcinomas, and melanoma being most common. A careful physical examination should be performed to identify potential sites of primary neoplasia that may have metastasized to the brain. Particular attention should be paid to the nose, lymph nodes, spleen, skin, mammary chain, and prostate gland. A complete blood count (CBC), serum biochemistry panel, and urinalysis should be performed to look for evidence of neoplasia or a paraneoplastic syndrome. Radiography of the thorax and abdomen and abdominal ultrasonography should be performed to search for a primary tumor or extraneural metastases. Also, most dogs and cats with intracranial neoplasia are older, and systemic evaluation for neoplasia has been reported to identify an unrelated extracranial neoplasm in up to 25% of cases, a finding that can have a major impact on prognosis and treatment decisions.

MRI is the most accurate advanced imaging modality for detection and characterization of intracranial tumors and differentiating tumors from inflammatory lesions. MRI can be used to characterize tumors as being intra-axial (parenchymal) versus extra-axial (surface), and can describe their location within the brain, degree of infiltration into surrounding tissues, shape, intensity compared with normal neural tissue on different MRI sequences, and contrast uptake. These imaging characteristics can be used to predict probable tumor type in approximately 70% of cases, but definitive diagnosis requires biopsy (Fig. 60.3).

Meningiomas are the most common intracranial tumors in dogs and cats, followed by an assortment of glial tumors in dogs and lymphoma in cats. Golden Retrievers are at increased risk for developing meningiomas, whereas brachycephalic breeds such as Boston Terriers and Boxers are especially predisposed to glial tumors. Because most intracranial tumors are poorly exfoliative, CSF collection and analysis rarely provide a definitive diagnosis. Identifying neoplastic cells in CSF is unusual except in patients with CNS lymphoma, carcinomatosis, and choroid plexus tumors. Dogs and cats with brain tumors may have normal CSF, normal CSF cytology with a slightly increased CSF protein content, or a mixed cell pleocytosis, complicating differentiation from inflammatory disorders based on CSF alone.

Treatment for brain tumors depends on the probable tumor type, tumor location, growth history, and neurologic signs. Once identified with CT or MRI, some small, superficially located, well-encapsulated, benign cerebral tumors; dorsal cerebellar tumors; and bony tumors of the skull are amenable to surgical removal by experienced neurosurgeons. In particular, there has been some success in removing feline cerebral meningiomas. Canine cerebral meningiomas are similarly superficially located and histologically benign, but they are not well encapsulated, making complete surgical removal more difficult. Median survival (MS) time after surgical removal of most primary brain tumors in dogs is approximately 140 to 150 days, with significant risk of mortality within the first 30 days after surgery. For meningiomas, MS times are longer (240 days with surgery alone, 1254 days using an ultrasonic surgical aspirator). Surgical removal of feline meningiomas has been associated with MS intervals of 22 to 27 months.

Radiotherapy is often used as an adjunct to surgery for resectable tumors and as the sole therapy for nonresectable primary (nonmetastatic) brain tumors in dogs. Many dogs

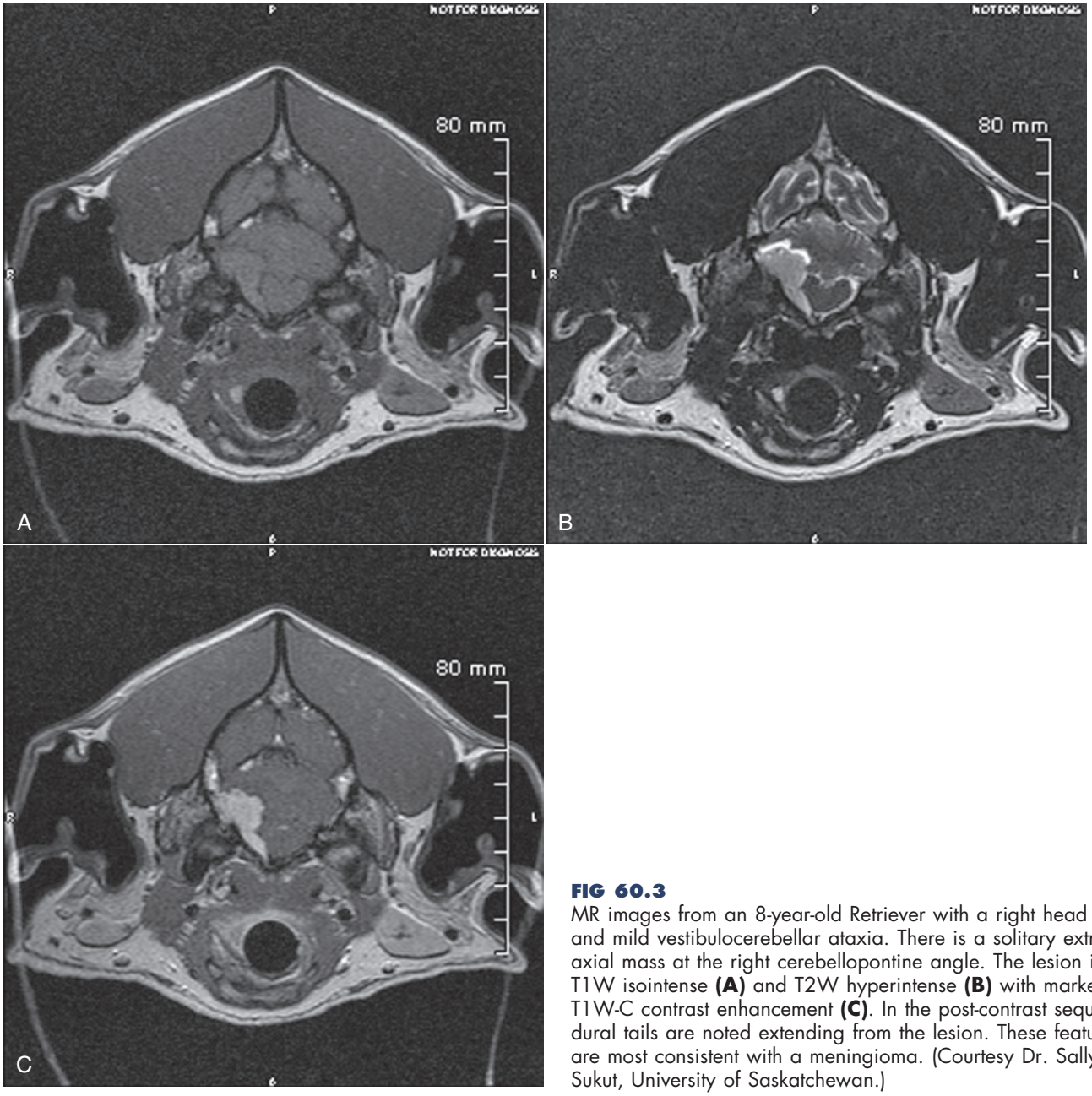


FIG 60.3
MR images from an 8-year-old Retriever with a right head tilt and mild vestibulocerebellar ataxia. There is a solitary extra-axial mass at the right cerebellopontine angle. The lesion is T1W isointense **(A)** and T2W hyperintense **(B)** with marked T1W-C contrast enhancement **(C)**. In the post-contrast sequence dural tails are noted extending from the lesion. These features are most consistent with a meningioma. (Courtesy Dr. Sally Sukut, University of Saskatchewan.)

that are stable neurologically before therapy show some clinical improvement. Dogs with brain masses causing neurologic signs (no specific diagnosis) have an MS time of approximately 2 years after radiotherapy, and MS of 14 to 30 months has been reported for canine meningioma when treated with surgery followed by radiation. An important drawback of conventional radiotherapy is that access to a referral center and multiple daily anesthesias are required to administer up to 20 fractionated doses of radiation. Stereotactic radiotherapy is a technique that uses a high dose of radiation delivered in a single (radiosurgery) or few fractions (stereotactic radiotherapy), decreasing the need for multiple anesthetics and hospital visits. Results and adverse effects reported with this technique are similar to those reported with conventional radiotherapy.

Supportive chemotherapy can be administered together with or instead of surgery and radiation. Glucocorticoid administration (prednisone 0.5-1 mg/kg/day, taper to q48h) may decrease edema surrounding the tumor and improve CSF absorption, decreasing neurologic signs and intracranial pressure. Chronic anticonvulsant therapy should be administered to control seizures. In the event of an acute exacerbation of tumor-related clinical signs, aggressive treatment to lower intracranial pressure is recommended, as outlined for head trauma (see Box 60.3). Specific chemotherapy for CNS lymphoma is possible, but most of the chemotherapeutic agents used for systemic therapy do not cross the blood-brain barrier. Cytosine arabinoside (Cytosar), lomustine (CCNU), and prednisone have some effect (see Chapter 79).

Suggested Readings

Bagley RS, Platt S. Coma, stupor, and mentation change. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Bentley RT. Magnetic resonance imaging diagnosis of brain tumors in dogs. *Vet J*. 2015;205:204–216.

Garosi L, et al. Cerebrovascular disease in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2010;40:65.

Motta L, et al. Canine and feline intracranial meningiomas: an updated review. *Vet J*. 2012;192:153–165.

Saito M, et al. The relationship between basilar artery resistive index, degree of ventriculomegaly and clinical signs in hydrocephalic dogs. *Vet Radiol Ultrasound*. 2003;44:687.

Snyder JM, et al. Canine intracranial primary neoplasia: 173 cases (1986-2003). *J Vet Intern Med*. 2006;20:669.

Thomas WB. Hydrocephalus in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2010;40:143.

Urkasemsin G, Olby NJ. Canine hereditary ataxia. *Vet Clin Small Anim*. 2014;44:1075–1089.

CHAPTER 61

Loss of Vision and Pupillary Abnormalities



GENERAL CONSIDERATIONS

Loss of vision or pupillary abnormalities may be detected during a physical examination for neurologic dysfunction or may be the primary reason for presentation. Owners rarely recognize a visual deficit until it is bilateral and complete, at which time the animal is brought in because of an apparently sudden onset of blindness. When an animal is evaluated for loss of vision, it is important to first determine whether there is actual blindness and to perform a complete ocular and neuroophthalmologic examination.

NEUROOPHTHALMOLOGIC EVALUATION

VISION

Vision should initially be assessed by observing the animal's response to the environment, including its ability to negotiate doorways and stairs and the attention it pays to rolling or falling silent objects such as cotton balls. If unilateral vision loss is suspected, the normal eye should be covered during testing. For vision to be present, the entire visual pathway must be intact. This includes the retina, optic nerve (which passes through the optic chiasm to the optic tract to synapse in the lateral geniculate nucleus [LGN] in the diencephalon), and axons projecting to the visual cortex in a band of fibers called the *optic radiation*. Most of the optic nerve axons cross in the optic chiasm (particularly those carrying information from the lateral visual field) and are continued in the contralateral optic tract, LGN, and optic radiations to the visual cortex (Fig. 61.1). The visual cortex must be functional for the animal to process and respond appropriately to visual cues.

MENACE RESPONSE

The menace response is a cortically mediated blink produced by a threatening gesture (Fig. 61.2). The sensory part of this response involves each of the components of the visual pathway (see Fig. 61.1). Normally the visual stimulus is directed at the nasal retina (i.e., the menacing gesture is in the lateral visual field coming from the side), and because almost all of the optic nerve axons that originate in the nasal retina cross in the optic chiasm, the menace response can be used to assess the visual cortex contralateral to the eye being menaced. The information interpreted in the visual cortex is forwarded to the motor cortex to initiate a blink response, requiring a functional facial nerve (CN7). The menace response is also coordinated in the cerebellum, with unilateral cerebellar lesions causing ipsilateral loss of the menace response but no loss of vision. The absence of a menace response could therefore be a result of ocular, retinal, or optic nerve disease; damage to the contralateral forebrain; an altered mental state; cerebellar disease; or an inability to blink (Box 61.1). The menace response is a learned response and may not be present in normal animals younger than 12 weeks of age.

PUPILLARY LIGHT REFLEX

The pupillary light reflex (PLR) should always be assessed whether or not an animal is able to see. A bright light is directed into the pupil, and the pupil is assessed for constriction (direct reflex). The opposite pupil should simultaneously constrict (consensual response). The sensory visual pathway is the same as that described for the menace response except that some optic tract axons synapse before the LGN in the pretectal nucleus located at the junction between the midbrain and the thalamus (Fig. 61.3). Most of the axons arising from this nucleus cross midline again and synapse in the parasympathetic (PSNS) component of the oculomotor nucleus ipsilateral to the eye being stimulated, inducing direct pupil constriction. Because some of the axons leaving the pretectal nucleus do not cross, there is also stimulation of the contralateral oculomotor nucleus, resulting in a somewhat weaker consensual pupillary response. The pupillary response to light can be minimal if the light used is not bright enough, if the animal is nervous and has high resting sympathetic tone, or if there is ocular disease (iris atrophy or greatly increased intraocular pressure) preventing pupillary constriction. The pupillary light response

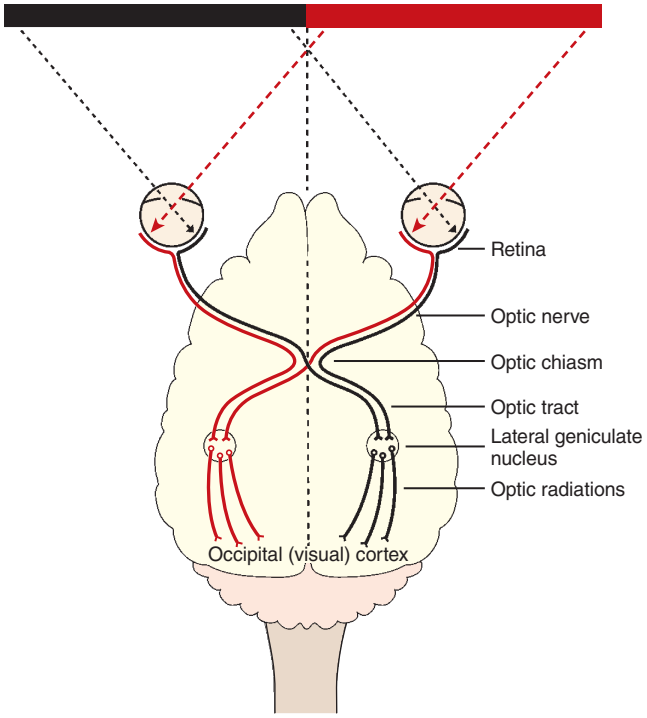


FIG 61.1
The visual pathways.



FIG 61.2
Menace response is evoked by making a threatening movement toward each eye in turn. The expected response is a blink. The stimulus is primarily directed toward the nasal retina, assessing the contralateral visual cortex.

requires fewer functional photoreceptors and optic nerve axons than vision, so partial lesions of the proximal visual pathways (retina, optic nerve, optic chiasm, optic tract) can sometimes cause loss of vision with normal PLRs, similar to lesions of the forebrain (Table 61.1).

BOX 61.1

Lesions Causing Loss of the Menace Response in Dogs and Cats

- Severe ocular disease
- Retinal disease
- Visual pathway lesion
  - Ipsilateral optic nerve
  - Optic chiasm
  - Contralateral optic tract, lateral geniculate nucleus, optic radiation
- Contralateral visual cortex (forebrain) lesion
- Altered mental status
  - Metabolic encephalopathy
  - Severe systemic illness
- Cerebellar disease
- Inability to blink (CN7)
- Immature reflex (<12 weeks of age)

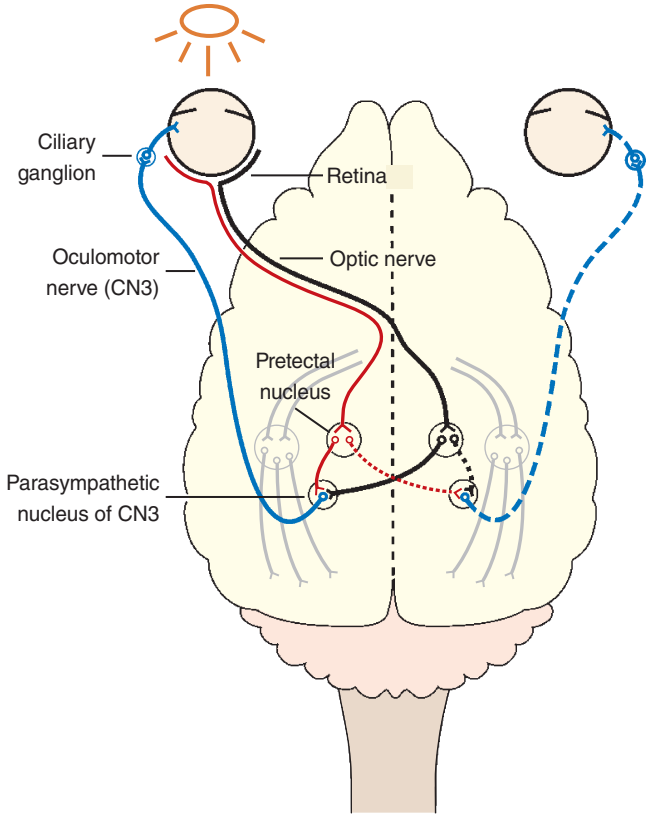


FIG 61.3
Pathway of the pupillary light reflex.

DAZZLE REFLEX

The dazzle response is the generation of a rapid blink when a very bright light is directed into the eye. The sensory visual pathway is as described for the PLR in that this is a subcortical ipsilateral reflex that does not require the visual cortex, but the motor pathway is mediated by the facial nerve (CN7) rather than the oculomotor nerve. A negative dazzle response

TABLE 61.1

Localization of Visual Pathway Lesions Based on Vision and Pupillary Light Reflexes

LOCATION OF COMPLETE LESION	VISION IN RIGHT EYE	VISION IN LEFT EYE	LIGHT IN RIGHT EYE	LIGHT IN LEFT EYE
Right retina/eye*	Absent	Normal	No response either eye	Both pupils constrict
Bilateral retina/eye*	Absent	Absent	No response either eye	No response either eye
Right optic nerve	Absent	Normal	No response either eye	Both pupils constrict
Bilateral optic nerves	Absent	Absent	No response either eye	No response either eye
Optic chiasm (bilateral)	Absent	Absent	No response either eye	No response either eye
Lesion caudal to optic chiasm *(right lateral geniculate nucleus, right optic radiation, or right visual cortex)*	Normal	Absent	Both pupils constrict	Both pupils constrict
Bilateral lesion caudal to optic chiasm	Absent	Absent	Both pupils constrict	Both pupils constrict
Right oculomotor nerve	Normal	Normal	Left pupil constricts; right pupil is dilated, no response	Left pupil constricts; right pupil dilated, no response

*Retinal or eye lesions must be very severe to cause loss of pupillary light reflexes.

in a blind eye implies a subcortical lesion affecting the retina or optic nerve. A positive dazzle response in a blind animal (with absent menace response) supports central (brain) disease.

PUPIL SIZE AND SYMMETRY

Pupil size and symmetry should be assessed in both room light and darkness to evaluate the pupils' ability to constrict (parasympathetic function) and dilate (sympathetic function). Pupil abnormalities causing dilation (mydriasis) or constriction (miosis) of only one pupil will result in unequal pupils (anisocoria). If the abnormal pupil is dilated and unable to constrict, the anisocoria will be most apparent in bright light. Anisocoria caused by a single miotic pupil, such as is seen in animals with Horner syndrome, will be most apparent in a darkened room as the normal pupil dilates but the affected pupil remains miotic. A complete ophthalmic examination should always be performed to ascertain whether pupillary abnormalities can be explained by non-neurologic abnormalities of the eye. Iris atrophy, iris hypoplasia, and glaucoma will cause mydriasis, whereas uveitis and painful conditions of the cornea commonly cause miosis. Hippus, a condition in which there are exaggerated oscillations of pupillary size in response to light, can be a nonspecific indication of central nervous system disease.

DISORDERS OF EYEBALL POSITION AND MOVEMENT

During the neurologic examination it is important to evaluate eye position and movement. The extraocular muscles are innervated by the oculomotor nerve (CN3), trochlear nerve (CN4), and abducent nerve (CN6), with lesions resulting in an abnormal eye position (strabismus) or failure of the eye to move appropriately when the head is moved during evaluation of the oculocephalic reflex (see Chapter 58). Strabismus can occur with lesions of individual nerves, swelling or fibrosis of extraocular muscles, or intracranial lesions (see Fig. 58.23). Simultaneous paralysis of all the extraocular muscles (external ophthalmoplegia) most often occurs when there is a mass in the region of the paired venous sinuses that lie on the floor of the calvarium adjacent to the pituitary gland in the mid-cranial vault (cavernous sinus syndrome). Mass lesions in this area also typically damage the PSNS fibers in the oculomotor nerve, causing internal ophthalmoplegia (a fixed midrange or mydriatic pupil with normal vision) and may also damage the ipsilateral ophthalmic and maxillary branches of the trigeminal nerve, causing diminished corneal and medial palpebral sensation and occasionally atrophy of the ipsilateral masticatory muscles.

LACRIMAL GLAND FUNCTION

The lacrimal gland and the lateral nasal gland are innervated by the parasympathetic portion of the facial nerve (CN7). Normal basal tear production is assessed by performing a Schirmer tear test, and function of the lateral nasal gland is assessed by examining the ipsilateral nostril for dryness. Lesions of the facial nerve can result in loss of the palpebral reflex because of an inability to blink, decreased basal tear production, and a dry nose. Sensory innervation of the cornea is provided by the trigeminal nerve (CN5), and corneal stimulation by touch, cold, wind, or other irritants normally results in a blink response and increased reflex tear production. Lesions of the ophthalmic branch of the trigeminal nerve (CN5) result in decreased reflex tear production and decreased blink frequency, which may lead to keratitis and corneal ulceration.

LOSS OF VISION

LESIONS OF THE RETINA, OPTIC DISK, AND OPTIC NERVE

Concurrent loss of vision and diminished or absent PLR indicate the presence of a lesion affecting both the visual and PLR pathways. Unilateral severe lesions of the retina, optic disk, or optic nerve before the optic chiasm result in impaired vision and loss of the direct PLR in the affected eye as well as a loss of the consensual PLR in the opposite eye when light is directed into the affected eye (see Table 61.1). The direct and consensual response should be normal (both pupils constrict) when light is directed in the unaffected eye. Ocular or optic nerve disease must be very severe to cause complete loss of PLRs. Whenever an animal is evaluated for blindness, the retina should be carefully examined to rule out disorders such as progressive retinal atrophy, retinal dysplasia, retinal detachment, retinal hemorrhage, and chorioretinitis (Fig. 61.4). Optic nerve atrophy secondary to glaucoma or trauma must also be eliminated as a cause of blindness and PLR loss.

Sudden Acquired Retinal Degeneration

Sudden acquired retinal degeneration syndrome (SARDS) is a syndrome causing sudden bilateral degeneration of retinal photoreceptors in dogs. Middle-aged and older dogs of any breed can be affected, with females and obese individuals predisposed. The primary presenting complaint is loss of vision, with complete blindness occurring over a period of hours to weeks and often overnight. Pupils are dilated and PLRs are sluggish in dogs examined shortly after vision loss and absent in dogs with advanced disease. Many affected dogs have concurrent polyuria, polydipsia, panting, weight gain, and lethargy with clinical, serum biochemical, and urinalysis findings typical of hyperadrenocorticism, but endocrine tests and advanced imaging of the pituitary and adrenal glands rarely (<20%) confirm that disorder. In the early stages of SARDS, both fundi appear normal, but with time a bilaterally symmetric retinal degeneration becomes apparent, with hyperreflectivity of the tapetal fundus and attenuation of retinal blood vessels. These retinal changes are indistinguishable from chronic retinal degeneration caused by other conditions. Early SARDS is differentiated from retrobulbar optic neuritis by its extinguished (flat-line) electroretinogram (ERG), demonstrating photoreceptor death. Pathogenesis of the disorder is uncertain. Systemic signs are usually transient and resolve without treatment, but the blindness is permanent.

Optic Neuritis

Inflammation of the optic nerves causes blindness and loss of PLRs. Funduscopic evaluation may reveal optic disk swelling and discoloration (red) with or without associated retinal detachment and hemorrhage. When optic neuritis occurs posterior to the globes (i.e., retrobulbar), the visible portion of the optic nerves will be normal. In dogs with blindness and loss of PLRs with a normal-appearing fundus, ERG is required to differentiate bilateral retrobulbar optic neuritis (normal ERG) from SARDS (flat-line ERG).

Optic neuritis is most commonly seen as an isolated idiopathic immune-mediated disorder affecting one or both optic nerves in dogs, but it may also be a manifestation of systemic infectious disease (Box 61.2), especially canine distemper, tick-borne diseases, fungal infections, and bacterial meningoencephalitis. Noninfectious disorders such as

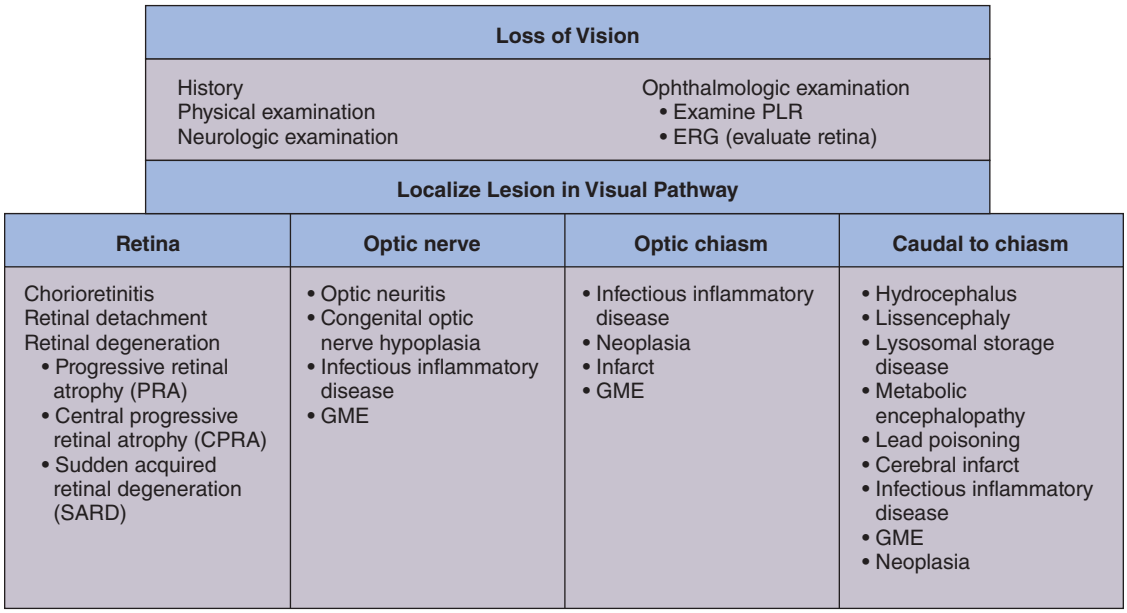


FIG 61.4
Diagnostic approach to a dog or cat with loss of vision. *ERG,* Electroretinogram; *GME,* granulomatous meningoencephalitis; *PLR,* pupillary light reflex.

BOX 61.2

Disorders Associated With Optic Neuritis

Infectious Disease
Systemic Fungal Infections
- Cryptococcosis
- Blastomycosis
- Systemic aspergillosis
- Coccidiodomycosis

Viral Diseases
- Canine distemper
- Feline infectious peritonitis
- Feline leukemia virus

Tick Borne Diseases
- Ehrlichiosis
- Lyme disease

Protozoal Infections
- Toxoplasmosis
- Neosporosis

Bacterial Disease
Noninfectious Inflammatory Disease
- Meningoencephalitis of unknown etiology
- Granulomatous meningoencephalitis
- Systemic lupus erythematosus
- Steroid-responsive meningitis arteritis

Neoplastic Disease
- Systemic neoplasia
- Optic nerve neoplasia
- Intracranial neoplasia

Idiopathic Immune-Mediated Optic Neuritis

granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), and optic nerve neoplasia can also result in optic neuritis.

Diagnosis of idiopathic (immune-mediated) optic neuritis is made only after infectious and neoplastic disorders are ruled out during a thorough workup for systemic and intracranial disease, including a complete blood count (CBC), serum chemistry profile, urinalysis, heartworm antigen test, serologic screening for infectious diseases, thoracic radiography, abdominal ultrasound, and cerebrospinal fluid (CSF) collection and analysis. CSF should be normal in optic neuritis; inflammatory cytology suggests that the changes in the optic nerves are secondary to meningoencephalitis. Magnetic resonance imaging (MRI) can be used to look for mass lesions of the optic chiasm and will occasionally reveal hyperintensity of inflamed optic nerves on T2-weighted images in animals with optic neuritis. If test results fail to identify meningoencephalitis or a neoplastic cause, primary immune-mediated optic neuritis is tentatively diagnosed.

Treatment of idiopathic optic neuritis should be initiated with orally administered glucocorticoids (prednisone 2 mg/kg/day for 2 weeks). If a favorable response is seen (i.e., improved vision and PLRs), the dose of steroids should be decreased to 1 mg/kg/day for 3 weeks, gradually decreased to alternate-day therapy and then discontinued while monitoring carefully. If there is no initial response to steroid therapy, or if relapse occurs during prednisone tapering, then additional immunosuppressive drugs should be administered (cyclosporine, azathioprine). Lifelong treatment is occasionally required. When the response to initial treatment is rapid, complete, and long-lasting, then the prognosis for return of vision is excellent. Inadequately treated optic neuritis leads to irreversible optic nerve atrophy and permanent blindness. Even with appropriate therapy, many cases will progress or relapse.

Papilledema

Edema of the optic disk usually results from increased intracranial pressure caused by a cerebral tumor or inflammatory mass lesion, but may also occur secondary to tumors or inflammation of the optic nerves. Papilledema is recognized as an enlarged optic disk with indistinct or fluffy margins, kinking of blood vessels as they pass over the disk, and occasionally congestion or hemorrhage of the adjacent retina. Papilledema may be difficult to distinguish from optic neuritis on funduscopic evaluation, although patients with a significant forebrain lesion causing papilledema should have clinical evidence of forebrain disease (i.e., abnormal mentation, behavior change, seizures). Despite reports that papilledema does not affect vision, most patients with papilledema caused by increased intracranial pressure are cortically blind. In patients with no loss of vision and no abnormal neurologic findings, enlargement of the optic disk with indistinct margins may simply represent hypermyelination, a normal finding in some breeds of dogs, especially Boxers, German Shepherd dogs, and Golden Retrievers.

LESIONS OF THE OPTIC CHIASM

Lesions of the optic chiasm cause bilateral blindness, mydriasis, and loss of the direct and consensual PLRs; fundic examination and ERG will be normal. Neoplasia and other space-occupying masses can occur at this location, especially lymphoma (cats), pituitary macroadenomas, meningiomas, and primary nasal tumors extending into the brain (Fig. 61.5). Vascular lesions such as hemorrhage and infarction, infectious inflammatory granulomas, and GME can also affect the optic chiasm. Evaluation should include a search for evidence of extraneural infectious or neoplastic disease, followed by cranial MRI, CSF collection and analysis, and endocrinologic testing as warranted.

LESIONS CAUDAL TO THE OPTIC CHIASM

Lesions in the LGN, optic radiations, or visual cortex prevent interpretation of the image, resulting in visual deficits in the eye opposite the lesion despite normal PLRs, normal fundic examination, and normal ERG. This is called cortical blindness. Other clinical signs of forebrain disease (e.g., seizures, circling, altered mentation) are usually evident in animals with forebrain lesions severe enough to cause cortical blindness but are not always present. Intracranial causes of cortical blindness include trauma-induced hemorrhage, edema, vascular infarcts, GME, infectious encephalitis, intracranial



FIG 61.5
Neoplasm of the optic chiasm identified with magnetic resonance imaging in a 7-year-old Doberman Pinscher with an acute onset of bilateral blindness and loss of pupillary light reflexes but no other neurologic deficits.

neoplasia, congenital malformations (e.g., hydrocephalus, lissencephaly), and degenerative disorders (see Box 60.1). Animals with functional disturbances of the forebrain caused by metabolic encephalopathies, intoxications, hypoxia, or postictal cerebral edema may also present with cortical blindness that is often transient or intermittent. Diagnostic evaluation for cortical blindness should follow the guidelines outlined in Chapter 60 for evaluation of animals with suspected intracranial disease and should include thorough physical, ophthalmologic, and neurologic examinations; a laboratory database; screening thoracic and abdominal radiographs and abdominal ultrasound; CSF analysis; and cranial MRI evaluation.

HORNER SYNDROME

Lesions disrupting the sympathetic innervation to the eye result in Horner syndrome. This condition causes miosis (constriction of the affected pupil), drooping of the upper eyelid (ptosis), and an inward sinking of the eyeball (enophthalmos) as well as partial protrusion of the third eyelid (nictitating membrane) (Box 61.3; Fig. 61.6).

Horner syndrome can result from injury to the sympathetic innervation of the eye anywhere along its pathway (Box 61.4; Fig. 61.7). Lesions are classified as first order (central), second order (preganglionic), or third order (postganglionic) according to the level of the lesion along the sympathetic pathway.

First-order neurons originate in the hypothalamus and rostral midbrain and travel down the brainstem and cervical spinal cord to terminate at the preganglionic cell bodies in



FIG 61.6
Horner syndrome in a domestic short-haired cat with otitis media/interna.

BOX 61.3

Components of Horner Syndrome

Miosis
Enophthalmos
Ptosis
Prolapsed nictitans

BOX 61.4

Common Causes of Horner Syndrome

First-Order (Central) Causes (Rare)

Intracranial neoplasia, trauma, infarct, inflammatory disease
Cervical spinal cord lesion
- Intervertebral disk protrusion
- Neoplasm
- Fibrocartilaginous embolism
- Trauma
- Infectious inflammatory disease
- Granulomatous meningoencephalitis

Second-Order (Preganglionic) Causes

Spinal cord lesion T1-T3 (trauma, neoplasia, fibrocartilaginous embolism, inflammation)
Brachial plexus avulsion
T1-T3 spinal nerve root tumor
Cranial mediastinal mass
Cervical soft-tissue neoplasia, trauma
Skull base trauma

Third-Order (Postganglionic) Causes

Otitis media/interna
Neoplasia in middle ear
Retrobulbar injury, neoplasia
Idiopathic

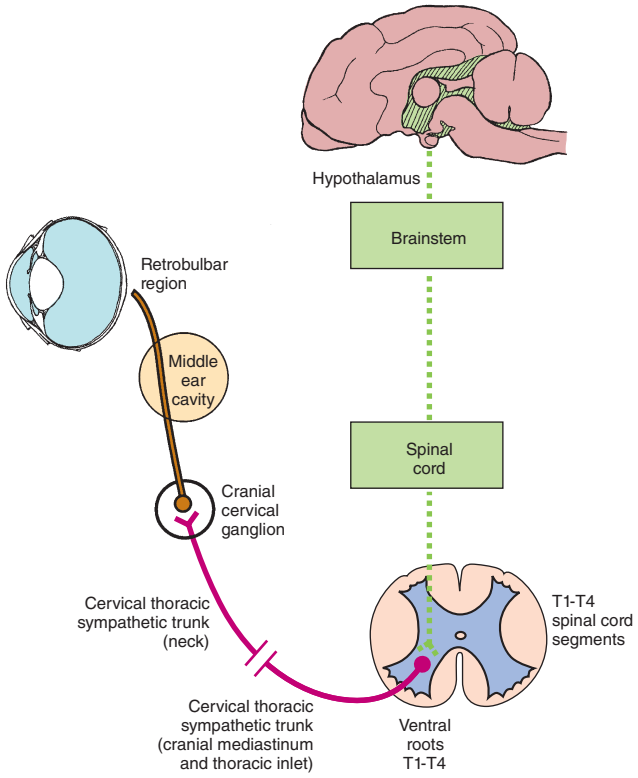


FIG 61.7
Sympathetic innervation to the eye. An injury anywhere along this pathway will result in Horner syndrome.

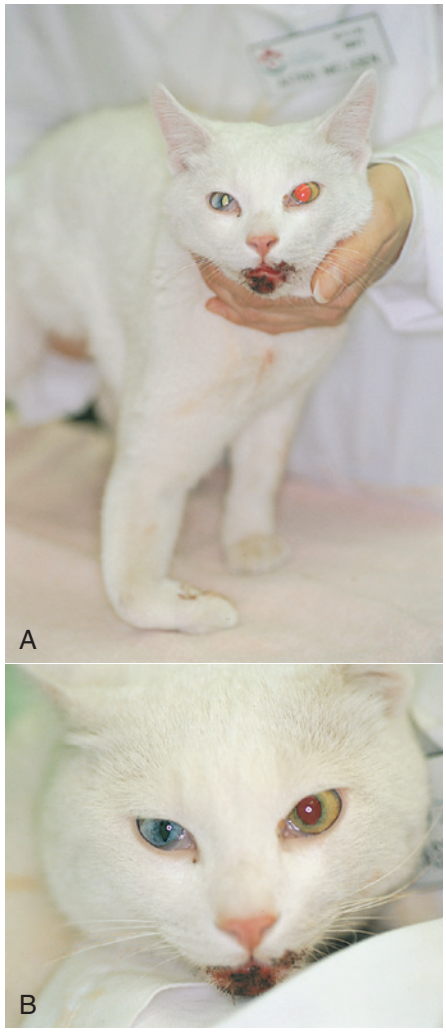


FIG 61.8
(A) and **(B)** Horner syndrome in a domestic short-haired cat with traumatic right brachial plexus avulsion.

the thoracic spinal cord. Upper motor neuron lesions in the brainstem or cervical spinal cord are a relatively rare cause of Horner syndrome but may occur secondary to trauma, infarction, neoplasia, or inflammatory disease. Ipsilateral hemiplegia and other concurrent neurologic abnormalities are expected in animals with first-order lesions (see Box 61.4).

The preganglionic cell bodies of second-order neurons are located in the lateral horn of the spinal cord gray matter at the level of the first three thoracic spinal cord segments (T1-T3). The second-order axons leave the spinal cord with the T1-T3 ventral nerve roots, but then leave the spinal nerves to form the thoracic sympathetic trunk, which courses cranially within the thorax. The sympathetic axons course cranially within the vagosympathetic trunk in the cervical region and synapse in the cranial cervical ganglion, ventral and medial to the tympanic bulla at the base of the skull. Injury to second-order neurons can occur when there is damage to the spinal cord at the cervical intumescence (C6-T2) caused by trauma, infarcts, neoplasia, or inflammatory disease. Affected animals will exhibit lower motor neuron (LMN) signs in the affected forelimb, upper motor neuron (UMN) signs in the ipsilateral rear limb, and Horner syndrome. In animals with brachial plexus avulsion, there will be complete LMN paralysis of the affected limb and an ipsilateral Horner syndrome that may be partial (miosis only) because of sparing of the T3 (and sometimes T2) nerve roots (Fig. 61.8). Horner syndrome can also occur when the second-order neurons are damaged by thoracic surgery, mediastinal masses (lymphoma or thymoma), bite wounds to the neck, strangulation injuries, invasive thyroid carcinoma, or errors made during thyroidectomy or surgery for cervical intervertebral disk disease. Physical and neurologic findings are often useful in localizing and determining the cause of preganglionic Horner syndrome.

Most dogs and cats with Horner syndrome have postganglionic (third-order) lesions. The postganglionic axons for ocular sympathetic innervation course rostrally through the tympanooccipital fissure into the middle ear and enter the cranial cavity with the glossopharyngeal nerve (CN9), leaving the cranial cavity via the orbital fissure for distribution to the smooth muscle of the orbit, the upper and lower eyelids, the third eyelid, and the iris muscles. Third-order Horner syndrome is common in patients with otitis media or neoplasia within the middle ear, often accompanied by evidence of peripheral vestibular (CN8) disturbance and



FIG 61.9
Dramatic muscle atrophy in a dog with masticatory muscle myositis has resulted in retraction of the globes into the orbits and protrusion of the third eyelid over most of the corneal surface.

sometimes facial nerve (CN7) paralysis. No underlying cause can be identified in most dogs with postganglionic Horner syndrome, and these cases have been called idiopathic Horner syndrome.

Pharmacologic testing has been recommended to help localize the cause of Horner syndrome in dogs and cats. When Horner syndrome has been present for at least 2 weeks, denervation hypersensitivity will occur in the affected eye secondary to the loss of sympathetic innervation. To localize Horner syndrome pharmacologically, a single drop of a very dilute concentration of a direct-acting sympathomimetic (0.1% phenylephrine: stock 10% solution diluted 1:100 with saline solution) is applied to both eyes. The pupil in the normal eye should not dilate with that dilute concentration. Dilation of the affected pupil will occur within 20 minutes in an animal with a postganglionic (third-order Horner syndrome) lesion. If neither pupil dilates within 20 minutes, repeat the test using a more concentrated adrenergic (1% phenylephrine) applied to the affected eye and then monitor pupil size every 2 minutes in both eyes. The time that it takes for the affected pupil to dilate to the same size as the unaffected pupil is the test endpoint. If dilation occurs within 20 minutes, the lesion is most likely postganglionic (third order). Dilation in 20 to 45 minutes has been reported in dogs with second-order lesions and 60 to 90 minutes in dogs with central lesions and dogs that have not had sympathetic denervation of the eye for at least 2 weeks. Although pharmacologic testing can be helpful in localizing the site of neuron injury in animals with Horner syndrome, results of pharmacologic testing can be equivocal and may not always contribute practical information regarding the cause or prognosis.

The diagnostic approach in an animal with Horner syndrome should include complete physical, ophthalmologic, neurologic, and otoscopic examinations. Neurologic findings can often help to locate the site of disruption of sympathetic innervation. Further tests should be recommended after lesion localization. Careful palpation of the soft tissues of the neck and radiographs of the thorax and the cervical and thoracic spine should be performed and advanced diagnostic imaging (MRI) should be considered if a first- or second-order lesion is suspected. When a postganglionic lesion is suspected, skull radiographs, CT, or MRI should be performed to evaluate the middle ear for signs of otitis media, neoplasia, or trauma. The most common causes of Horner syndrome in cats are middle ear disease and injury to the soft tissues of the neck. Dogs more frequently have brachial plexus avulsion, nerve root tumors of the brachial plexus, C6-T2 spinal cord injury, middle ear disease, and cervical soft tissue injuries or tumors. Most dogs with Horner syndrome (>50%) have no other neurologic abnormalities, and a cause for their Horner syndrome is not identified; these animals are classified as having idiopathic disease. Idiopathic postganglionic Horner syndrome is especially common in Golden Retrievers. The prognosis for resolution of idiopathic Horner syndrome is excellent as most cases resolve spontaneously within 4 to 6 months. Treatment is rarely required, but occasionally in dogs with bilateral disease vision is obscured by the prolapsed third eyelids and some periodic relief can be provided by administering topical phenylephrine (1%).

PROTRUSION OF THE THIRD EYELID

In dogs and cats the third eyelid may protrude over the corneal surface in the presence of corneal or conjunctival irritation, or space-occupying retroorbital disease. This may also occur if the animal experiences a decrease in periorbital mass as a result of dehydration, a loss of retrobulbar fat or muscle (Fig. 61.9), or a loss of volume within the eye (i.e., microphthalmos, phthisis bulbi).

Protrusion of the third eyelid is a conspicuous feature of both Horner syndrome (with miosis) and dysautonomia (with mydriasis). Systemic illness or tranquilization can also result in third eyelid protrusion in some dogs and cats. A peculiar syndrome of dramatic bilateral third eyelid protrusion with no obvious cause (i.e., Haw syndrome) has been observed in cats and occasionally in dogs. Affected cats are usually younger than 2 years of age and in good health otherwise, although digestive disturbances or heavy intestinal parasite loads have occasionally been documented. Instillation of sympathomimetic drops (phenylephrine 10%) causes the membrane to rapidly retract. The condition resolves spontaneously within several weeks or months.

Suggested Readings

Cottrill NB. Differential diagnosis of anisocoria. In: Bonagura JD, ed. *Current veterinary therapy XIII small animal practice*. Philadelphia: WB Saunders; 2000.

Grahn BH, Cullen CC, Peiffer RL. Neuro-ophthalmology. In: Grahn BH, Cullen CL, Peiffer RL, eds. *Veterinary ophthalmology essentials*. Philadelphia: Elsevier; 2004.

Hamilton HL, et al. *Diagnosis of blindness. Current veterinary therapy XIII*. Philadelphia: WB Saunders; 2000.

Komaromy AM, et al. Sudden acquired retinal degeneration syndrome (SARDS) – a review and proposed strategies towards a better understanding of pathogenesis, early diagnosis and treatment. *Vet Ophthalmol*. 2016;19:319.

Penderis J. Disorders of eyes and vision. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Simpson KM, Williams DL, Cherubini GB. Neuropharmacological lesion localization in idiopathic Horner's syndrome in Golden Retrievers and dogs of other breeds. *Vet Ophthalmol*. 2015; 18:1–5.

CHAPTER 62

Seizures and Other Paroxysmal Events



SEIZURES

A seizure is the clinical manifestation of excessive or hypersynchronous abnormal electrical activity in the brain. The clinical features of seizures can be separated into four components: prodrome, aura, ictal period, and postictal period. The *prodrome* is the period of time (hours to days) before the seizure begins, when the owner may report unusual behavior such as restlessness or anxiety. The prodrome may be barely noticeable in some animals and distinct enough to enable owners to accurately predict seizure onset in others. The *aura* is the period of time immediately before the seizure when animals may exhibit stereotypical sensory or motor activity (pacing, licking, swallowing), autonomic patterns (salivation, vomiting, urination), or abnormal behavior (hiding, attention seeking, whining, or agitation) for seconds to minutes before seizure onset. The *ictus* is the seizure itself, when the animal exhibits a variety of signs that may include loss or derangement of consciousness, altered muscle tone or movements, paddling of the limbs, jaw chomping, salivation, and involuntary urination and defecation. This phase usually lasts only seconds to minutes. The *postictal period* immediately follows the seizure and reflects transiently abnormal brain function (seconds to several hours), during which time the animal may exhibit abnormal behavior, disorientation, somnolence, or actual neurologic deficits such as blindness, ataxia, weakness, or proprioceptive deficits. Identification of a postictal phase is highly suggestive that the preceding paroxysmal event was a seizure. Regardless of etiology, seizures can occur singly or in clusters, where two or more seizures occur within a 24-hour period. *Epilepsy* is a term used for any condition characterized by chronic recurrent seizures.

NONEPILEPTIC PAROXYSMAL EVENTS

Dogs and cats are occasionally affected by nonepileptic paroxysmal disorders during which they may experience altered behavior, collapse, abnormal movements, transient neurologic symptoms, or paralysis. Distinguishing these paroxysmal transient events from focal seizures can be challenging but important for diagnosis and treatment. Cardiac arrhythmias causing syncope; weakness caused by hypoglycemia, hypocortisolemia, or electrolyte disturbances; and myasthenia gravis can all cause transient neurologic signs. Nonepileptic neurologic disorders causing repeated paroxysms of neurologic signs in animals that are normal between episodes include acute vestibular "attacks" (see Chapter 63); paroxysmal dyskinesias (PDs); narcolepsy and cataplexy; and several inherited disorders of neurotransmission or function. Descriptions of the event and the animal's activity and demeanor immediately preceding, during, and after the event will often help distinguish these events from seizures (Box 62.1). Observing a videotaped episode will be helpful in the diagnosis of disorders that have a very characteristic appearance. Discussion of some of the important or common neurologic nonepileptic paroxysmal events that are often confused with seizures can be found at the end of this chapter.

SEIZURE DESCRIPTIONS

Most true seizures in dogs and cats are tonic-clonic, generalized-onset motor seizures in which the animal experiences a period of extremely increased extensor muscle tone (tonus), falls into lateral recumbency in opisthotonus with its legs extended, and then has periods of tonus alternating with periods of relaxation (clonus), resulting in rhythmic contractions of muscles manifested as paddling or jerking of the limbs and chewing movements. Animals typically lose consciousness during severe generalized seizures, although their eyes may remain open. Autonomic signs such as salivation, urination, defecation, and mydriasis are common.

Less common than generalized-onset, symmetric tonic-clonic seizures in dogs and cats are focal seizures (also called *partial seizures*) arising in part of one cerebral hemisphere, resulting in asymmetric signs initially. Focal seizures may progress to generalized motor seizures in some animals.

BOX 62.1

Paroxysmal Disorders Confused With Epileptic Seizures

- Syncope (reduced cerebral blood flow)
  - Cardiac arrhythmias
  - Hypotension
- Episodic weakness
  - Hypoglycemia
  - Low blood cortisol
  - Electrolyte disturbances
- Myasthenia gravis
- Acute vestibular "attacks"
- Sleep disorders
  - Narcolepsy
  - Cataplexy
- Movement disorders (dyskinesias)
- Exercise-induced weakness or collapse disorders
  - dynamin-associated Exercise-Induced Collapse (dEIC)
  - Border Collie collapse

Although it is often stated that partial motor seizures are associated with focal intracranial pathology, many dogs and cats with idiopathic epilepsy (IE) experience focal seizures with or without progression to generalized seizures. Focal motor seizure manifestations may include abnormal movements or postures such as turning of the head to one side, focal twitching, rhythmic contraction of limb or facial muscles, lip smacking, or chewing movements. Labrador Retrievers, Poodles, and occasionally other breeds may experience partial seizures that resemble episodes of staggering, loss of balance, confusion, trembling, or crawling without loss of consciousness. Circling, rapid running, and climbing activity is common in epileptic cats and may suggest temporal lobe involvement. Focal sensory seizures can cause tingling, pain, or visual hallucinations, resulting in tail chasing, limb chewing, compulsive digging, or "fly biting." It can be very difficult to distinguish sensory seizures from compulsive stereotypic behavior in dogs.

Repetitive episodes of autonomic signs may occur as unusual manifestations of a focal seizure disorder. Signs may include vomiting, diarrhea, apparent abdominal discomfort, drooling, repetitive swallowing or gulping, compulsive licking of the carpet or floor, or eating grass. Signs may last for hours rather than the seconds to minutes usually associated with epileptic seizures. Affected dogs are normal between episodes, and extensive gastrointestinal evaluations looking for a cause of their signs are typically negative. Many affected dogs have resolution of their episodes with chronic oral anticonvulsant therapy, supporting the suspicion that these are seizure events. A phenobarbital (PB)-responsive syndrome of drooling, retching, and dysphagia in dogs with painful enlargement of the mandibular salivary glands and salivary gland necrosis likely also represents a focal seizure with prominent autonomic signs.

Complex focal seizures, also known as *psychomotor seizures* or *automatisms,* are focal seizures with altered mentation. Animals may appear confused, disoriented, or unresponsive to owner commands while head pressing, pacing, aimlessly walking, circling, or staggering. Some complex focal seizures are associated with episodes of howling, unprovoked aggression, or extreme fearfulness. "Rage syndrome" or "episodic dyscontrol" in St. Bernards and Springer Spaniels may be a complex focal seizure disorder.

Reflex seizures are seizures that can be consistently provoked by specific stimuli or events. The most common precipitating factor in people is a flickering light, but certain sounds and eating have also been identified as triggers. Reflex focal, generalized, or myoclonic seizures in response to high-pitched repetitive sound stimuli have been well described in cats, characterizing a disorder called feline audiogenic reflex seizures. Wirehaired Dachshunds with Lafora disease have been reported to have myoclonic seizures triggered by auditory and visual stimuli.

SEIZURE CLASSIFICATION AND LOCALIZATION

Seizure disorders can be classified according to their cause as being idiopathic, intracranial, or extracranial in origin (Box 62.2). IE is the most common cause of recurrent seizures in dogs but is less common in cats. Animals with IE have no identifiable extracranial or intracranial cause for their seizures, are neurologically normal between seizures, and their seizures are presumed to be genetically based. Intracranial (structural) causes (e.g., anomaly, inflammation, neoplasia, infarct, trauma, scar) are responsible for seizures in approximately 35% of dogs and most cats with seizures (see Chapter 60). Extracranial causes of seizures such as ingestion of toxins or metabolic or endocrine derangements occur less frequently (see Box 62.2).

Seizure activity always indicates a functional or structural abnormality of the forebrain, particularly of the frontal or temporal lobes of the cerebrum. Metabolic and toxic disorders can cause functional alterations of the balance between inhibitory and excitatory neurotransmitters, leading to seizures. Defined localizing neurologic deficits are unlikely to be detected interictally (between seizures) in patients with extracranial causes of seizures. Animals with an intracranial lesion causing seizures typically exhibit multiple signs localizing disease to the forebrain, including behavior change, circling toward the side of the lesion, contralateral hemiparesis and postural reaction deficits, and contralateral vision loss and facial hypalgesia. Animals with small intracranial lesions will, however, sometimes be normal interictally, with no other identifiable neurologic deficits.

IE is a condition wherein the seizure threshold is decreased. This disorder has been shown to be inherited in a few dog breeds, and a familial basis for the condition is suspected in others. Affected animals are normal interictally, and extensive diagnostic evaluation, including histologic examination of the brain, is normal.

BOX 62.2

Common Disorders Resulting in Seizures

Extracranial Causes (Reactive Seizures)

Toxins
Metabolic diseases
- Hypoglycemia
- Liver disease
- Hypocalcemia
- Hyperlipoproteinemia
- Hyperviscosity
- Hypertension
- Electrolyte disturbances
- Hyperosmolality
- Severe uremia
- Hyperthyroidism (cats)
- Hypothyroidism (dogs)—predisposition to intracranial infarcts

Intracranial Lesions (Structural Epilepsy)

Congenital malformations
- Hydrocephalus
- Lissencephaly

Neoplasia
- Primary brain tumors
- Metastatic tumors

Inflammatory disease
- Infectious inflammatory diseases
- Meningoencephalitis of unknown etiology (dogs)
  - Granulomatous meningoencephalitis
  - Necrotizing meningoencephalitis
  - Necrotizing leukoencephalitis

Vascular disease
- Hemorrhage
- Infarct

Metabolic storage diseases
Degenerative conditions

Scar Tissue–Related Acquired Epilepsy

Idiopathic Epilepsy (Primary Epileptic Seizures)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a patient with seizures includes IE, intracranial disease, scar tissue–related acquired epilepsy, and extracranial disorders (see Box 62.2).

IDIOPATHIC EPILEPSY

IE is the most common cause of seizures in the dog and is characterized by repeated episodes of seizures with no demonstrable cause. Affected dogs are normal between seizures. The diagnosis can be suspected clinically based on breed, age of onset, normal interictal neurologic examination, typical seizure recurrence pattern, and failure to progress to systemic or neurologic abnormalities over time, but the diagnosis remains uncertain unless diagnostic evaluation has eliminated metabolic and structural causes for seizures. IE has always been considered to be uncommon in cats, but most recent reports suggest that 20% to 50% of cats with recurrent seizures may have IE. Intracranial causes of seizures are, however, much more common in cats than in dogs, so an intracranial evaluation is still recommended in all cats with recurrent seizures.

A genetic basis for IE is strongly suspected or proven in German Shepherd dogs, Belgian Tervurens, Keeshonds, Beagles, Dachshunds, Labrador Retrievers, Golden Retrievers, Poodles, Border Collies, Shetland Sheepdogs, Irish Wolfhounds, Vizslas, Bernese Mountain Dogs, and English Springer Spaniels. Genetic factors are likely in other affected breeds as well, and IE is often called familial epilepsy.

The first observed seizure in dogs with IE usually occurs between 6 months and 3 years of age, although seizures are not observed until 5 years of age or older in some dogs. In most breeds it seems that the younger the age at the onset of a seizure disorder, the more difficult the disorder will be to control. Cats with IE typically experience their first seizure between 3 and 5 years of age.

The seizures in dogs and cats with IE are often generalized-onset, tonic-clonic, and associated with a loss of consciousness lasting from 1 to 2 minutes. However, dogs and cats with IE can have a variety of focal-onset seizures or a combination of focal-onset and generalized seizures. Some dog breeds, especially Labrador Retrievers and Miniature Poodles, very commonly experience a mild generalized type of seizure during which they maintain consciousness but exhibit staggering, loss of balance, confusion, a crouched posture or crawling stance, uncontrollable trembling, or muscular rigidity. In Retrievers, common triggers for these unusual seizures include exercise, excitement, or hyperventilation, prompting some diagnostic confusion with Exercise Induced Collapse (EIC, see page 1106). Many of these epileptic Labrador Retrievers experience a postictal phase, develop more classical generalized tonic-clonic seizures later in life, and respond to chronic oral anticonvulsant therapy, confirming that these paroxysmal events are seizures.

The frequency of seizures varies greatly between dogs and cats with IE, but seizures typically recur at regular intervals, with weeks or months intervening between seizures. As the animal ages, the frequency and severity of seizures may increase, especially in large-breed dogs. In some dogs, particularly large breeds, seizures can eventually occur in clusters in which multiple seizures occur during a 24-hour period. Cluster seizures are not seen in association with the first observed seizure in most dogs or cats with IE, so this presentation should prompt consideration of intracranial causes. The most common time for seizures to occur in dogs and cats with IE is when an affected animal is sleeping, drifting off to sleep, or waking up abruptly, but in some patients seizures seem to be provoked by specific stimuli such as certain sounds, excitement, hyperventilation, or exercise.

IE is the most likely diagnosis in a young adult, neurologically normal animal with a long history (>1 year) of a nonprogressive intermittent seizure disorder and a lengthy interictal period (>4 weeks). The diagnosis of IE is one of

exclusion; although it can be suspected based on typical signalment, seizure history, and unremarkable physical, neurologic, and ophthalmologic evaluations, diagnosis requires the exclusion of underlying metabolic and toxic causes through clinicopathologic testing and imaging. Intracranial evaluation, when performed, is normal (Fig. 62.1).

INTRACRANIAL DISEASE

Intracranial disease localized in the forebrain commonly causes seizures. Congenital disorders, inherited degenerative conditions, and many infectious causes of encephalitis are most often seen in young animals, whereas neoplasia is more common in dogs and cats older than 6 years of age. Most of the intracranial disorders discussed in Chapter 60 and the inflammatory disorders discussed in Chapter 64 can cause seizures (see Box 62.2). Focal or multifocal neurologic deficits identified interictally strongly suggest that structural forebrain pathology exists, but not all patients with intracranial disease will have an abnormal neurologic examination. Diagnosis requires careful physical, neurologic, and ophthalmologic examination; evaluation for concurrent systemic manifestations of infectious and neoplastic disorders; and often intracranial evaluation, including cerebrospinal fluid (CSF) analysis, and advanced diagnostic imaging (Fig. 62.2).

SCAR TISSUE–RELATED ACQUIRED EPILEPSY

Scar tissue in the brain after an inflammatory, traumatic, toxic, metabolic, or vascular insult can result in a seizure

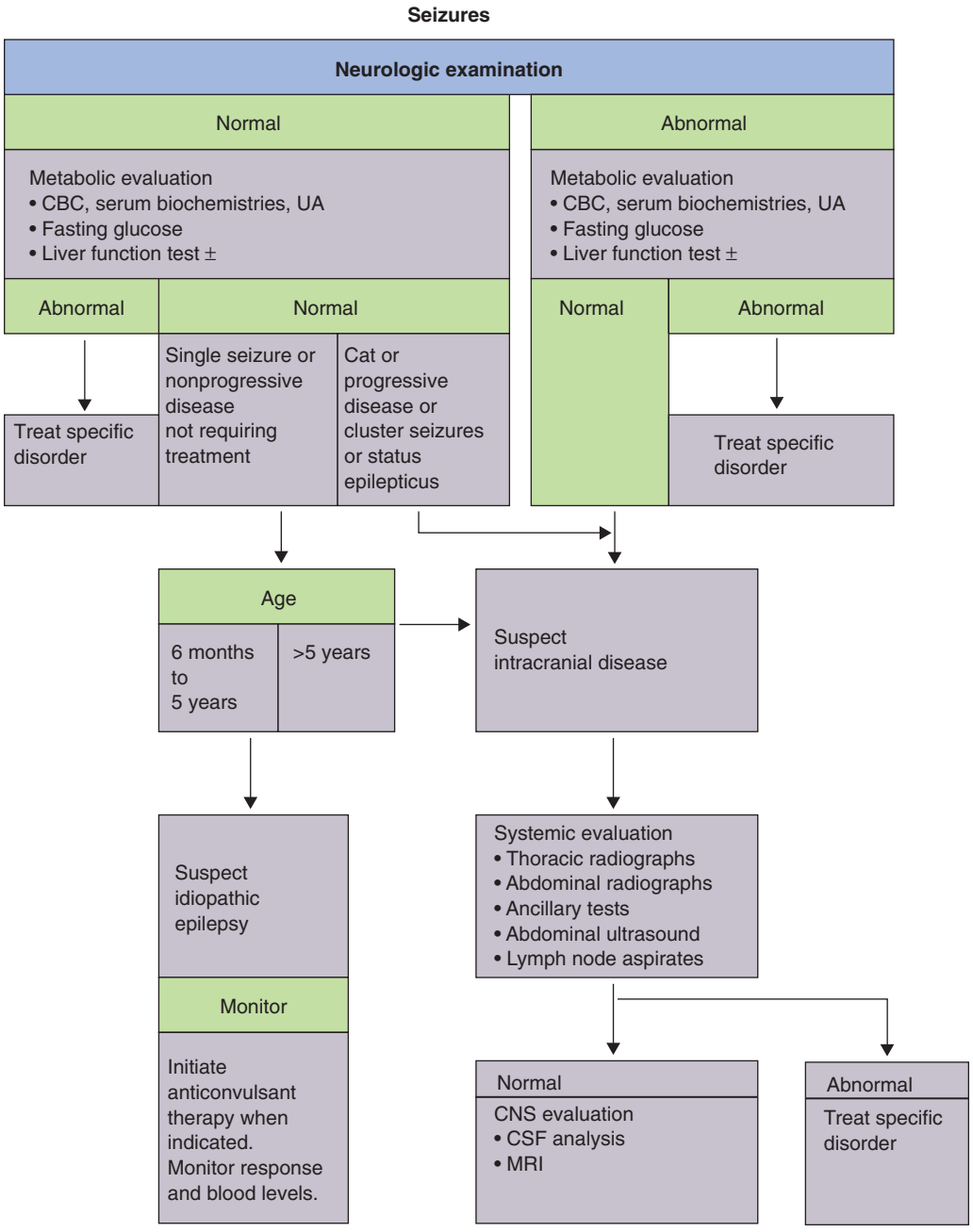


FIG 62.1 Diagnostic approach used in dogs or cats with seizures. *CBC,* Complete blood count; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *MRI,* magnetic resonance imaging; *UA,* urinalysis.

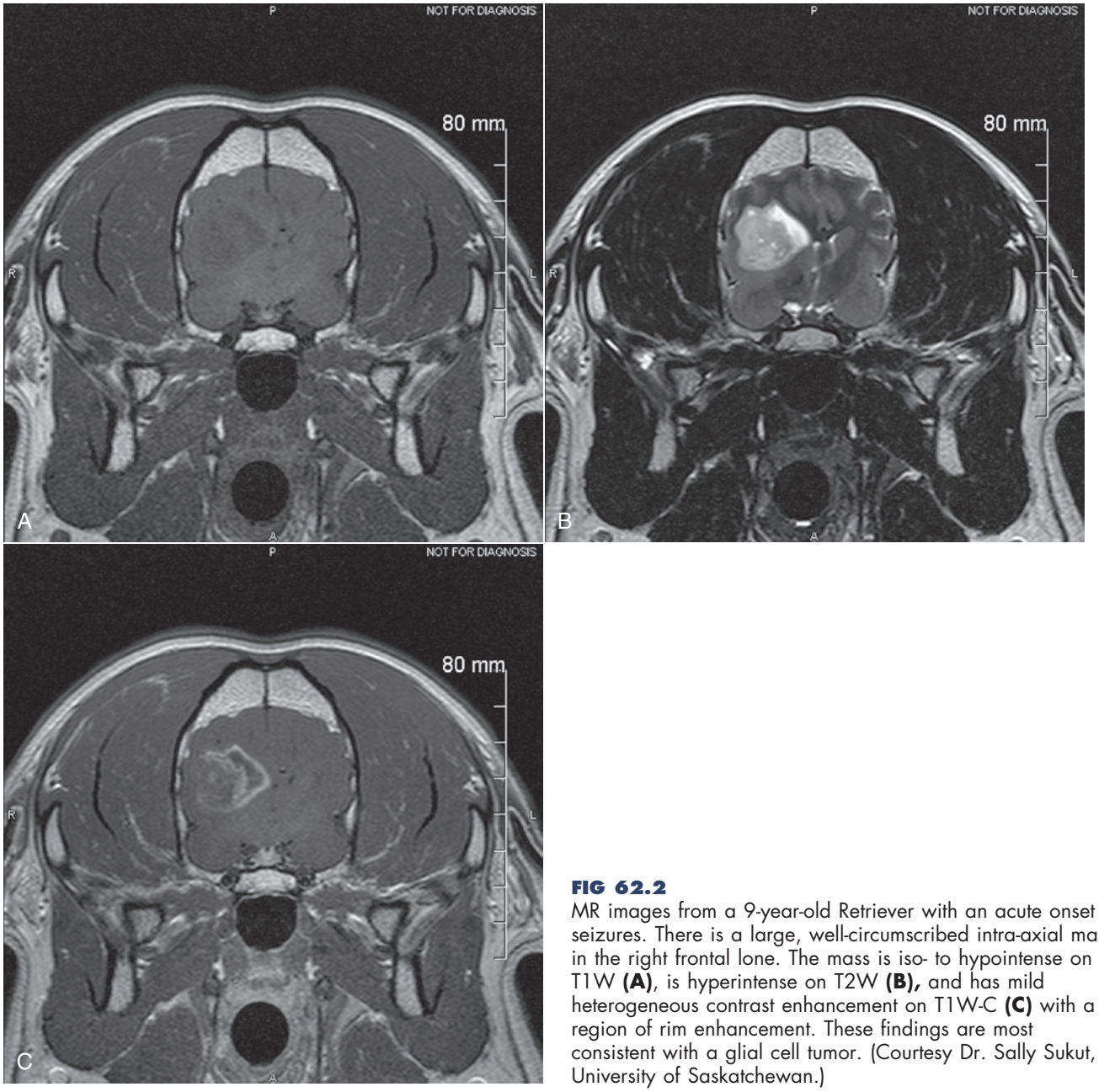


FIG 62.2
MR images from a 9-year-old Retriever with an acute onset of seizures. There is a large, well-circumscribed intra-axial mass in the right frontal lone. The mass is iso- to hypointense on T1W **(A)**, is hyperintense on T2W **(B),** and has mild heterogeneous contrast enhancement on T1W-C **(C)** with a region of rim enhancement. These findings are most consistent with a glial cell tumor. (Courtesy Dr. Sally Sukut, University of Saskatchewan.)

disorder. If a history of significant trauma or infection can be ascertained, that event usually precedes the onset of the seizure disorder by 6 months to 3 years. Findings from physical and neurologic examinations, clinicopathologic tests, and CSF analysis are normal. It is not usually possible to detect a structural abnormality using magnetic resonance imaging (MRI), and even necropsy will not reliably demonstrate a lesion. Treatment is the same as for IE (i.e., anticonvulsant therapy), but the prognosis for seizure control and lack of progression may be better for those with scar tissue–related acquired epilepsy than for those with IE.

EXTRACRANIAL DISEASE

Seizures with an extracranial cause are known as reactive seizures. Reactive seizures reflect a response by a normal brain to a transient metabolic or toxin-induced disturbance in cerebral function. Metabolic disorders including hypoglycemia, hepatic encephalopathy, hypocalcemia, and primary hyperlipoproteinemia commonly cause seizures in dogs and cats. Hyperviscosity syndromes (e.g., multiple myeloma, polycythemia), severe electrolyte disturbances (e.g., hypernatremia), hyperosmolality (e.g., untreated diabetes mellitus), heatstroke, severe hypertension, feline hyperthyroidism, and prolonged severe uremia also occasionally cause seizures (see Box 62.2). Hypothyroidism does not directly induce seizures in dogs but can cause atherosclerotic vascular changes that predispose to intracranial infarcts.

Systemic signs and physical and neurologic examination findings may increase suspicion of an extracranial cause of seizures. Many metabolic encephalopathies intermittently or

permanently alter consciousness, causing dull mentation, confusion, or delirium. Symmetrical signs including cortical blindness, diminished facial sensation, and impaired proprioceptive positioning can all be seen. All patients with seizures should be evaluated for an extracranial cause. Results of a complete blood count (CBC), serum biochemistry panel, and urinalysis often help establish the diagnosis. Hepatic encephalopathy resulting from portosystemic shunting can occasionally cause seizures in the absence of other clinical or clinicopathologic abnormalities, especially in cats, so evaluation of liver function is an important component of the initial evaluation for metabolic causes of seizures. More detailed information on the diagnosis and management of these metabolic disorders is contained elsewhere in this text. Common intoxications causing seizures are described in Box 62.3, and treatment of some common intoxications is outlined in Box 62.4.

DIAGNOSTIC EVALUATION

A complete and accurate history must be obtained in every animal presenting for a seizure. The owner's description is crucial to determining whether the observed paroxysmal event was actually a seizure. The relationship of seizures to daily activity (e.g., exercise, sleep, eating, excitement), seizure duration and frequency, and a description of any observed postictal abnormalities should be recorded. Recent systemic signs such as cough, vomiting, diarrhea, polyuria, polydipsia, and weight loss or weight gain could suggest a metabolic encephalopathy or systemic disease (infection, neoplasia) spread to the brain. Vaccination status, diet, potential exposure to infectious causes of encephalitis, access to drugs or toxins, and history of serious head injury should also be determined. When seizures have occurred intermittently over a prolonged period of time (weeks to months), the seizure pattern and frequency should be assessed. Owners should be asked whether they have noticed any changes in the animal's behavior, gait, vision, or sleep patterns, characteristics that might indicate a structural forebrain lesion. When IE or an inherited neurodegenerative disorder is considered likely, owners should be encouraged to contact the breeder to ascertain whether litter mates or other related dogs are affected.

Neurologic, physical, and ophthalmologic examinations should be performed in every animal presented for seizures. In the immediate postictal period, cerebral edema and altered cerebral metabolism can cause transient symmetric neurologic abnormalities such as blindness, altered consciousness, and postural reaction deficits, so these should not be overinterpreted. Neurologic abnormalities that persist beyond the postictal period suggest an intracranial cause for seizures requiring further evaluation. A complete physical examination with particular attention to lymph node and abdominal palpation as well as mammary gland and prostate examination should always be performed in dogs and cats with seizures to evaluate for primary neoplasia that could have spread to the brain. Ophthalmologic examination is often abnormal in infectious and neoplastic causes of seizures and can also reveal changes suggestive of hemorrhage, hypertension, or increased intracranial pressure.

Every animal evaluated for seizures should have a CBC, serum biochemistry panel, and urinalysis and blood pressure measurement performed. Additional testing may be recommended based on the age, breed, seizure pattern, and physical and neurologic examination findings. Blood glucose should be measured during any observed seizure, and whenever insulinoma is a possibility, random blood glucose measurement should be performed during the day to include samples after a 12-hour fast and 15 minutes after eating. Young dogs and cats with a seizure history, animals with initial laboratory results suggesting hepatic dysfunction, and all seizure patients that might potentially be treated with an antiepileptic drug (AED) metabolized by the liver should have their liver function evaluated with serum bile acids or ammonia testing (see Chapter 36). Thyroid function should be evaluated in mature dogs with an acute onset of seizures because of the association between hypothyroidism and intracranial infarcts. All cats with seizures should be screened for feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody.

The animal's signalment and history as well as the onset and progression of the seizure disorder allow ranking of likely differential diagnoses. Congenital structural disorders such as hydrocephalus and lissencephaly are likely causes of a seizure disorder in very young animals. Infectious causes of encephalitis typically cause rapidly progressive neurologic dysfunction rather than seizures alone. In aging animals, primary or metastatic cerebral neoplasia, vascular infarct or hemorrhage, and acquired metabolic disturbances are the most likely causes of seizures. Animals with IE nearly always have their first observed seizure between 6 months and 5 years of age, so it is not a likely diagnosis in a dog or cat with seizures that began late in life.

When the systemic, neurologic, and screening laboratory tests are all normal in an animal with seizures, recommendations for further testing are based on history and signalment. Dogs between 1 and 5 years of age presenting with a single generalized seizure, or a history of a few generalized seizures weeks or months apart, most likely have IE; further evaluation may not be required. The frequency and severity of the seizures should be monitored, and, when necessary, treatment initiated with an AED. IE is not likely if cluster seizures or status epilepticus occur during a dog's first presentation for seizures or if seizures have a rapidly progressive course, prompting recommendations for a full systemic and intracranial evaluation. IE is relatively uncommon in cats, so even when all routine screening tests and systemic evaluation are normal, intracranial evaluation should be recommended.

When a metabolic or systemic cause for seizures cannot be identified with initial screening, further testing, including intracranial evaluation, should be recommended in all cats with seizures, in dogs with interictal neurologic

BOX 62.3

Intoxications Resulting in Acute Neurologic Dysfunction

Strychnine

Common use: rat, mole, gopher, and coyote poison
Clinical findings: stiff extension of legs and body, erect ears, tetanic spasms induced by auditory stimuli
Diagnosis: history of access or ingestion, characteristic signs, chemical analysis of stomach contents
Treatment: vomiting (if no neurologic signs), gastric lavage, diazepam as needed, pentobarbital to effect; establish diuresis

Metaldehyde

Common use: snail, slug, and rat poison
Clinical findings: anxiety, hyperesthesia, tachycardia, hypersalivation, muscle fasciculations, and tremors; not worsened by auditory stimuli; nystagmus in cats; may convulse; depression; respiratory failure
Diagnosis: history of access or ingestion, characteristic signs, acetaldehyde odor on breath, analysis of stomach contents
Treatment: gastrointestinal decontamination: induce vomiting if mild signs, administer activated charcoal with sorbitol as cathartic, diazepam bolus or CRI, methocarbamol (55-220 mg/kg slow IV, repeat in 12 h if needed). Propofol or pentobarbital if needed to effect; establish diuresis.

Tremorgenic Mycotoxins

Common use: moldy dairy products, nuts, grains, compost, garbage
Clinical findings: vomiting, tremors, ataxia, seizures
Diagnosis: history of access or ingestion, characteristic signs, analysis of stomach contents
Treatment: gastrointestinal decontamination: induce vomiting if mild signs, administer activated charcoal with sorbitol as cathartic, diazepam bolus or CRI, methocarbamol (55-220 mg/kg slow IV, repeat in 12 h if needed). Propofol or pentobarbital if needed.

Chlorinated Hydrocarbons

Common use: agricultural products and insecticides; lipid-soluble products usually absorbed through skin
Clinical findings: apprehension, hypersensitivity, hypersalivation, exaggerated response to stimuli, muscle twitching of face and neck progressing to severe fasciculations and tremors; tonic-clonic seizures may occur
Diagnosis: history of access, characteristic signs, insecticide smell to haircoat, analysis of stomach contents
Treatment: wash with warm soapy water to prevent further exposure; if ingested (rare), gastric lavage and instill activated charcoal; pentobarbital to effect

Organophosphates and Carbamates

Common use: insecticides
Clinical findings: excessive salivation, lacrimation, diarrhea, vomiting, and miosis; twitching of facial and tongue muscles, progressing to extreme depression and tonic-clonic seizures
Diagnosis: history of exposure, characteristic signs, analysis of stomach contents, low serum acetylcholinesterase activity
Treatment: prevent further exposure; wash if topical exposure; gastric lavage and activated charcoal if ingested; atropine (0.2 mg/kg IV initially and 0.2 mg/kg SC as needed q6-8h); pralidoxime (20 mg/kg IM q12h) if within 48 hours of exposure or if was dermal exposure

Lead

Common use: ubiquitous in environment in linoleum, rug padding, old lead-based paints (before 1950s), putty and caulking material, roofing materials, batteries, grease, used motor oil, golf balls, fishing sinkers, pellets, and lead shot
Clinical findings: gastrointestinal signs of anorexia, abdominal pain, vomiting and diarrhea, and megaesophagus; neurologic signs of hysteria, aggression, nervousness, barking, tremors, seizures, blindness, hypermetria and nystagmus (cats), and dementia
Diagnosis: history of exposure, characteristic signs, CBC changes (basophilic stippling of RBCs, increase in nucleated RBCs); blood lead level (heparinized tube: >0.5 ppm [50 mg/dL], diagnostic; >0.25 ppm, suggestive); radiographs may reveal radiopaque material in gastrointestinal system
Treatment: emetics, gastric lavage, activated charcoal, enemas; surgery or endoscopy if lead in stomach; diazepam or pentobarbital as needed to stop seizures; specific to chelate lead and hasten excretion: calcium ethylenediaminetetraacetic acid (Ca EDTA) (25 mg/kg, IV or SC, q6h as 1% solution in dextrose for 2-5 days) or succimer (10 mg/kg PO q8h for 5 days, then q12h for 14 days; Chemet, Sandofi Pharm, NY)

Ethylene Glycol

Common use: automobile antifreeze, color film processing solutions
Clinical findings: ataxia, severe depression, polyuria-polydipsia, vomiting; seizures are rare
Diagnosis: history of exposure, characteristic signs, severe metabolic acidosis, calcium oxalate crystalluria; eventually, decreased urine production and acute renal failure. Diagnosis and treatment of this disorder are discussed in detail in Chapter 44.

CBC, Complete blood count; *CRI,* constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *ppm,* parts per million; *RBC,* red blood cell; *SC,* subcutaneous.

BOX 62.4

Emergency Treatment of Intoxications

Prevent Further Absorption of Intoxicant

Remove intoxicant from skin and haircoat

If:
1. Toxin was cutaneously absorbed.

How:
1. Remove flea collar if that is source of toxin.
2. Wash animal in warm soapy water; rinse and repeat.
3. Flush with warm water for 10 minutes.

Induce emesis

If:
1. Ingestion of intoxicant occurred fewer than 3 hours before presentation.
2. Product ingested was not caustic, petroleum based, strong acid, or strong base.
3. Animal has a normal gag reflex and is not convulsing or very depressed (danger of aspiration).

How:
1. At home can recommend oral syrup of ipecac (6.6 mL/kg) or 3% hydrogen peroxide (1-2 mL/kg PO); 5 mL = 1 teaspoon.
2. Administer apomorphine subcutaneously (0.08 mg/kg) or in conjunctival sac (1 crushed tablet or 1 disk [6 mg]: rinse eye with saline solution after emesis).
3. Administer xylazine (cats: 0.44 mg/kg IM).

Vomiting is most successful if stomach is full: feed first, then induce vomiting.

Save vomitus for analysis.

Gastric lavage

If:
1. Ingestion of intoxicant occurred fewer than 3 hours before presentation.
2. Attempts to produce emesis were unsuccessful or emesis was not recommended.

How:
1. Induce anesthesia, place cuffed endotracheal tube, inflate cuff.
2. Place in right lateral recumbency, lower head relative to body.
3. Pass a large-bore stomach tube to level of stomach.
4. Use water (5-10 mL/kg body weight) for each washing; aspirate with syringe.
5. Repeat 10 times or until clear.

Save stomach contents for analysis.

Gastrointestinal adsorbents

How:
1. If gastric lavage has been performed, administer activated charcoal* slurry (1-3 g/kg) using a 20% slurry (1 g of activated charcoal/5 mL of water) or a commercially available 10% slurry into the empty stomach after the last lavage. Let this sit for 20 minutes, then administer a cathartic.
2. If gastric lavage was not necessary, administer slurry (dose as above) via stomach tube or orally or administer tablets of activated charcoal.

Cathartics

How:
1. Sodium or magnesium sulfate (250 mg/kg); can be administered 30 minutes after activated charcoal is administered.
2. Alternatively, the first dose of activated charcoal can contain sorbitol as a cathartic.

Diuresis

How:
1. Administer saline solution to effect diuresis.
2. Mannitol (20% solution, 1-2 g/kg IV) or furosemide (2-4 mg/kg IV) may be added to enhance diuresis if needed.

Administer Specific Antidotes

See Box 62.3.

Supportive and Symptomatic Care

*Repetitive dosing of activated charcoal can result in hypernatremia, so it should be used only with fluid support and patient monitoring.

abnormalities, in dogs older than 5 years of age when their first seizure is observed, and in dogs with multiple seizures that take place within a 1-month period. When neurologic or systemic signs are present that could be caused by infectious diseases endemic to the region, noninvasive and relatively inexpensive serologic testing may be beneficial. Thoracic and abdominal radiographs and abdominal ultrasound should be performed to look for systemic manifestations of infectious causes of seizures and for primary or metastatic neoplasia. If these tests are negative, advanced imaging of the brain with MRI is recommended; CSF collection and analysis may be warranted when inflammatory disorders are suspected based on finding multifocal neurologic deficits or lesions identified on MRI.

ANTIEPILEPTIC DRUG THERAPY

Chronic management of dogs and cats with seizures can be attempted using AEDs. Because this requires a large financial, emotional, and time commitment by owners, they should be involved in the decision to initiate treatment. Not every animal with seizures requires AED therapy, but there is some evidence that dogs treated early in the course of their seizure disorder may have better long-term control of their seizures compared with dogs that are allowed to have many seizures before treatment is initiated. Maintenance treatment with AEDs should be recommended in all dogs and cats with the following: (1) seizures caused by an identifiable structural intracranial lesion, (2) one or more episodes of cluster

seizures or status epilepticus, (3) seizures that occur more often than once every 12 weeks, (4) seizures that are becoming more frequent, (5) seizures with severe or unusual postictal signs, or (6) seizures that occur within 1 month of a traumatic brain injury (Box 62.5).

Complete control of seizures in dogs and cats with IE is rarely possible, but a decrease in the frequency and severity of seizures is a realistic goal that can be accomplished in 70% to 80% of animals. Owners should keep a log detailing the frequency and severity of seizures so the effects of the medication can be monitored. Adverse effects of the medication and plans for monitoring blood concentrations and dose adjustments should be discussed. Owners should be told to never alter the dose of medication without veterinary consultation and should understand that missing even a single dose could precipitate seizures. Emergency situations (e.g., status epilepticus) should be described to owners and specific recommendations for treatment and veterinary assistance provided.

A minimum database, including a CBC, serum biochemistry profile, and urinalysis, should always be obtained immediately before the start of AED therapy, and if one was not recently performed, a liver function test is also recommended. Whenever possible, animals should be initially treated with a single AED (monotherapy) to reduce possible drug interactions and adverse effects, optimize owner compliance, and decrease overall costs of drugs and monitoring.

Therapeutic drug monitoring is often used to determine the proper dose of an AED for a patient. A standard dose of the chosen oral AED is administered initially, and when steady-state serum concentrations have been achieved (based on 5 elimination half-lives) the trough (pre-pill) serum concentration of the AED should be measured. Once a stable dose has been identified that maintains the serum drug concentration within an optimal range, then a seizure log should be used to assess the effect of the AED on seizure frequency. An AED is considered effective if seizure frequency is reduced by at least 50%. If the initial drug administered is ineffective in spite of optimal serum drug concentrations, then another AED should be added or substituted (Box 62.6). See Table 62.1.

BOX 62.5

Indications for Initiating Chronic Anticonvulsant Therapy

1. Unresolvable intracranial disease causing seizures
2. Cluster seizures
3. At least one episode of status epilepticus
4. Interictal period less than 12 weeks
5. Increasing seizure frequency or severity
6. Unusual or severe postictal signs

ANTIEPILEPTIC DRUGS

PHENOBARBITAL

For decades, PB has been considered the drug of choice for initial and ongoing treatment of seizures in most dogs and cats. PB is a relatively safe, effective, and inexpensive AED. It has a high bioavailability and is rapidly absorbed, with peak plasma concentration 4 to 8 hours after oral administration in dogs and 1 to 2 hours in cats. PB is metabolized primarily by the liver. An appropriate starting dose is 2.5 to 3 mg/kg given orally twice a day, but autoinduction often

BOX 62.6

Guidelines for Chronic Oral Anticonvulsant Therapy in Dogs

1. Initiate treatment with PB (2.5-3 mg/kg PO q12h).
2. At least 10 days after initiating therapy, measure the trough (pre-pill) serum PB concentration. If the concentration is less than 25 µg/mL (107 µmol/L), increase the PB dose by 25% and reevaluate the serum concentration 2 weeks later. Repeat until the trough serum PB concentration is between 25 and 35 µg/mL (107-150 µmol/L), ideally near the middle of the range.
3. If seizures are adequately controlled, maintain dose and monitor serum PB concentration and liver enzymes/function once or twice a year.
4. If seizure control is inadequate despite adequate serum concentration of PB, add potassium bromide therapy (15 mg/kg PO q12h with food).
5. If necessary to control seizures, increase the dose of potassium bromide to 20 mg/kg PO q12h.
6. Measure the potassium bromide concentration in 3 to 4 months. It should be 1 to 2 mg/mL (10-20 mmol/L).

PB, Phenobarbital; *PO,* by mouth.

TABLE 62.1

AEDs for Treating Epilepsy in Dogs

DRUG	DOSAGE	THERAPEUTIC RANGE
Phenobarbital	2.5-3.0 mg/kg q12h	25-35 µg/mL
Potassium bromide		
Monotherapy	20 mg/kg q12h	2.5-3.0 mg/mL
with PB	15 mg/kg q12h	1.5-2.0 mg/mL
Levetiracetam	20 mg/kg q8h	variable
Zonisamide	5-10 mg/kg q12h	10-40 µg/mL
Monotherapy	5 mg/kg q12h	10-40 µg/mL
with PB	10 mg/kg q12h	10-40 ρg/mL
Gabapentin	10-20 mg/kg q8h	4-16 mg/L

necessitates subsequent increases in dose to maintain trough serum concentration in the therapeutic range. Cats may be more susceptible to the sedative effects of PB, so a lower dose (1-2 mg/kg twice daily) might be used to initiate therapy.

After 2 to 3 weeks of therapy, the fasted morning pre-pill (trough) blood PB concentration should be determined. This should be in the therapeutic range of 25 to 35 µg/mL (107-150 µmol/L) in dogs and 20 to 30 µg/mL (90-129 µmol/L) in cats. Many references allow a wider therapeutic range in dogs (15 to 35 µg/mL) but report that seizure control is improved at serum concentrations greater than 25 µg/mL. If the measured serum concentration is too low, the dose of PB should be increased by approximately 25% (see Box 62.6) and the trough serum concentration determined again 2 to 3 weeks later. If the serum concentration is still inadequate, the dose of PB should be increased in 25% increments every 2 to 3 weeks while the blood concentration is monitored. Once the measured blood concentration of PB is within the therapeutic range, the dog or cat should be observed by the owner for a long enough period of time (time required for two or three cycles of seizures), and, if control is acceptable, therapy is maintained at that dosage. Blood PB concentrations should be reevaluated routinely every 6 months, 2 weeks after any change in dosage, and whenever two or more seizures occur between scheduled PB evaluations. Serum separator tubes should not be used to collect serum for this purpose, because their use will underestimate the concentration of PB.

PB is well tolerated in most dogs and cats at therapeutic serum concentrations. Sedation and ataxia may be pronounced for the first 7 to 10 days of therapy or after an increase in dosage, but these adverse effects resolve with time (10-21 days) as the animal acquires a tolerance for the sedative effects of the drug. Transient (7 days) hyperexcitability occurs as an idiosyncratic effect in up to 40% of dogs and cats. The most common persistent adverse effects of PB include polyuria, polydipsia, and polyphagia. Owners should be advised to refrain from overfeeding dogs receiving PB, even though their pet may seem ravenous. Neutropenia or thrombocytopenia has been recognized in a few dogs within the first 6 months of starting PB, but in most cases these blood dyscrasias are immune-mediated and they resolve when the PB is discontinued. Acute idiosyncratic hepatotoxic reactions with rapid elevations of alanine aminotransferase (ALT) are rare, but should prompt immediate transition to an alternative AED. PB may also be a risk factor for the development of superficial necrolytic dermatitis in dogs.

The most life-threatening potential complication of chronic PB therapy is drug-induced hepatotoxicity. PB is a potent inducer of hepatic enzymes, and mild to moderate elevations in serum alkaline phosphatase (ALP) and alanine transaminase (ALT) activities are seen in virtually all dogs receiving PB; significant hepatotoxicity is uncommon. Significant chronic hepatotoxicity is most likely to occur when peak serum PB concentrations are at the high end of the therapeutic range (>35 µg/mL; >150 µmol/L). Clinical features of significant hepatotoxicity include anorexia, sedation, ascites, and occasionally icterus. Laboratory testing typically reveals a large increase in ALT compared with ALP, decreased serum albumin, abnormal bile acids, and an increasing PB concentration despite no increase in the administered dose. All animals receiving chronic PB therapy should be evaluated every 6 months to assess the effectiveness of their drug regimen, serum concentration of PB, liver enzyme activities, and serum albumin concentration. Liver function testing should be performed if ALT levels suddenly increase or if serum albumin levels start to decrease. When chronic hepatotoxicity is suspected, PB should be discontinued, the patient should be rapidly switched to an alternative AED, and supportive measures should be initiated for liver failure. The hepatotoxicity is occasionally reversible if discovered early.

PB increases the biotransformation of drugs metabolized by the liver, decreasing the systemic effects of many drugs administered concurrently. PB also increases the rate of thyroid hormone elimination, decreasing measured serum total and free T_4 and increasing serum thyroid-stimulating hormone concentrations, but this is rarely associated with clinical signs of hypothyroidism (see Chapter 48). PB administration does not alter endogenous ACTH concentrations, the response to exogenous ACTH, or results of low-dose dexamethasone suppression testing. Drugs that inhibit microsomal enzymes (e.g., chloramphenicol, tetracycline, cimetidine, ranitidine, enilconazole) may dramatically inhibit the hepatic metabolism of PB, resulting in increased serum concentrations of PB and potentially causing toxicity.

Seizures are controlled in 70% to 85% of dogs and most cats treated with PB monotherapy if serum PB concentrations are maintained within the target range. If seizures continue to occur at an unacceptable frequency or severity despite adequate serum concentrations, therapy with additional drugs must be considered.

POTASSIUM BROMIDE

The addition of potassium bromide (KBr) to already established PB therapy in dogs with poorly controlled seizures despite adequate serum concentrations of PB effectively decreases seizure numbers by 50% or more in 70% to 80% of dogs (see Box 62.6). KBr is also effective as a single agent and is considered by many to be the initial AED of choice in dogs with hepatic dysfunction and in large-breed dogs and working dogs that have unacceptable side effects from PB. The drug should not be administered to cats because it can cause severe progressive bronchitis in that species that can be fatal.

Bromide is excreted unchanged by the kidney. It is not metabolized by the liver and does not cause hepatotoxicity. KBr is typically administered as an inorganic salt dissolved in double distilled water to achieve a concentration of 200 to 250 mg/mL. Administration of the salt in gelatin capsules is also possible, but the concentrated drug in this form is more likely to cause gastric irritation and vomiting.

Dietary chloride should remain constant in dogs treated with KBr, because chloride competes with bromide for renal reabsorption. High chloride intake (e.g., chips, rawhide bones) increases renal excretion of KBr, decreasing serum concentrations and potentially leading to seizures. Alternatively, switching a dog to a lower-sodium diet can cause dramatically increased bromide concentrations and signs of toxicity.

An appropriate starting dose of KBr is 20 mg/kg orally twice daily for monotherapy and 15 mg/kg orally twice daily when used as an add-on drug to PB. KBr serum concentrations are usually measured 1 month after initiating therapy, when concentrations are expected to be approximately 50% of the level at steady-state and then 8 to 12 weeks later when a steady-state is achieved. The goal is to achieve a serum concentration of 2.5 to 3 mg/mL (25-30 mmol/L) of KBr when used as monotherapy and 1.5 to 2 mg/mL (15-20 mmol/L) when used together with PB. Serum PB concentrations should continue to be maintained in the midtherapeutic range in animals receiving KBr and PB.

When maintenance doses of KBr are administered, there is a long lag period between initiation of treatment and achieving steady-state serum concentrations. If KBr must be administered as the only anticonvulsant therapy in a dog with a severe or progressive seizure disorder or in a dog that must be switched from PB to KBr because of toxicity, it is possible to achieve therapeutic serum concentrations of KBr more rapidly using a loading-dose protocol. Oral loading can be accomplished by administering 50 mg/kg of KBr orally four times a day (every 6 hours) for 2 to 3 days with food, followed by administration of maintenance doses.

Adverse effects of KBr include polyuria, polydipsia, and polyphagia, but in many dogs these are less dramatic than the changes induced by PB therapy. Transient sedation, incoordination, anorexia, and constipation are most pronounced in the weeks after initiating treatment or after a dosage increase, particularly in dogs receiving concurrent PB. Reversible limb stiffness, lameness, and muscle weakness rarely occur unless serum bromide levels are excessive. Vomiting due to gastric irritation from the hyperosmolality of the drug is a very common complaint; this can be diminished by further splitting the daily dose (into four equal doses administered approximately every 6 hours) or by feeding a small amount of food with each dose. Pancreatitis occurs rarely. Bromide toxicity (bromism) can develop when serum concentrations are at or near the upper end of the recommended range. Signs include stupor or coma, blindness, ataxia, tetraparesis with normal or decreased spinal reflexes, dysphagia, and megaesophagus. If bromism occurs, it is managed by temporarily stopping the KBr and initiating diuresis with intravenous (IV) saline and furosemide, but if blood levels drop too low, seizures will occur. Serum biochemical abnormalities are not common in dogs treated with KBr monotherapy, but because some laboratory assays cannot distinguish bromide from chloride, there may be an artifactual increase in measured chloride.

ZONISAMIDE

Zonisamide (Zonegran [Elan]) is a sulfonamide-based AED that suppresses epileptic foci and blocks propagation of epileptic discharges. This drug is well absorbed, is hepatically metabolized, and has a relatively long half-life (15 hours) in dogs not concurrently receiving PB or other drugs that induce microsomal enzymes. Steady-state levels are achieved in 3 to 4 days. Zonisamide is effective as a sole agent, and as an add-on drug that improves seizure control in 70% to 90% of dogs with seizures poorly controlled by other drugs. Mild adverse effects reported include sedation, ataxia, vomiting, inappetence, and decreased tear production. Rarely, hepatotoxicity and renal tubular acidosis have been reported. Patients with a history of sulfa drug hypersensitivity should not be prescribed zonisamide. The initial starting dose is 5 mg/kg twice daily in dogs not receiving PB and 10 mg/kg twice daily in dogs receiving concurrent PB. A serum concentration of 10 to 40 μg/mL is reported to be therapeutic. Zonisamide can also be administered to cats; an appropriate starting dose is 5 to 10 mg/kg once daily or 5 mg/kg twice daily.

LEVETIRACETAM

Levetiracetam (Keppra) is an effective anticonvulsant that is very well tolerated, with minimal side effects. The drug is well absorbed and rapidly metabolized, with an elimination half-life of 3 to 4 hours in dogs not taking PB and 1.7 hours in dogs taking PB, but seizure control is more prolonged than the half-life would suggest. Most of the drug is excreted unchanged in the urine, and the remainder is metabolized by hydrolysis in multiple organs, with no significant hepatic metabolism. Levetiracetam decreases seizure frequency by over 50% in many epileptic dogs and cats when used as an add-on drug. Levetiracetam has also been used effectively as monotherapy in some dogs and cats. A starting dose of 20 mg/kg q8h is recommended in dogs and cats, although much higher doses can be administered to dogs without toxicity and may be required to achieve seizure control, especially when used in conjunction with PB. Therapeutic monitoring is not usually recommended with levetiracetam because the drug has a wide margin of safety and there is little correlation between serum concentrations and seizure control. Adverse effects include minimal sedation, salivation, vomiting, and decreased appetite in a few dogs and cats. Administering an injectable formulation of levetiracetam (30-60 mg/kg) as a slow IV bolus over 5 minutes has been used with some success in the treatment of cluster seizures and status epilepticus in dogs.

GABAPENTIN

Gabapentin (Neurontin [Parke-Davis]) is a structural analog of γ-aminobutyric acid (GABA) that readily crosses the blood-brain barrier but does not bind to GABA receptors as its mechanism of action, instead inhibiting flow through neuronal voltage-gated calcium channels. This drug is most commonly used to treat neuropathic pain in dogs and cats but has some utility as an AED. Gabepentin is rapidly

absorbed and renally excreted, with some hepatic metabolism. The elimination half-life in dogs is very short (3-4 hours), requiring dosing every 6 to 8 hours. Gabapentin improves seizure control in more than 50% of dogs when added to PB or KBr. Starting doses of 10 to 20 mg/kg q8h have been recommended in dogs, but the dose can be increased gradually as needed (up to 80 mg/kg q8h) as long as excessive sedation does not occur, which is the only reported adverse effect. Serum concentrations are rarely monitored, but the suspected therapeutic range for dogs is 4 to 16 mg/L. An oral dose of 5 to 10 mg/kg every 8 to 12 hours has been recommended and used with limited success in cats.

FELBAMATE

Felbamate (Felbatol [Wallace]) can be an effective AED in dogs when used alone or as an add-on drug in dogs refractory to AED therapy with PB and KBr. After urinary excretion of 70% of the orally administered dose, felbamate is metabolized by hepatic microsomal P450 enzymes. The recommended starting dose is 15 mg/kg q8h. Felbamate appears to have a wide margin of safety, and the daily dose can be increased in 15-mg/kg increments until the seizures are adequately controlled, with reports of dosages as high as 70 mg/kg q8h without significant toxicity. Trough serum concentrations between 25 and 100 mg/L may be therapeutic, but the target range is not well established in dogs. Felbamate is an unusual AED in that it does not cause sedation. Potential side effects include nervousness and keratoconjunctivitis sicca. Mild reversible thrombocytopenia and leukopenia have also been reported. The potential for aplastic anemia and fatal hepatopathy has limited the use of felbamate in human patients, but anemia has not been reported in dogs. Approximately 30% of dogs treated with felbamate as an add-on drug with PB do develop hepatotoxicity, however, so monitoring of CBCs, biochemistry panels, and liver function tests is recommended every 3 months during treatment.

PREGABALIN

Pregabalin (Lyrica [Pfizer]) is a structural analog of GABA. The mean elimination half-life in dogs is approximately 7 hours. This AED is renally excreted and has few drug interactions. Efficacy as an add-on AED has been promising in dogs. The initial recommended dose is 4 mg/kg orally every 8 to 12 hours. Adverse effects are limited to sedation and ataxia.

DIAZEPAM

Diazepam (Valium [Roche]) is of limited use as a chronic oral AED in dogs because of its expense, its very short half-life, physical dependence, and the rapid development of tolerance to its anticonvulsant effects. Oral diazepam (0.5-2.0 mg/kg q8-12h) has been shown to be of some benefit for the long-term management of seizures in cats because it has a long elimination half-life in that species and a functional tolerance to its anticonvulsant effect does not seem to be a problem in cats. Diazepam is eliminated by hepatic metabolism, and the only common adverse effect is sedation, although idiosyncratic severe, life-threatening hepatotoxicity has been documented in a few cats receiving daily oral diazepam for 5 to 11 days. This potentially fatal reaction warrants close owner observation of appetite and attitude and periodic monitoring of liver enzymes in all cats treated with oral diazepam. PB is a better choice for chronic AED therapy in cats.

Diazepam also has a place in the emergency management of seizures and in the at-home treatment of dogs with IE experiencing cluster seizures. In dogs with a recognizable preictal phase or an aura preceding the seizure, an injectable preparation of diazepam (5 mg/mL) can be administered rectally (2 mg/kg) by the owner at the onset of these premonitory signs. Alternatively, this dose can be administered just after each observed seizure, with a maximum of three doses in 24 hours (each dose separated by at least 10 minutes). At-home rectal administration of diazepam decreases the occurrence of cluster seizures and the development of status epilepticus as well as dramatically decreasing the need for owners to seek expensive emergency treatment for their epileptic dogs. Diazepam dispensed for at-home rectal administration should be stored in a glass vial because plastic will adsorb the drug, decreasing its effectiveness. For administration, the drug can be drawn into a syringe and injected through a 1-inch plastic teat cannula or rubber catheter directly into the rectum.

ALTERNATIVE THERAPIES

Approximately 20% to 25% of dogs treated for epilepsy using standard AED therapy are never well controlled, despite attempts at therapeutic drug monitoring and appropriate dose adjustments. It is important to evaluate poorly controlled animals for underlying metabolic or intracranial disease that could be specifically treated. Alternative treatments should also be considered in these animals, including hypoallergenic diets, acupuncture, surgical division of the corpus callosum, and vagus nerve stimulation.

EMERGENCY THERAPY FOR DOGS AND CATS IN STATUS EPILEPTICUS

Status epilepticus is a series of seizures or continuous seizure activity lasting for 5 minutes or longer without periods of intervening consciousness. Status epilepticus increases arterial blood pressure, body temperature, heart rate, cerebral blood flow, and cerebral oxygen consumption. It also decreases blood pH (because of lactic acidosis) and may decrease effective ventilation. As seizures continue, metabolic deterioration, increased intracranial pressure, acidosis, hyperthermia, and cardiac dysrhythmias are common, leading to progressive cerebral ischemia and neuronal death. Permanent neurologic damage can result, and mortality rates

of up to 25% are reported in dogs with IE during an episode of status epilepticus.

Status epilepticus is always a medical emergency. The most common reasons for a known idiopathic epileptic patient to present in status epilepticus include poor chronic seizure control of cluster seizures and abrupt withdrawal of AED medications (missed doses). Nonepileptics may present in status epilepticus as a result of various metabolic, toxic, and intracranial disorders. History and physical examination findings help determine the cause of status epilepticus in an individual patient. Diagnostic testing for metabolic causes of seizures (especially hypoglycemia, hypocalcemia, electrolyte disturbances) should always be performed and specific treatment initiated when warranted. When intoxication is suspected, treatment should be directed at reducing further absorption of the toxin, increasing toxin excretion, and controlling the neurologic manifestation of seizures (see Box 62.4).

The goals of treatment are to stabilize the animal, stop the seizure activity, protect the brain from further damage, and allow recovery from the systemic effects of prolonged seizure activity. Oxygen is administered, as well as fluid therapy and supportive care, to minimize systemic effects. Diazepam is administered (intravenously or rectally) to stop the seizures. If this is effective but seizures recur then diazepam can be administered as a continuous rate infusion (CRI). An intravenous bolus of levetiracetam can also be effective. A longer-acting drug, usually PB, should be administered to prevent seizure recurrence. Distribution of PB to the central nervous system may take up to 30 minutes, so if the seizures were not stopped by diazepam or levetiracetam administration more aggressive treatment will usually be required. This involves a propofol or pentobarbital infusion to stop seizure activity. Mannitol or hypertonic saline is also recommended (as for head trauma, see Box 62.2) to decrease the brain edema secondary to prolonged seizure activity. Details regarding the treatment of status epilepticus are outlined in Box 62.7.

BOX 62.7

Status Epilepticus Treatment in Dogs and Cats

1. If possible, insert an IV catheter.
2. Administer diazepam 2 mg/kg rectally if no IV access. If IV access is possible, administer 1 mg/kg intravenously. Repeat every 2 minutes if ineffective or if seizures recur. Administer maximum of four doses if necessary. If patient responds to diazepam administration but seizures recur, *consider a diazepam CRI* (1 mg/kg/h) in 0.9% saline or in D_5W. Continue the CRI for at least 6 hours; if no seizures occur, can then taper by 25%/h.
3. Administer a loading dose of PB to prevent further seizures (6 mg/kg slow IV or IM twice, 10 minutes apart). This will take 20 to 30 minutes for maximum effect. Repeat 6-mg/kg dose IM q6h until oral dosing can be performed.
4. If seizures have not responded to diazepam or to the initial dose of PB, it will be necessary to stop the seizures using either:
   Sodium pentobarbital (3-15 mg/kg slow IV to effect), giving 25% of the dose at a time as a bolus until seizures stop and dog is anesthetized.
   Repeat as needed (q4-8h) to maintain anesthesia or place on CRI: (2-5 mg/kg/h to effect) in saline. *Continue CRI for at least 6-12 h before tapering.*
   or
   Propofol (4-6 mg/kg slow IV over 2 minutes), giving 25% of the calculated dose every 30 seconds until seizures stop and dog is anesthetized.
   Maintain on CRI (0.10-0.25 mg/kg/min; 6-15 mg/kg/h).
   Maintain anesthesia for 6-12 h, then taper CRI by 25% every 2-4 h to recover.
5. Maintain a patent airway and monitor respirations. Intubate and ventilate if necessary.
6. Initiate IV fluids (maintenance rate).
7. Assess body temperature. If >41.4° C (>105° F), cool with cool water enemas.
8. If hyperthermic or if seizure activity was prolonged (>15 minutes), administer:
   Mannitol: 1 g/kg IV over 15 minutes
   and/or
   Hypertonic saline solution (4 mL/kg of 7.2% HSS over 5 minutes)

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous; *PB,* phenobarbital.

PAROXYSMAL EVENTS THAT ARE NOT SEIZURES

PAROXYSMAL DYSKINESIAS

PDs are a heterogenous group of inherited disorders that result in involuntary movements or postures in fully conscious individuals. These movement disorders have only occasionally been described in dogs and cats, and they may be very difficult to distinguish from focal seizures or stereotypical behavior disorders. Signs consist primarily of episodic, unpredictable, rhythmic, involuntary contractions of a group of skeletal muscles causing limb hyperextension or hyperflexion; head bobbing; or the adoption of abnormal postures. Episodes occur spontaneously or may be initiated by a trigger such as a sudden movement, sustained exercise, excitement, stress, or fatigue. Episodes start and end abruptly, and last several minutes to a few hours. PDs are familial and are all thought to be caused by genetic mutations that disrupt brain metabolism, blood-brain barrier glucose transport, or neurotransmitter production or release. Causative mutations have been identified in many human PD disorders and in a few canine disorders. Most PD disorders in dogs appear to be inherited as an autosomal recessive trait.

It can be challenging to differentiate PDs from focal seizures. Affected dogs maintain consciousness and normal mentation during episodes and have no associated neurologic abnormalities. Interictal and intraictal EEGs (when

performed) do not exhibit epileptic activity. There are generally no premonitory or postictal abnormalities, no autonomic signs associated with the episode, and no apparent response to AED medications. Episodes typically recur throughout the dog's lifetime, and there is no progression to a generalized seizure disorder or other neurologic signs. Movement disorders that may be dyskinesias have been reported in Norwich Terriers, Cavalier King Charles Spaniels, Malteses, Soft-Coated Wheaten Terriers, Chinooks, Border Terriers, Scottish Terriers, Labrador Retrievers, and Jack Russell Terriers.

Head bobbing. Canine idiopathic head tremor (IHT) is a poorly understood breed-specific tremor condition. Intermittent paroxysmal vertical (up and down nodding) or lateral (side-to-side head shaking) rhythmic head movements have been described in Boxers, English Bulldogs, and Doberman Pinschers. Typical age of onset is approximately 2 years. Episodes are most likely to occur when the dogs are at rest and last from a few seconds to several hours. Mentation is normal, and many affected dogs can be distracted out of an episode. Episodes may decrease in frequency or disappear as dogs mature. This head-bobbing disorder is thought to be a dyskinesia, but this is controversial because isolated head tremor has not been described as a PD in people.

Scotty cramp is a disorder in which affected Scottish Terriers develop paroxysmal dramatic gait abnormalities and collapse in association with stress, excitement, or exercise. The first episode of collapse occurs from 6 weeks to 18 months of age (most at 6 months). During exercise the forelimbs abduct and become stiff, followed by arching of the spine and pelvic limb stiffness resulting in falling or somersaults. Signs are evident for less than 10 minutes and then resolve. A similar disorder has been seen in Cairn Terriers, West Highland White Terriers, and Norwich Terriers. A few dogs have a milder phenotype, with the cramping limited to the pelvic limbs causing skipping and bunny hopping but no falling. No lesions are identified on imaging or postmortem examination. Episodes can be induced by administering drugs that are serotonin antagonists and prevented by administering serotonin agonists, suggesting that signs may be related to a relative CNS deficiency of the inhibitory neurotransmitter 5-hydroxytryptamine (serotonin) but brain serotonin concentrations are normal. The condition may improve with time and appropriate lifestyle changes. Many affected dogs respond favorably to fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI).

Episodic falling in Cavalier King Charles Spaniels is a PD disorder in which affected dogs between 3 and 7 months of age (occasionally 2-3 years) develop a peculiar gait and collapse during exercise. Dogs are normal when not exercising, but exercise induces progressive hypertonicity in the thoracic and pelvic limbs resulting in a bounding gait with stiff legs, bunny hopping, arching of the spine, a lowered head, and collapse with no loss of consciousness. Triggers include exercise, excitement, and stress. This was the first genetically mapped PD in dogs, and a genetic test is available. The autosomal recessive genetic mutation disrupts axonal, a CNS neurotransmission. Treatment with the benzodiazepine clonazepam (0.5 mg/kg q8h) can result in remission of signs, but tolerance to the drug commonly develops. Some dogs respond to acetazolamide.

Canine epileptoid cramping syndrome in Border Terriers is now more correctly called paroxysmal gluten-sensitive dyskinesia (PGSD). Signs become evident when dogs are 3 months to 6 years, with a median age of onset of 3 years. Exercise and movement are not recognized as triggers, but stress may be a trigger in some dogs. Episodes last minutes to hours and often occur in clusters of four to five episodes separated by several months. During episodes, there are abnormal contractions of limb muscles and muscles in the neck and back causing dogs to fall over. Many owners of affected dogs report that they can predict episodes as affected dogs exhibit staring or attention-getting behavior. Also mild to severe gastrointestinal signs such as vomiting, diarrhea, or borborygmi are common before, during, or after an episode. Reported response to AED therapy is variable. A recent study showed marked clinical improvement when an exclusively gluten-free diet is fed.

Soft-Coated Wheaton Paroxysmal Dyskinesia. A PD described in Soft-Coated Wheaton Terriers affects male and female dogs with a median age of onset of 2 years. Neurologic examination between episodes is unremarkable. Stress, exercise, and loud noises may serve as triggers for episodes that last several minutes to 4 hours. Typical episodes consist of pronounced flexion or extension of hind legs with varying degrees of truncal dystonia. Signs can alternate between the two rear limbs, or both hind limbs can be lifted off the ground simultaneously. Postmortem examination and MRI are normal. Recently the causative genetic mutation has been identified. Signs tend to worsen with age, and many affected dogs are euthanized.

EXERCISE-INDUCED COLLAPSE DISORDERS

Disorders that cause paroxysmal episodes of weakness or collapse with strenuous exercise are often confused with partial seizures. Dynamin-associated exercise-induced collapse (dEIC) causes reversible rear leg weakness and collapse after strenuous exercise in affected Labrador Retrievers and a few other breeds. Border Collie collapse (BCC) causes altered mentation and an abnormal gait in affected dogs after strenuous exercise. Other systemic and neuromuscular disorders causing exercise intolerance or weakness are discussed in Chapter 67.

Dynamin-associated exercise-induced collapse (dEIC) is an autosomal recessive CNS disorder common in Labrador Retrievers and occasionally identified in Chesapeake Bay Retrievers, Curly-Coated Retrievers, and Boykin Spaniels. The causative mutation has also been rarely identified in Pembroke Welsh Corgis, Bouvier des Flanders, German Wirehaired Pointers, Old English Sheepdogs, and Cocker Spaniels. Dogs are susceptible to collapse when they are homozygous for the causative mutation in dynamin-1, a protein required for repackaging of brain and spinal cord

neurotransmitters during exercise, excitement, and the hyperthermia associated with exercise. This disorder is the most common reason for exercise-induced weakness or collapse in Labrador Retrievers that seem otherwise normal and healthy.

Affected dogs are normal at rest and with moderate exercise, but prolonged (>10 minutes) strenuous exercise with excitement induces weakness and then collapse. Some affected dogs collapse whenever they are exercised strenuously; other dogs only exhibit collapse sporadically. Most affected (homozygous) Labradors will have their first episode of collapse when they are 7 months to 2 years old.

Typically during dEIC-related collapse, the rear limbs become weak and unable to support weight and dogs will continue to run while dragging their back legs (Fig. 62.3). Dogs develop a wide-based, long, loose stride rather than the short, stiff strides typically associated with muscle weakness. In some dogs the rear limb collapse progresses to forelimb weakness and occasionally to a total inability to move. Signs often become more pronounced in the first few minutes after exercise is terminated. Muscles of the rear limbs are relatively flaccid during collapse, and there is loss of the patellar reflex during collapse and for a short time during recovery. A few dogs appear to have a loss of balance and may fall over, particularly as they recover from collapse. Dogs are not painful or stiff during the collapse or upon recovery. Affected dogs may be extremely hyperthermic during collapse (> 41.5° C [106.7° F]) but not different from unaffected dogs performing the same exercise. A few dogs have died during or immediately after an episode of exercise-induced collapse, presumably due to hyperthermia or failure to ventilate adequately, so an affected dog's exercise should always be stopped immediately and cooling attempted at the first hint of incoordination or weakness.



FIG 62.3
A young Labrador Retriever with dynamin-associated exercise-induced collapse (dEIC) walks with a crouched rear limb gait after 10 minutes of retrieving exercise.

This disorder is very common in Labrador Retrievers, with initial genetic screening (2010) revealing that more than 30% of dogs in this breed had at least one copy of the causative mutation and that approximately 5% of all Labrador Retrievers were homozygous and susceptible to collapse. Labrador Retrievers with episodes of collapse that occur with exercise should, however, always have a full evaluation to rule out other causes of collapse that could be confused with dEIC (see Chapter 67). Dogs with dEIC have unremarkable physical and neurologic examinations during exercise, and no associated laboratory abnormalities. Episodes of collapse caused by dEIC always occur during prolonged strenuous exercise, are most likely to occur in hot weather, start with primarily pelvic limb signs, and are associated with normal mentation. Diagnosis is made by observing typical episodes of collapse, eliminating other causes of exercise intolerance, and demonstrating that the dog is homozygous for the DNM1 mutation.

Border Collie collapse (BCC) is an episodic neurologic disorder in Border Collies and related breeds. It is most common in dogs used for working stock but has also been seen in dogs training for agility or flyball competitions and in dogs repetitively retrieving a ball. Affected dogs are normal at rest, but they may become abnormal after 5 to 15 minutes of strenuous activity, particularly in warm weather. Affected dogs abruptly lose focus on the task being performed and are dull, dazed, or confused during episodes. They may wander aimlessly or walk compulsively. They are ataxic in all limbs and have increased extensor tone and scuffing and knuckling of the pelvic limbs or all limbs. They may develop truncal sway and stagger or fall to the side. A few dogs exhibit squinting eyelids and rapid blinking during each episode. Dogs are abnormal for 5 to 30 minutes, but then recover completely with no residual lameness or muscle stiffness or discomfort. Body temperatures are very high during an episode (often > 41.7° C [>107° F]), but not higher than unaffected dogs performing the same exercise. Cardiac, metabolic, and neurologic evaluations are normal, and muscle biopsies are normal. Chronic oral treatment with PB has not been effective at preventing episodes, and EEGs in a few affected dogs between and during episodes have not revealed epileptiform activity. Genetic studies are under way. Australian Kelpies, Australian Shepherds, Shetland Sheepdogs, Bearded Collies, and Whippets may be affected by a similar or identical disorder. Affected dogs can still live fairly normal lives, but they may have to have their participation in trigger activities limited, especially in warm weather. If they do have an episode, then attempts should be made to cool their body temperature to speed recovery.

SLEEP DISORDERS

Narcolepsy is a disorder characterized by abnormalities in the sleep/wake cycle related to an imbalance in central nervous system neurotransmitters important in maintaining normal sleep patterns. This disorder is inherited in Doberman Pinschers, Labrador Retrievers, Miniature Poodles, and Dachshunds, and occurs sporadically in other breeds.

Genetic testing is available for Labradors and Dobermans, where the disorder is inherited as an autosomal trait. The predominant sign in dogs and cats is cataplexy, characterized by an abrupt paroxysmal loss of muscle tone without loss of consciousness frequently induced by excitement such as eating or playing. Episodes occur abruptly and last from a few seconds to 30 minutes or more. Animals with narcolepsy may also exhibit excessive sleepiness during the day, prolonged deep sleep, and "sleep attacks" where they abruptly transition from an active and alert state to REM sleep with closed eyelids, loss of consciousness, and twitching. Treatment is generally focused on reducing cataplexic attacks using tricyclic antidepressants such as imipramine (0.4-1.0 mg/kg orally q8-12h) or serotonin reuptake inhibitors like Fluoxetine (1 mg/kg orally q24h). Stimulants can also be administered to decrease daytime drowsiness.

Suggested Readings

Bagley RS, Platt S. Tremors, involuntary movements and paroxysmal disorders. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Barnes HL, et al. Clinical signs, underlying cause and outcome in cats with seizures: 17 cases (1997-2002). *J Am Vet Med Assoc*. 2004;225:1723.

Bhatti SF, et al. International Veterinary Epilepsy Task Force consensus proposal:medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015;11:176.

Pakozdy A, et al. Treatment and long term follow-up of cats with suspected primary epilepsy. *J Feline Med Surg*. 2012;15:267.

Pakozdy A, et al. Retrospective clinical comparison of idiopathic versus symptomatic epilepsy in 240 dogs with seizures. *Acta Vet Hung*. 2008;56:471.

Patterson EE. Status epilepticus and cluster seizures. *Vet Clin North Am Small Anim Pract*. 2014;44:1103.

Podell M, et al. 2015 ACVIM small animal consensus statement on seizure management in dogs. *J Vet Intern Med*. 2016;30:477.

Podell M. Seizures. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Rossmeisl JH, Inzana KD. Clinical signs, risk factors and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy. *J Am Vet Med Assoc*. 2009;234:1425.

Taylor SM. Exercise-induced weakness/collapse in Labrador Retrievers. In: Tilley LP, Smith FW, eds. *Blackwell's five minute veterinary consult: canine and feline*. ed 6. Ames, Iowa: Blackwell; 2016.

Thomas WB. Idiopathic epilepsy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2010;40:161.

Wahle AM, et al. Clinical characterization of Epilepsy of unknown cause in cats. *J Vet Intern Med*. 2014;28:182.

CHAPTER 63

Head Tilt



GENERAL CONSIDERATIONS

Head tilt is a common neurologic abnormality in dogs and cats. It indicates a lesion of the vestibular system, which consists of central and peripheral parts.

The peripheral vestibular system includes sensory receptors for vestibular input located in the membranous labyrinth of the inner ear within the petrous temporal bone of the skull and the vestibular portion of the vestibulocochlear nerve (CN8), which carries information from these receptors to the vestibular nuclei in the brainstem and cerebellum. The central vestibular structures include vestibular nuclei and pathways located within the brainstem (medulla oblongata), caudal cerebellar peduncles, and flocculonodular lobe of the cerebellum (Fig. 63.1). Abnormalities involving the central or peripheral vestibular system typically cause head tilt, loss of balance, tight circling, falling, rolling, ataxia, and spontaneous nystagmus.

NYSTAGMUS

Nystagmus is defined as an involuntary rhythmic oscillation of the eyeballs. In the jerk nystagmus typical of vestibular disease, eye movements have a slow phase in one direction and a rapid recovery phase in the opposite direction. *Jerk nystagmus direction* is described as the direction of the fast phase, despite the fact that the slow phase is typically directed toward the abnormal side. Abnormal jerk nystagmus results from disturbed vestibular input to the neurons innervating the extraocular eye muscles. Nystagmus characterized by small oscillatory movements of the eyeballs with no slow or fast phase is termed *pendular nystagmus* and is commonly observed as an incidental finding in Siamese, Birman, and Himalayan cats secondary to a congenital visual pathway abnormality.

In a normal animal, rotation of the head will result in a jerk nystagmus with the slow phase in the direction opposite the head rotation, followed by a fast phase in the direction of head rotation. This *physiologic nystagmus,* elicited during assessment of the *oculocephalic reflex,* only occurs while the head is moving. Nystagmus that occurs when the head is held motionless is called *spontaneous nystagmus* or *resting nystagmus,* and this is always abnormal. Some animals with compensated vestibular disease (either central or peripheral) do not have detectable spontaneous nystagmus but develop *positional nystagmus* when their head is held in an unusual position or they are rolled over on their back (see Fig. 58.26), making this manipulation an important part of the neurologic examination. Spontaneous or positional nystagmus in a patient with peripheral vestibular disease is always either horizontal or rotary, and although the intensity of nystagmus may change when the head is held in different positions, the direction of the fast phase will not. The nystagmus in animals with central vestibular diseases can be horizontal, rotary, or vertical, and may change direction as the position of the head is changed.

LOCALIZATION OF LESIONS

Head tilt indicates vestibular dysfunction. The first step in evaluating a patient with a head tilt should always be an attempt to localize disease to either the central or peripheral components of the vestibular system (Box 63.1). The clinician can usually accomplish this goal with a careful physical and neurologic examination.

Severe problems of balance resulting in ataxia, incoordination, falling, and rolling are prominent in animals with either central or peripheral vestibular disease. The head tilt (ear pointed toward the ground) is typically on the same side as the lesion as it reflects loss of anti-gravity muscle tone on that side. Tight circling toward the affected side is common. Ipsilateral ventral or ventrolateral strabismus may be seen when the nose is elevated (Fig. 63.2). Spontaneous or positional jerk nystagmus typically has its fast phase (compensatory phase) toward the side opposite the lesion and slow phase (pathologic phase) toward the side with diminished function (see Video 58.2). Vomiting, salivation, and other signs of motion sickness are often apparent. None of these features helps distinguish central from peripheral vestibular disease.

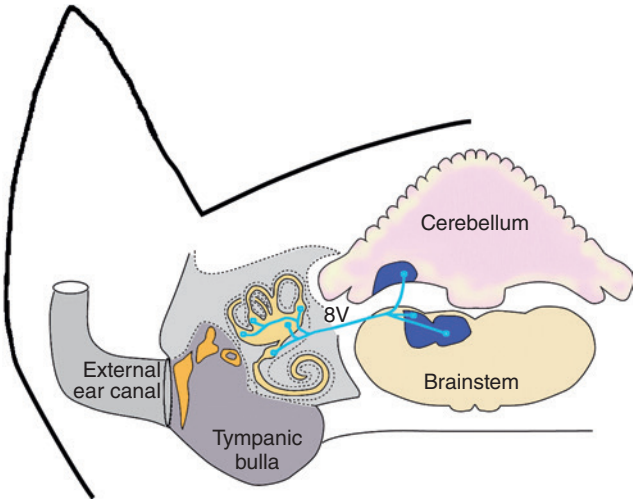


FIG 63.1
Anatomy of the central and peripheral vestibular system. Sensory receptors for vestibular input are located in the membranous labyrinth of the inner ear. Input from these receptors enters the brain via the vestibular portion of CN8 (8V), and fibers terminate in central vestibular nuclei in the brainstem and cerebellum.

PERIPHERAL VESTIBULAR DISEASE

Animals with peripheral vestibular disease should have normal mentation and consciousness. They have normal strength and postural reactions, although these tests may be difficult to assess because affected animals have impaired balance and a tendency to fall and roll. Spontaneous and positional nystagmus is horizontal or rotary or alternates between the two in animals with peripheral vestibular disease and will not change fast-phase direction when the animal is held in multiple positions or examined repeatedly during the day. Damage to inner ear receptors or the axons of CN8 occasionally results in concurrent deafness.

Peripheral vestibular lesions often involve the middle and inner ear. Middle ear lesions localized within the tympanic bulla typically produce head tilt and pathologic horizontal or rotary nystagmus. Disorders that affect both the middle and inner ear usually have more pronounced signs of vestibular ataxia, falling, circling, rolling, and positional strabismus. Damage to the axons of the facial nerve (CN7) within the inner ear and the sympathetic innervation to the eye within the middle or inner ear can result in facial nerve paralysis and Horner syndrome in animals with peripheral vestibular dysfunction (Fig. 63.3).

Animals with bilateral peripheral vestibular disease do not usually have a head tilt or pathologic nystagmus. They typically exhibit a wide-based crouched stance, loss of balance when turning or leaning to either side, and wide swinging excursions of the head from side to side. Sometimes the ability to elicit normal physiologic nystagmus (oculocephalic reflex) during head movement is lost. When the animal is held suspended by the pelvis and lowered toward the ground, an affected animal may curl its head and neck toward the sternum instead of raising its head and extending the thoracic limbs toward the floor for weight bearing. The diagnostic approach for bilateral peripheral vestibular disease is the same as that used in dogs and cats with unilateral peripheral vestibular disease.

BOX 63.1

Vestibular Disease Clinical Findings

Central and Peripheral Vestibular Disease

Incoordination, loss of balance, disoriented
Head tilt toward lesion
Circling/falling/rolling toward the side of the lesion
±Ventral strabismus on side of lesion
Vomiting, salivation
Spontaneous or positional nystagmus (fast-phase, away from lesion)

Peripheral Vestibular Disease

Nystagmus, when present, is horizontal or rotary
No change in nystagmus direction
Postural reactions and proprioception normal
With middle/inner ear disease, may see concurrent CN7 deficit and/or Horner syndrome
No other cranial nerve deficits

Central Vestibular Disease

Occasionally indistinguishable from peripheral disease
Findings that confirm disease as central:
- Vertical nystagmus
- Nystagmus that changes direction with head position
- Abnormal postural reactions on side of lesion
- Multiple cranial nerve deficits
- May be depressed, stuporous, comatose

Paradoxical Vestibular Syndrome (Cerebellar Lesion)

Head tilt and circling away from side of lesion
Fast-phase nystagmus toward the lesion
Horizontal, rotary, or vertical nystagmus
Abnormal postural reactions on side of lesion
±Multiple cranial nerve deficits on side of lesion
±Hypermetria, truncal sway, and head tremor

CENTRAL VESTIBULAR DISEASE

Certain clinical findings only occur with central vestibular dysfunction, but a central lesion cannot be excluded (especially early in the course of disease) simply because these localizing signs are not evident. With time and progression, however, most animals with central vestibular disease manifest signs indicating brainstem involvement. Vertical nystagmus and upper motor neuron (UMN) limb deficits are the most consistent signs that vestibular disease is central. Although spontaneous nystagmus can be in any direction, a vertical nystagmus or a nystagmus that changes fast-phase direction with different head positions strongly suggests central vestibular disease (brainstem or cerebellum).





FIG 63.2
Mild head tilt (**A**) and positional ventrolateral strabismus (**B**) in a young Border Collie with hypermetria, loss of balance, and intermittent positional vertical nystagmus. Necropsy revealed cerebellar and brainstem compression secondary to progressive hydrocephalus and hydromyelia.

UMN paresis and postural reaction deficits (abnormal knuckling, hopping) commonly develop on the side of a brainstem lesion because the UMN pathways to the limbs are damaged; affected animals may lose the ability to walk. If the animal is recumbent, extensor tone is decreased in the limbs on the side of the lesion and increased in limbs on the opposite side, creating a tendency to roll toward the side of the lesion. The presence of multiple cranial nerve abnormalities other than facial nerve paralysis and Horner syndrome in an animal with vestibular signs usually indicates central (i.e., brainstem) disease. Neoplasms or granulomas located at the cerebellomedullary angle commonly result in simultaneous



FIG 63.3
Adult cat with peripheral vestibular disease and Horner syndrome on the left side caused by otitis media-interna.

dysfunction of the vestibular (CN8), facial (CN7), and trigeminal (CN5) nerves, so the trigeminal nerve (i.e., facial and nasal sensation) should always be assessed carefully in animals with vestibular signs.

PARADOXICAL (CENTRAL) VESTIBULAR SYNDROME

A head tilt to one direction with hypermetria or postural reaction deficits affecting the limbs on the opposite side (contralateral limbs) is called *paradoxical vestibular syndrome* and usually indicates a lesion involving the caudal cerebellar peduncle or the flocculonodular lobe of the cerebellum on the side of the body opposite the head tilt. Postural reaction deficits in the limbs, when present, always indicate ipsilateral central disease, and are therefore the most reliable clinical feature allowing lesion localization (right vs. left). Other signs of cerebellar dysfunction (e.g., ipsilateral hypermetria, truncal sway, head tremor) are often seen. Paradoxical vestibular syndrome suggests central vestibular dysfunction originating in the cerebellum, so diagnostic evaluation is the same as that for other intracranial disorders (see Chapter 60).

DISORDERS CAUSING PERIPHERAL VESTIBULAR DISEASE

Peripheral vestibular disease is much more common in dogs and cats than central disease and generally carries a better prognosis. The most common disorders causing peripheral vestibular signs are infection, polyps, or neoplasia affecting the middle and inner ear and transient idiopathic vestibular syndromes. Peripheral vestibular disease can also occur as a congenital problem, as a result of trauma, and rarely as a result of aminoglycoside-induced receptor degeneration (Box 63.2). Peripheral vestibular signs with or without facial nerve paralysis have also been seen in hypothyroid-associated polyneuropathy in dogs.

BOX 63.2

Disorders Causing Head Tilt

Peripheral Vestibular Disease

Otitis media-interna
Neoplasia in middle ear
Feline nasopharyngeal polyps in middle ear
Geriatric canine vestibular disease
Feline idiopathic vestibular syndrome
Trauma
Congenital vestibular syndromes
Aminoglycoside ototoxicity
Chemical ototoxicity
Hypothyroid neuropathy

Central Vestibular Disease

Trauma or hemorrhage
Infectious disorders
Granulomatous meningoencephalitis (dogs)
Necrotizing leukoencephalitis (dogs)
Primary or metastatic neoplasia
Vascular infarct
Thiamine deficiency
Neurodegenerative disorders
Metronidazole intoxication

Diagnostic evaluation of patients with peripheral vestibular signs should include external palpation of the bullae for asymmetry or pain. If ototoxic drugs or treatments have been administered, these should be discontinued and improvement monitored over 24 to 48 hours. Systemic evaluation for inflammatory, neoplastic, or metabolic disease (including hypothyroidism in dogs) should be considered. Radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) of the tympanic bullae (middle ear) should be evaluated. CT and MRI are much more sensitive for detection of subtle abnormalities than radiography. When warranted based on the results of otoscopic examination or imaging, a myringotomy can be used to collect a sample from the middle ear for cytologic analysis and culture.

OTITIS MEDIA-INTERNA

Otitis media-interna (OM-OI) is one of the most common causes of peripheral vestibular signs in dogs and cats. Concurrent facial nerve paralysis or Horner syndrome affecting the same side is sometimes apparent (Figs. 63.3 and 63.4). All dogs and cats with peripheral vestibular disease should be evaluated for ear disease. Most animals develop OM-OI as an extension of obvious otitis externa, and many have a tympanic membrane that appears abnormal or ruptured. Otoscopic diagnosis of OM-OI can, however, be difficult when chronic otitis externa results in stenosis or hyperplasia of the external ear canal, making visualization of the tympanic membrane and sampling of the middle ear cavity impossible. Rarely, animals with OM-OI will have a normal



FIG 63.4
(A) Adult Cocker Spaniel with left peripheral vestibular disease caused by otitis media-interna. **(B)** Radiograph reveals thickening of the left bulla wall, with an increase in density within the bulla. Osteotomy of the ventral bulla revealed bilateral otitis media-interna.

otoscopic examination and an intact tympanum at the time of diagnosis, necessitating further testing.

Bulla radiographs, CT, or MRI may reveal fluid or soft tissue accumulations with the bullae as well as secondary reactive or remodeling changes. When performing a radiographic bulla series, rostrocaudal open-mouth radiograph and oblique views taken under general anesthesia are most often diagnostic (see Figs. 66.7 and 63.4). CT and MRI are more sensitive than radiography for evaluating the bullae in patients with OM-OI. Typical MRI findings include hyperintense material within the tympanic bulla on T2-weighted images, isointense material within the tympanic bulla on T1-weighted images, and gadolinium ring enhancement along the inner margin of the tympanic bulla. Animals with inner ear disease may also have loss of the normally visible intralabyrinthine fluid signal and contrast enhancement in the petrous portion of the temporal bone. While the animal

is sedated or anesthetized for imaging, a culture should be obtained from the external ear canal, and the ear canal and the tympanic membrane should be carefully examined using an otoscope or a small endoscope. If imaging suggests fluid is present within the middle ear, a sample of that fluid should be collected for cytologic analysis and culture. If the tympanic membrane is ruptured, the sample can be obtained directly under visualization. If the tympanic membrane appears to be intact, a myringotomy can be performed after the external ear canal is cleansed by flushing with warm 0.9% saline until the flush fluid obtained is clear and any excess fluid suctioned away. Using a 22-gauge, 3.5-inch spinal needle attached to a 6-mL syringe, the clinician punctures the ventral tympanic membrane just caudal to the malleus at the 6 o'clock position and gently aspirates fluid from the middle ear into the syringe. If fluid is not obtained, 0.5 to 1 mL of sterile saline can be instilled, then aspiration can be repeated. After the diagnostic sample is obtained, the middle ear should be flushed repeatedly with sterile saline to remove exudate from the bulla.

Medical treatment of dogs and cats with bacterial OM-OI consists of a 6- to 8-week course of systemic antibiotics, with the choice of antibiotic based on culture and sensitivity results. Pending culture results, antibiotic treatment can be initiated using a broad-spectrum antibiotic such as a first-generation cephalosporin (e.g., oral [PO] cephalexin, 22 mg/kg q8h), a combination of amoxicillin and clavulanic acid (Clavamox, 12.5-25 mg/kg PO q8h), or enrofloxacin (5 mg/kg PO q12h). Identification and treatment of factors predisposing to otitis externa and topical or systemic antiinflammatory therapy are also important. If conservative treatment does not resolve the infection or if there is radiographic evidence of chronic bone changes in the bulla, ventral bulla osteotomy or total ear canal ablation procedures should be performed, followed by a course of antibiotic therapy. Early recognition of OM-OI and prompt initiation of appropriate therapy result in a good prognosis for recovery. When facial nerve paralysis is present, it may be permanent despite treatment. Failure to aggressively treat OM-OI can result in ascent of the infection up the nerves into the brainstem, resulting in neurologic deterioration, central vestibular signs, and sometimes death.

GERIATRIC CANINE VESTIBULAR DISEASE

Geriatric canine vestibular disease (i.e., old dog vestibular disease), an idiopathic syndrome, is the most common cause of acute unilateral peripheral vestibular dysfunction in older dogs, with a mean age of onset of 12.5 years. The disorder is characterized by the very sudden onset of head tilt, loss of balance, and ataxia with a horizontal or rotatory nystagmus (Fig. 63.5; see Video 58.2). Clinical signs are often very severe, with inability to stand, rolling and falling toward the lesion, and vomiting. Proprioception and postural reactions are normal, although they may be difficult to assess. Facial paresis and Horner syndrome are not present, and no other neurologic abnormalities are observed.

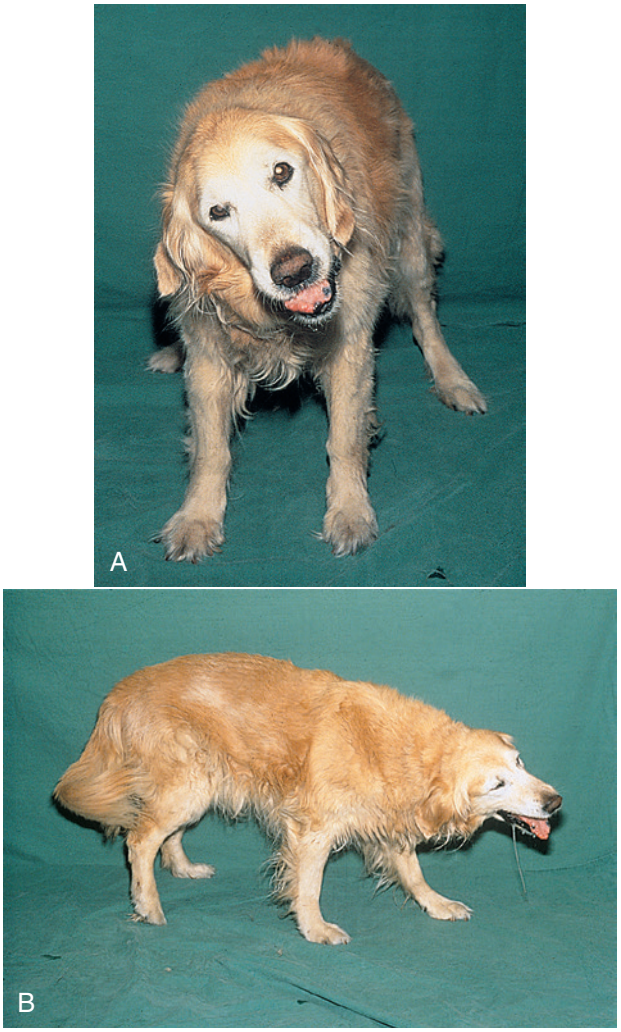


FIG 63.5
Twelve-year-old Golden Retriever with **(A)** head and **(B)** body tilt caused by geriatric canine vestibular disease.

Any older dog with a peracute onset of unilateral peripheral vestibular disease but no other neurologic abnormalities should be suspected to have geriatric canine vestibular disease. A careful physical examination, neurologic examination, and otoscopic examination should be performed. Further extensive diagnostic testing is often delayed for a few days while the dog is supported and monitored for improvement.

Diagnosis of geriatric canine vestibular disease is based on signalment, neurologic findings, exclusion of other causes of peripheral vestibular dysfunction, and alleviation of clinical signs with time. The spontaneous nystagmus usually resolves within a few days and is replaced by a transient positional nystagmus in the same direction. The ataxia gradually abates by 1 to 2 weeks, as does the head tilt. Occasionally the head tilt is permanent.

The prognosis for recovery is excellent; no therapy is recommended. When vomiting is severe, H_1 histaminergic receptor antagonists (subcutaneous [SC] diphenhydramine, 2-4 mg/kg q8h), M_1 cholinergic receptor antagonists

(chlorpromazine, 1-2 mg/kg PO q8h), or vestibulosedative drugs (meclizine, 1-2 mg/kg PO q24h) can be administered for 2 to 3 days to alleviate the emesis associated with motion sickness. Recurrent attacks are unusual but may occur on the same or opposite side. A similar acute nonprogressive course of peripheral vestibular signs has been reported occasionally in nongeriatric dogs and should be evaluated as a mononeuropathy (see Chapter 66).

FELINE IDIOPATHIC VESTIBULAR SYNDROME

Feline idiopathic vestibular syndrome is an acute nonprogressive disorder similar to the idiopathic geriatric vestibular syndrome that occurs in dogs, but it affects cats of any age. The disease may be more prevalent in the summer and early fall and in certain geographic locations, particularly the northeastern and mid-Atlantic United States, suggesting a possible role for an infectious or parasitic cause. This syndrome is characterized by peracute onset of peripheral vestibular signs (e.g., severe loss of balance, disorientation, falling and rolling, head tilt, spontaneous nystagmus), with no abnormalities of proprioception or in other cranial nerves. The diagnosis is based on clinical signs and the absence of ear problems or other disease. If radiographs, CT, or MRI of the tympanic bullae are obtained, the findings are normal, as are the results of cerebrospinal fluid (CSF) analysis. Spontaneous improvement is usually seen within 2 to 3 days, with a complete return to normal within 2 to 3 weeks.

NEOPLASIA

Tumors involving the inner and middle ear may damage peripheral vestibular structures and result in peripheral vestibular dysfunction. Tumors can arise from regional soft tissues, the osseous bulla, or the external ear canal. The most common primary aural tumors causing vestibular dysfunction are squamous cell carcinoma, ceruminous gland adenoma/adenocarcinoma, sebaceous adenoma/adenocarcinoma, and lymphoma. Less commonly, tumors of CN8 (e.g., neurofibroma, neurofibrosarcoma) or tumors of the osseous bulla (osteosarcoma, fibrosarcoma, chondrosarcoma) result in peripheral vestibular dysfunction.

Aural neoplasia may be evident on otoscopic examination, with aspiration or biopsy providing the diagnosis. When otoscopic examination is unremarkable but middle and inner ear disease is suspected, imaging is recommended. Soft-tissue density within the bullae and associated bone lysis suggests tumor. Advanced imaging with CT or MRI is necessary to provide additional detail regarding the extent of tumor if cytoreductive surgery or radiation therapy are to be considered. Diagnosis can be confirmed by biopsy. The invasive nature of tumors in the middle and inner ear makes total resection difficult. Radiotherapy or chemotherapy may be beneficial in some animals (see Chapters 75 and 76).

NASOPHARYNGEAL POLYPS

Nasopharyngeal inflammatory polyps originate at the base of the Eustachian tube in kittens and young adult cats and grow passively into the nasopharynx, nose, or middle ear. Most affected cats exhibit stertorous breathing or nasal discharge as a result of respiratory obstruction by these polyps, but cats with polyps in the middle and inner ear can be presented with peripheral vestibular signs and sometimes Horner syndrome and facial nerve paralysis. Otoscopic examination is often normal, although bulging of the tympanic membrane or extension of a polyp into the external ear canal is possible. A diagnosis of multiple nasopharyngeal polyps should be suspected when a young cat is presented with concurrent peripheral vestibular dysfunction and nasopharyngeal obstruction. Skull radiographs or CT reveal soft tissue within the bullae and thickening of the bone but no bone lysis. Traction polypectomy of pharyngeal or external ear canal polyps is usually successful, but polyps in the tympanic cavity must usually be removed surgically via ventral bulla osteotomy/ear canal ablation. The prognosis is excellent for cure if all abnormal tissue is removed, particularly when followed by a 2- to 4-week course of prednisolone (see Chapter 15).

TRAUMA

Trauma to the petrous temporal bone damaging the middle and inner ear will result in peripheral vestibular signs, often accompanied by Horner syndrome and facial nerve paralysis. Facial abrasions, bruises, and fractures may be evident on initial examination. Hemorrhage in the external ear canal may be evident on an otoscopic examination. Radiographs or advanced imaging will reveal the extent of the problem. Supportive treatment for head trauma and possible posttraumatic infection should be initiated. Vestibular signs usually resolve with time, whereas facial paralysis and Horner syndrome may persist.

CONGENITAL VESTIBULAR SYNDROMES

Purebred dogs and cats that show peripheral vestibular signs before 3 months of age are likely to have a congenital vestibular disorder. Congenital unilateral peripheral vestibular syndromes have been recognized in the German Shepherd dog, Doberman Pinscher, Akita, English Cocker Spaniel, Beagle, Smooth Fox Terrier, and Tibetan Terrier, as well as in Siamese, Burmese, and Tonkinese cats. Clinical signs may be present at birth or develop during the first few months of life. Head tilt, circling, and ataxia may initially be severe, but, with time, compensation is common, and many affected animals make acceptable pets. The diagnosis is based on the early onset of signs and exclusion of other disorders. If ancillary tests such as radiography and CSF analysis are performed, findings are normal. Deafness may accompany the vestibular signs, particularly in the Doberman Pinscher, Akita, and Siamese cat.

AMINOGLYCOSIDE OTOTOXICITY

Rarely aminoglycoside antibiotics cause degeneration within the vestibular and auditory systems of dogs and cats. This ototoxicity is usually associated with systemic administration of high doses or prolonged use (>14 days) of these antibiotics, particularly in animals with impaired renal function.

Degeneration within the vestibular system may result in unilateral or bilateral peripheral vestibular signs and loss of hearing. In most cases, the vestibular signs resolve if therapy is discontinued immediately, but deafness may persist.

CHEMICAL OTOTOXICITY

Many drugs and chemicals are potentially toxic to the inner ear. If the integrity of the tympanic membrane is in doubt, topical otic products containing chlorhexidine, dioctyl-sulfo succinate (DOSS), or aminoglycosides should not be used. Warm saline or 2.5% acetic acid solutions should be used for flushing ears. Whenever vestibular dysfunction becomes evident immediately after instilling a substance in an ear canal, the product should be removed and the ear canal flushed with copious quantities of saline. Vestibular signs will usually resolve within a few days or weeks, but deafness, if it occurs, may persist.

HYPOTHYROIDISM

Peripheral vestibular dysfunction has occasionally been reported in association with hypothyroidism in adult dogs. Concurrent facial nerve paralysis may be seen, and a few dogs exhibit weakness, suggesting a more generalized polyneuropathy. Other systemic signs of hypothyroidism, such as weight gain, poor haircoat, and lethargy, may or may not be present. Clinicopathologic testing may show abnormalities suggestive of hypothyroidism (e.g., mild anemia, hypercholesterolemia). The diagnosis is established through thyroid function testing (see Chapter 48). The response to replacement thyroid hormone is variable, but improvement typically occurs within 2 months if hypothyroidism was the cause.

DISORDERS CAUSING CENTRAL VESTIBULAR DISEASE

Central vestibular disease is much less common in dogs and cats than peripheral vestibular disease and generally carries a poor prognosis. Central vestibular disease can be caused by any inflammatory, neoplastic, vascular, or traumatic disorders affecting the brainstem or vestibular portion of the cerebellum (see Box 63.2).

A standard workup for intracranial disease is performed in animals that have central vestibular signs. Complete physical, neurologic, and ophthalmologic examinations are essential to look for evidence of disease elsewhere in the body. Clinicopathologic testing, thoracic and abdominal radiographs, and abdominal ultrasound are warranted to search for neoplastic or infectious inflammatory systemic disease. When systemic evaluation does not provide a diagnosis, brain MRI should be performed. MRI abnormalities are identified in almost every patient with evidence of central vestibular dysfunction. When inflammatory disease is suspected, CSF collection and analysis should also be considered. (See Chapter 60 for a more thorough discussion of the diagnostic approach taken in animals with intracranial disease.)

INFLAMMATORY DISEASES

Most of the infectious and noninfectious inflammatory diseases discussed in Chapter 64 can cause central vestibular signs. In particular, granulomatous meningoencephalitis, canine distemper, necrotizing leukoencephalitis, Rocky Mountain spotted fever, and feline infectious peritonitis (cats) seem to have a predilection for this region of the brain. Adult-onset neosporosis and steroid-responsive tremor syndrome also commonly affect the cerebellum, resulting in central vestibular signs. See Chapter 64 for a discussion of the diagnosis and treatment of intracranial inflammatory disorders.

THIAMINE DEFICIENCY

Thiamine deficiency can occur due to prolonged anorexia, maldigestion/malabsorption disorders, inadequate dietary intake, or ingestion of thiaminase in raw fish. Cats are much more susceptible than dogs, developing a rapidly progressive encephalopathy with neurologic signs suggesting diffuse vestibular dysfunction including vestibular ataxia, circling, and wide excursions of the head and neck. Other signs can include blindness, mydriasis, ventroflexion of the head and neck, seizures, coma, and even death. Magnetic resonance (MR) imaging can be normal or can reveal bilaterally symmetrical hyperintense foci on T2-weighted and FLAIR (fluid attenuation recovery) in grey matter regions of the brainstem, cerebrum, and cerebellum. Supplementation with parenteral and oral thiamine and changing the diet to include adequate thiamine will usually result in a rapid recovery and resolution of all neurologic signs, including seizures. Thiamine (12.5-30 mg/cat IM or SC q24h) is often administered to cats with undiagnosed neurologic signs suggesting an intracranial lesion, particularly those with vestibular signs or seizures (see Chapter 60).

INTRACRANIAL NEOPLASIA

Intracranial tumors such as meningiomas and choroid plexus tumors have a tendency to develop in the cerebellopontomedullary (caudal fossa) region, making central vestibular signs common. Central vestibular signs may result from any intracranial tumor that causes compression or invasion of vestibular nuclei, increased intracranial pressure, early brain herniation, or obstructive hydrocephalus. Presumptive diagnosis is usually made with MRI, but definitive histologic diagnosis requires biopsy. Prognosis is dependent on tumor histologic type, neuroanatomic location, and severity of the neurologic signs. Cytoreductive surgery and radiotherapy may be treatment options. Palliative treatment with glucocorticoids (prednisone, 0.5-1 mg/kg/day PO) may temporarily improve clinical signs.

CEREBROVASCULAR DISEASE

Ischemic infarcts have been increasingly recognized as a cause of acute-onset, nonprogressive central vestibular signs, often affecting the vestibulocerebellum and resulting in paradoxical vestibular signs. In dogs, thrombotic occlusion of the rostral cerebellar artery is especially common, resulting in

peracute to acute onset of nonprogressive neurologic deficits including vestibular ataxia, loss of balance, and hypermetria. Approximately 50% of affected dogs have a head tilt or spontaneous nystagmus. Proprioceptive deficits are relatively uncommon (<25%), occurring either as a result of brainstem compression by the edematous cerebellum or secondary to infarction of collateral arterial branches supplying the pons and medulla. Infarcts or hemorrhage primarily involving the brainstem would be expected to cause more significant UMN paresis, postural reaction deficits, altered mentation, cranial nerve deficits, and potentially death.

Whenever infarcts are suspected based on the neurologic findings and acute non-progressive course, the animal should be evaluated for underlying hypertension, hypothyroidism, hyperadrenocorticism, and cardiac or renal disease as well as for systemic inflammatory or neoplastic disease (see Chapter 60). Cerebellar infarction associated with atherosclerotic vascular disease has been recognized in dogs, especially in Labrador Retrievers with occult hypothyroidism, so evaluation of thyroid function is always warranted when a dog is suspected to have had a cerebrovascular infarct. Spaniels and Spaniel-crosses may be predisposed to cerebellar infarctions without evidence of an underlying cause. Chiari-like malformations, which are common in Cavalier King Charles Spaniels, may cause flow disturbances in the cerebellar vasculature, predisposing to rostral cerebellar infarction. Chapter 60 discusses diagnostic evaluation (including MRI) and treatment of cerebrovascular infarcts.

ACUTE VESTIBULAR ATTACKS

Peracute onset of loss of balance, nystagmus, and severe ataxia that lasts only 1 to 30 minutes is occasionally seen in dogs. Head tilt may be mild or absent, and consciousness is maintained. Neurologic examination during an episode does not reveal postural reaction deficits or cranial nerve abnormalities; a few dogs have had vertical nystagmus, suggesting central vestibular or cerebellar disease. Dogs completely recover within minutes to a few hours, with no residual neurologic abnormalities and no obvious postictal signs. Some affected dogs have gone on to develop brain (especially cerebellar) infarcts weeks or months later, which suggests that these events could be transient ischemic attacks (TIAs). Hypertension has been associated with recurrent vestibular paroxysms in dogs, presumably by predisposing to TIAs. Dogs with a history of these acute vestibular attacks should have a careful physical and neurologic examination performed, as well as systemic screening tests for inflammatory or neoplastic disease, disorders of coagulation, and hypertension. An otoscopic examination should also be performed to rule out early OM-OI causing episodic peripheral vestibular dysfunction. Advanced diagnostic imaging (MRI) to evaluate the middle ear and brain may be warranted in dogs with recurrent TIA-like episodes, but imaging in dogs with small transient vascular lesions is often unrewarding (see Chapter 60). Clinically it can be difficult to differentiate acute vestibular attacks (presumed TIAs) from focal seizures. When postictal signs are noted or there is progression over time to recognizable generalized epileptic seizures, vestibular paroxysms are thought to be a manifestation of a seizure disorder (see Chapter 62).

NEURODEGENERATIVE DISORDERS

Numerous lysosomal storage diseases, neuroaxonal dystrophy, neonatal ataxia in Coton de Tulear dogs, and several other inherited neurodegenerative disorders in dogs and cats cause progressive cerebellovestibular signs including ataxia and incoordination. Diagnosis of these disorders is suspected when a young animal of a susceptible breed develops a progressive symmetrical neurologic disorder with characteristic features as described in that breed. (See Chapter 60 for a discussion of the diagnostic approach to these patients.)

METRONIDAZOLE TOXICITY

Central vestibular or vestibulocerebellar signs have been reported in dogs after administration of metronidazole (Flagyl [Pharmacia and Searle]). Signs of metronidazole toxicity are most likely to develop when the drug is administered orally at high doses (usually >60 mg/kg/day) for 3 to 14 days, but individual animal susceptibilities to the toxic effects are variable. Initial signs include anorexia and vomiting, with rapid progression to ataxia and vertical nystagmus. The ataxia may be very severe, making walking impossible and resulting in a characteristic "bucking" gait. Seizures and head tilt occasionally occur. Treatment consists of stopping the medication and providing supportive care. The prognosis is good for recovery, but complete recovery may take 2 weeks. Diazepam (0.5 mg/kg once intravenously and then orally q8h for 3 days) has been shown to dramatically speed recovery. Metronidazole toxicity has also been reported in cats, but forebrain signs including seizures and altered mentation usually predominate in this species.

Suggested Readings

deLahunta A, Glass E, Kent M. Vestibular system: special proprioception. In: *Veterinary neuroanatomy and clinical neurology*. St Louis: WB Saunders; 2015.

Munana KR. Head tilt and nystagmus. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Palmiero BS, et al. Evaluation of outcome of otitis media after lavage of the tympanic bulla and long-term antimicrobial drug treatment in dogs: 44 cases (1998-2002). *J Am Vet Med Assoc*. 2004;225:548.

Rossmeisl JH. Vestibular disease in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2010;40:81.

Sturges BK, et al. Clinical signs, magnetic resonance imaging features, and outcome after surgical and medical treatment of otogenic intracranial infection in 11 cats and 4 dogs. *J Vet Intern Med*. 2006;20:648.

Thomsen, et al. Neurological signs in 23 dogs with suspected rostral cerebellar ischemic stroke. *Acta Vet Scand*. 2016;58:40.

Troxel MT, Drobatz KJ, Vite CH. Signs of neurologic dysfunction in dogs with central versus peripheral vestibular disease. *J Am Vet Med Assoc*. 2005;227:570.

CHAPTER 64

Encephalitis, Myelitis, and Meningitis



GENERAL CONSIDERATIONS

Bacterial, viral, protozoal, mycotic, rickettsial, and parasitic pathogens are all recognized as etiologic agents of infectious inflammatory central nervous system (CNS) disease in dogs and cats. More common than the known infectious meningitis and encephalitis disorders in dogs are a group of CNS disorders that have no known identifiable cause but are presumed to have an immunologic basis. Some of these disorders, such as steroid-responsive meningitis arteritis (SRMA) and eosinophilic meningoencephalitis, have very characteristic clinical and laboratory features and are recognizable as specific disorders. Some of the other noninfectious inflammatory disorders are collectively known as *meningoencephalitis of unknown etiology* (MUE), with distinctions between the individual disorders less defined and often presumptive unless brain biopsies or postmortem examinations are available.

The clinical signs of CNS inflammation vary and depend on both anatomic location and severity of inflammation. Cervical pain and rigidity are common in dogs with meningitis of any etiology, causing a reluctance to walk, an arched spine, and resistance to passive manipulation of the head and neck (Fig. 64.1). Fever may occur with any disorder causing severe meningitis. Inflammation of the spinal cord (myelitis) will cause associated upper motor neuron (UMN) or lower motor neuron (LMN) deficits in the limbs, depending on the spinal cord region involved. Animals with inflammation in the brain (encephalitis) can experience vestibular dysfunction, seizures, hypermetria, or disorders of consciousness reflecting the distribution of intracranial lesions.

Diagnosis of inflammatory CNS disease involves a process of confirming the presence of inflammation, performing appropriate tests to look for infectious causes, and looking for characteristic lesions via diagnostic imaging. A thorough physical and ophthalmologic examination and searching for systemic abnormalities using laboratory tests and imaging should always be performed. Dogs and cats with bacterial meningitis/meningoencephalitis usually have an infected site from which the infection has spread to the CNS. Animals with viral, protozoal, fungal, or rickettsial meningitis/meningoencephalitis may have involvement of other organs (e.g., lung, liver, muscle, eye), which may aid in diagnosis. Cerebrospinal fluid (CSF) analysis is necessary to confirm a suspected diagnosis of CNS inflammatory disease. Analysis of the cells found in the CSF, together with the clinical and neurologic findings, may aid in determining the etiology of the inflammation in an individual case (see Box 59.3). Analysis of CSF protein, CSF culture, immunohistochemistry on CSF cytology, measurement of serum and CSF antibody titers for likely infectious agents, and CSF polymerase chain reaction (PCR) analysis may also be of diagnostic value. These results, together with other ancillary diagnostic tests, may allow diagnosis of a specific disorder and the initiation of prompt appropriate treatment (Table 64.1).

NECK PAIN

Neck pain is a sign commonly associated with compressive or inflammatory diseases of the cervical spinal cord. Animals with neck pain typically have a guarded horizontal neck carriage and are unwilling to turn their neck to look to the side; they will instead pivot the entire body. As part of every routine neurologic examination, the presence or absence of cervical hyperesthesia should be assessed by deep palpation of the vertebrae and cervical spinal epaxial muscles and by resistance to flexion, hyperextension, and lateral flexion of the neck (see Fig. 58.21). The spinal cord itself does not have pain receptors, so cervical pain is related to inflammation or compression of or traction on surrounding tissues or structures. Anatomic structures that can cause neck pain include the meninges, nerve roots, joints, bones, and muscles. Neck pain has also been recognized as a clinical symptom of increased intracranial pressure, particularly as a result of forebrain mass lesions (Box 64.1; see also Box 58.8).

The diagnostic approach to the patient with neck pain is fairly standardized. First, confirm and localize the site of painfulness using physical and neurologic examination, and then look for the cause of pain. Clinicopathologic testing

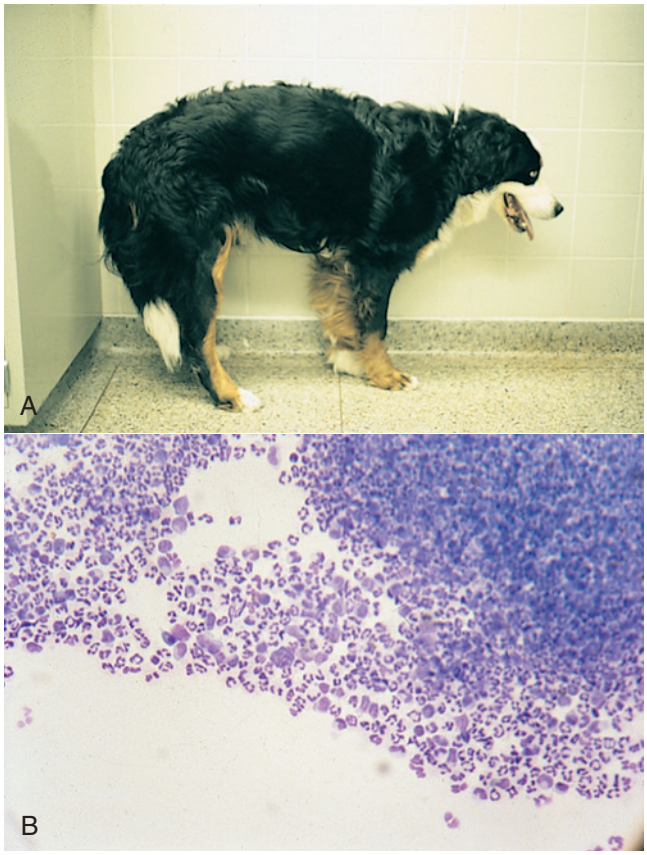


FIG 64.1
(A) Pain causes this young Bernese Mountain dog with steroid-responsive meningitis arteritis to stand with an arched spine and be reluctant to walk. **(B)** Cerebrospinal fluid from this dog is inflammatory, with a dramatic neutrophilic pleocytosis. (From Meric S et al: Necrotizing vasculitis of the spinal pachyleptomeningeal arteries in three Bernese Mountain Dog littermates, *J Am Anim Hosp Assoc* 22:463, 1986.)

BOX 64.1

Causes of Neck Pain in the Dog

MUSCLE: Myositis (immune, infectious), muscle injury
BONE: Fracture/luxation, diskospondylitis, vertebral osteomyelitis, neoplasia
JOINT (facetal joints): Polyarthritis (immune, infectious), degenerative joint disease (osteoarthritis)
NERVE ROOT: Neoplasia, compression (by disk, tumor, fibrous tissue, perineural cysts)
MENINGES: Neoplasia, inflammation (immune, infectious), compression/traction (synovial cysts, disk prolapse, atlanto-axial instability, cervical spondylomyelopathy, syringomyelia)
BRAIN: Mass lesion (neoplasia, inflammatory)

TABLE 64.1

Ancillary Tests in Diagnosis of Infectious Inflammatory Central Nervous System Disease

DISORDER SUSPECTED	ANCILLARY DIAGNOSTICS
Acute distemper (D)	Conjunctival scrapings Ophthalmic exam Thoracic radiographs Skin biopsy immunohistochemistry RT-PCR on blood, CSF CSF antibody titer
Bacterial (D, C)	Ear/throat/eye exam Thoracic radiographs Cardiac and abdominal ultrasound Spinal radiographs or CT Skull CT or MRI Blood/urine cultures CSF culture
Toxoplasmosis (D, C)	Ophthalmic exam ALT, AST, CK activities CSF, serum titers PCR on CSF, aqueous humor, blood, tissues
Neosporosis (D)	AST, CK activities CSF, serum titers Muscle immunohistochemistry PCR on CSF
Feline infectious peritonitis (C)	Ophthalmic exam Serum globulin Abdominal palpation/ultrasound Coronavirus antibody in CSF, serum Coronavirus immunohistochemistry on tissues Coronavirus PCR on CSF, affected tissues
Cryptococcosis (D, C)	Ophthalmic exam Thoracic radiographs Skull/brain MRI Nasal swab cytology Lymph node aspirates Test for capsular antigen in serum, CSF CSF culture
Rocky Mountain spotted fever (D)	Thoracic radiographs CBC, platelet count Serum globulin Skin biopsy: IFA Serum titer (demonstrate rise)
Ehrlichiosis (D)	CBC, platelet count Serum titer Ophthalmic examination

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *C,* cat; *CBC,* complete blood count; *CK,* creatine kinase; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *D,* dog; *IFA,* immunofluorescent antibody analysis; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *RT-PCR,* reverse transcriptase–polymerase chain reaction.

(complete blood count [CBC], chemistry including creatine kinase [CK] and urinalysis) and survey spinal radiographs are warranted in most cases. When these tests are negative, advanced imaging (computed tomography [CT], magnetic resonance imaging [MRI]), and synovial fluid and CSF collection and analysis are usually recommended.

NONINFECTIOUS INFLAMMATORY DISORDERS

STEROID-RESPONSIVE MENINGITIS-ARTERITIS

SRMA is one of the most common forms of meningitis diagnosed in most veterinary hospitals. An immunologic cause is suspected, resulting in vasculitis/arteritis affecting the meningeal vessels throughout the entire length of the spinal cord and brainstem. This disorder has also been called *aseptic meningitis, steroid-responsive suppurative meningitis, necrotizing vasculitis, juvenile polyarteritis,* and *Beagle pain syndrome.* Affected dogs are usually juveniles or young adults (6-18 months of age), but middle-aged and older dogs are occasionally affected. Large-breed dogs are most commonly affected. SRMA may be seen as a breed-associated syndrome in Beagles, Bernese Mountain dogs, Boxers, German Shorthaired Pointers, Bassett Hounds, and Nova Scotia Duck Tolling Retrievers.

Clinical signs of SRMA include fever (50%-90%), reluctance to move, neck pain, and vertebral pain that may wax and wane early in the course of disease. Affected dogs are alert and systemically normal, with a common owner complaint being that the dog will not eat or drink unless the bowl is raised to head level. Neurologic deficits (e.g., paresis, paralysis, ataxia) are very uncommon but can develop in chronically affected or inadequately treated dogs as a result of concurrent myelitis, spinal cord hemorrhage, or infarction. Signs of intracranial extension of inflammation are rare. The vast majority of dogs with SRMA are presented for neck pain and fever but have a normal neurologic examination.

Laboratory changes typically include a neutrophilic leukocytosis with or without a left shift. Hypoalbuminemia and hyperglobulinemia suggest systemic inflammation. Cervical radiographs are often performed to look for evidence of diskospondylitis and are normal. Spinal fluid analysis shows a neutrophilic pleocytosis (often >100 cells/μL; >75% neutrophils) and an increased protein concentration. Early in the course of the disease, when neck pain is intermittent, CSF may be normal or minimally inflammatory. Within 24 hours of administration of a single dose of prednisone, CSF may be normal or show a predominance of mononuclear cells; therefore CSF should always be collected for diagnosis when a dog is symptomatic before initiating therapy. High immunoglobulin (Ig)A concentrations are found in the CSF and serum of most dogs (>90%) with SRMA, aiding diagnosis, but this finding lacks specificity. Some dogs with SRMA have concurrent immune-mediated polyarthritis (IMPA). Bacterial cultures of the CSF and blood are negative. To date, no etiologic agent has been identified.

Treatment with glucocorticoids consistently and rapidly alleviates the signs of fever and cervical pain. Dogs not treated early in the course of the disease occasionally develop neurologic deficits associated with spinal cord infarction and meningeal fibrosis; treatment may not resolve the resultant neurologic signs in these dogs. Glucocorticoids should be administered initially at immunosuppressive dosages and then tapered to alternate-day therapy and decreasing dosages over a period of 4 to 6 months (Box 64.2). Dogs that do not respond completely to prednisone and dogs that relapse during prednisone tapering may benefit from the addition of oral (PO) azathioprine (Imuran [Burroughs Wellcome], 2.2 mg/kg PO q24h) to their treatment for 8 to 16 weeks. The prognosis for survival and complete resolution is excellent, with 60% to 80% of dogs with acute signs recovering with treatment and never relapsing. Older dogs and Beagles, Bernese Mountain dogs, Nova Scotia Duck Tolling Retrievers, and German Shorthaired Pointers with breed-associated SRMA may have disease that is more difficult to control, so treatment with prednisone and azathioprine from the outset and a more prolonged schedule for tapering of prednisone dose may be warranted. Lifelong treatment is rarely required.

CANINE MENINGOENCEPHALITIS OF UNKNOWN ETIOLOGY

Nonsuppurative meningoencephalitis of unknown cause is a frequent finding in dogs. Unsuccessful systematic efforts to identify infectious causes, particularly viral and protozoal agents, have resulted in the conclusion that these disorders are likely to have an immune-mediated or hereditary pathogenesis. Although attempts are made to differentiate three distinct disorders—granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME), and necrotizing leukoencephalitis (NLE)—based on clinical and laboratory features, imaging characteristics, and breed predisposition, a definitive diagnosis cannot be obtained without



BOX 64.2

Treatment Recommendations for Steroid-Responsive Meningitis Arteritis

1. Prednisone 2 mg/kg q12h orally for 2 days
2. Prednisone 2 mg/kg q24h orally for 14 days
3. Assess clinical response.

If clinical signs have resolved, the dose of prednisone is gradually tapered:
1 mg/kg q24h for 4-6 weeks
1 mg/kg q48h for 4-6 weeks
0.5 mg/kg q48h for 8 weeks

If clinical signs are present or if they recur during tapering, return to step 2 and add azathioprine (2 mg/kg/day) to treatment for 8-16 weeks. Continue prednisone, tapering after signs resolve.

histopathology. Assessments of treatment efficacy are therefore almost always based on only a presumptive diagnosis.

GRANULOMATOUS MENINGOENCEPHALITIS

GME is an idiopathic inflammatory disorder of the CNS that occurs primarily in young adult dogs of small breeds, with Poodles, toy breeds, Pekingese, and Terriers most commonly affected. Large-breed dogs are occasionally affected. Most dogs with GME are 2 to 6 years of age, although the disease may affect older dogs or dogs as young as 6 months. Females may be predisposed. Cats are not affected.

There are three distinct forms of GME. The *ocular* form is the least common and results in optic neuritis with an acute onset of blindness and dilated nonresponsive pupils (see Chapter 61). Fundiscopic examination may reveal a hyperemic, edematous optic disk or hemorrhage. Dogs with ocular GME may concurrently or later develop disseminated GME. The *focal* form of GME induces clinical signs suggestive of a single enlarging space-occupying mass with neurologic signs that progress slowly over 4 to 6 months, similar to a tumor. Focal GME most often affects the caudal cranial fossa, resulting in vestibulocerebellar signs or the cerebrum causing forebrain signs including seizures. The *disseminated* form of GME causes rapidly progressive signs of multifocal or disseminated disease affecting the cerebrum, brainstem, cerebellum, cervical spinal cord, or meninges. Affected dogs may be febrile, and neck pain is common.

Clinical signs reflect the location and nature of the lesion. About 20% of affected dogs exhibit seizures, circling, or behavior change. Other common features may include brainstem signs such as nystagmus, head tilt, loss of balance, and cranial nerve deficits. Cervical pain occurs in up to 10% of dogs with GME, suggesting meningeal inflammation, focal spinal cord involvement, or increased intracranial pressure. Spinal cord infiltration occurs in approximately 10% of cases. Some dogs (50%) with the disseminated form of GME have a fever and peripheral neutrophilia but no other evidence of systemic disease. The disseminated form of the disease has an acute to subacute progression over days to weeks to months, with 25% of the cases dead within 1 week and most dead within 21 days. The focal form is more insidious, with slow progression over 4 to 6 months.

The diagnostic approach to patients with progressive intracranial or spinal cord disease should include careful systemic evaluation for infectious or neoplastic disease. Screening laboratory tests, thoracic radiographs, abdominal ultrasound, lymph node aspirates, and ophthalmic examination should all be performed. If these tests are unremarkable then advanced imaging is recommended. Focal GME may be identified on MRI as a single space-occupying mass lesion with irregular margins, hyperintensity of T2-weighted images and FLAIR, variable intensity of T1-weighted images (usually isointense or hypointense), and variable contrast enhancement. Disseminated GME usually causes multiple poorly defined lesions of the parenchyma and meninges. CT is not as sensitive as MRI at identifying the parenchymal lesions of GME, but contrast enhancement is common, reflecting inflammation. Imaging results not conclusive for neoplasia should prompt collection and analysis of CSF.

CSF analysis from dogs with GME typically reveals an increase in protein concentration and a mild to marked mononuclear pleocytosis. Small lymphocytes, monocytes, and occasional plasma cells predominate (Fig. 64.2). Anaplastic mononuclear cells with abundant lacy cytoplasm are sometimes present. Neutrophils are seen in two thirds of the samples, usually making up less than 20% of the cells. A single sample of CSF may be normal in 10% to 15% of cases. CSF electrophoresis typically shows evidence of blood-brain barrier disruption, and chronically affected dogs have dramatically increased intrathecal production of gamma globulins. Evaluation for infectious causes of meningoencephalomyelitis through bacterial culture and appropriate serum and CSF titers (Neospora, Toxoplasma, tick-borne diseases, West Nile virus) and antigen tests or PCR should always precede a presumptive diagnosis of GME. Definitive diagnosis requires biopsy or necropsy for histologic examination, but this is rarely performed. A tentative diagnosis is

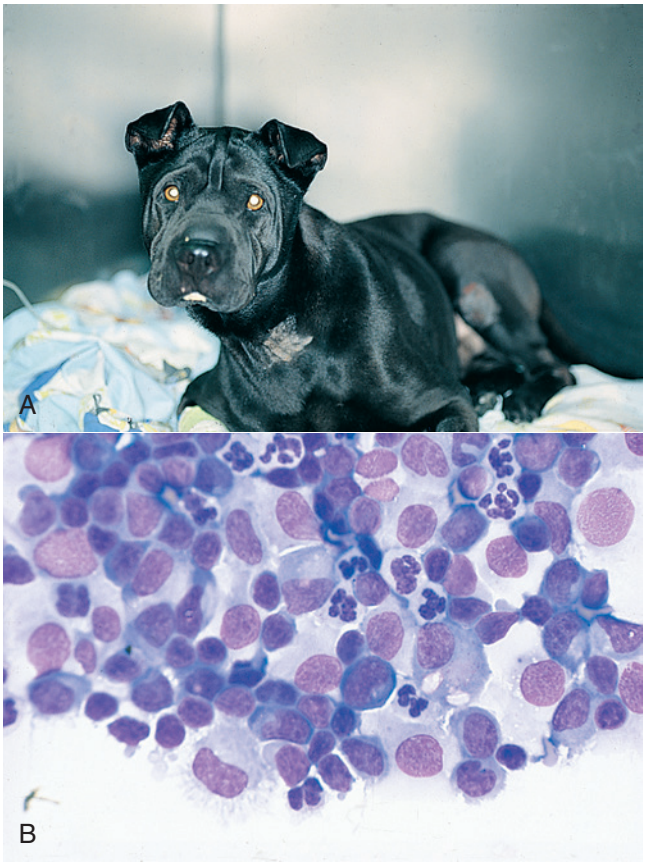


FIG 64.2
(A) Young Chinese Shar-Pei with incoordination, depression, vertical nystagmus, and a slight head tilt resulting from disseminated granulomatous meningoencephalomyelitis. **(B)** Cerebrospinal fluid from this dog has increased cellularity—primarily lymphocytes, monocytes, plasma cells, and neutrophils.

made antemortem based on the typical MRI and CSF findings and elimination of infectious and neoplastic diseases on the list of likely differentials.

Glucocorticoids can temporarily halt or reverse the progression of clinical signs in dogs with GME, particularly in animals with slowly progressive signs associated with focal disease. Clinical signs often recur quickly, with the median survival time highly variable (7-114 days) depending on type and location of disease. More prolonged improvement in clinical signs and survival can be seen when more aggressive chemotherapy protocols are used, with median survival times longer than 12 months expected when dogs with focal disease are treated with combinations of immunosuppressive drugs. Recommended drugs and protocols are outlined in Box 64.3.

Comparative efficacy between protocols is difficult to assess because of disease and patient variability and the failure to obtain a definitive pretreatment diagnosis. Dogs with GME or MUE in the author's hospital are usually treated with a combination of prednisone, 4 cycles of cytosine arabinoside, and either cyclosporine or azathioprine. Although most dogs improve with treatment, the prognosis for permanent recovery is poor. Dogs with forebrain signs have a significantly longer survival than dogs with multifocal or brainstem signs, but dogs with seizures or MRI evidence of cerebral edema have limited survival. Some treatment protocols recommend monitoring of MRI images and CSF cytology before tapering drug doses, but that is rarely performed. Radiation therapy has been reported to benefit some dogs with focal intracranial masses resulting from GME, and results are similar to chemotherapy.

BOX 64.3

Chemotherapy Options for Presumed Granulomatous Meningoencephalitis

Prednisone

1 mg/kg PO q12h for 2 weeks, then 1 mg/kg PO q24h for 4 weeks, then 1 mg/kg q48h
Slowly taper to lower dose (0.5 mg/kg PO q48h) when used in combination drug protocol

Cytosine Arabinoside (Cytosar [Pfizer])

50 mg/m^2 body surface area SC q12h on 2 consecutive days every 21 days for 3-4 cycles
Alternatively administer on 2 consecutive days every 21 days for 4 cycles, then every 28 days for 4 cycles, every 35 days for 4 cycles, every 42 days for 4 cycles

Procarbazine (Matulane [Sigma-Tau Pharmaceuticals])

25-50 mg/m^2 body surface area PO q24h for 30 days, then q48h

Cyclosporine (Neoral [Novartis])

6 mg/kg PO q12h (trough target 200-400 ng/mL)

Azathioprine (Imuran [Roxane Laboratories])

2 mg/kg PO q24h for 30 days, then q48h

Leflunomide (Arava [Aventis Pharma])

2-4 mg/kg PO q24h

Mycophenolate Mofetil (CellCept [Roche])

20 mg/kg PO q12h for 30 days, then 10 mg/kg PO q12h

PO, By mouth; *SC,* subcutaneous.

NECROTIZING MENINGOENCEPHALITIS

NME is a breed-specific idiopathic inflammatory condition affecting the brain of Pugs (Pug encephalitis) and Maltese Terriers. It has also been seen sporadically in the West Highland White Terrier, Chihuahua, Pekingese, Shih Tzu, Papillon, Coton du Tulear, and Lhasa Apso. Affected dogs first show clinical signs between 9 months and 7 years of age, with a mean age of onset about 18 months in Pugs and 29 months in other breeds. Female Pugs may be predisposed.

Most dogs with NME are presented with an acute onset of seizures and neurologic signs referable to the cerebrum and meninges. They may have difficulty walking or may be weak or lack coordination. Circling, head pressing, behavior change, cortical blindness, and neck pain are common. Neurologic deterioration is rapid, and without treatment most dogs develop uncontrollable seizures or become recumbent, unable to walk, and comatose within 5 to 7 days.

A few dogs (especially Pugs) occasionally present with a more slowly progressive form of NME. They are presented with a single generalized or partial motor seizure, but they are neurologically normal after that seizure. Seizures then recur at varying intervals from a few days to a few weeks, followed by the gradual development of other neurologic signs referable to the cerebral cortex. Survival times with this more slowly progressive manifestation of NME are typically fewer than 6 months.

A diagnosis of NME should be suspected on the basis of signalment and characteristic clinical, clinicopathologic, and imaging features. Hematologic and serum biochemistry findings are unremarkable, and testing for metabolic encephalopathies is negative. Imaging studies are consistently abnormal, with CT and MRI showing focal cavitations filled with high-protein fluid within the brain parenchyma. Hyperintense (T2W) infiltrative lesions are typically in the white matter of the cerebral hemispheres just lateral to the ventricles and at the junction between cerebral gray and white matter, resulting in loss of the normal sharp demarcation on MRI. CSF analysis reveals a high protein concentration and an increased nucleated cell count, with the predominant cell type being the small lymphocyte, with a few larger mononuclear cells. Even in typical cases, testing should be performed to eliminate an infectious etiology (Toxoplasma, Neospora, canine distemper). Definitive diagnosis requires autopsy or brain biopsy. NME is distinguished from GME by finding characteristic necrotic lesions and cavitations in cerebral white or grey matter.

No specific treatment has been shown to consistently alter the course of this disease, but long-term remission has been achieved in a few dogs using treatment protocols as outlined for GME (see Box 64.3). Treatment with antiepileptic doses of phenobarbital may decrease the severity and frequency of seizures. The prognosis for long-term improvement and survival must be considered poor.

NECROTIZING LEUKOENCEPHALITIS

NLE is a breed-specific idiopathic multifocal necrotizing, nonsuppurative encephalitis affecting the brains of Yorkshire Terriers, French Bulldogs, and occasionally Maltese Terriers. Dogs first show clinical signs between 1 and 10 years of age, with a mean age of onset around 4.5 years. Males and females are affected equally.

Lesions predominate in the white matter ("leuko-") of the cerebrum, thalamus, and brainstem. Signs may include altered mentation, seizures, visual deficits, head tilt, nystagmus, cranial nerve abnormalities, and proprioceptive deficits. Neurologic deterioration is rapid, and within 5 to 7 days most dogs are recumbent or dead. A diagnosis of NLE should be suspected on the basis of signalment and characteristic rapidly progressive cortical and brainstem signs. MRI studies show multiple asymmetric hyperintense (T2W) lesions and cystic areas of necrosis restricted to the white matter of the cerebrum, thalamus, and brainstem. CSF analysis reveals a mild to moderate increase in protein and a mixed inflammatory pleocytosis consisting of macrophages, monocytes, lymphocytes, and plasma cells. Treatment as for GME is recommended, but the prognosis for recovery is poor.

CANINE STEROID-RESPONSIVE TREMOR SYNDROME

An acute-onset whole-body tremor disorder is most commonly recognized in small white dogs such as Maltese and West Highland White Terriers and Bichon Frise, leading to the name "little white shaker syndrome." Although this disorder is most common in young adult dogs of the small white breeds, it can occur in any breed and in dogs of any coat color. Cairn Terriers and Miniature Pinschers are also predisposed. Affected dogs are presented for evaluation of tremors and incoordination. Tremors can range from mild to incapacitating and tend to worsen with exercise, stress, and excitement. In most dogs, signs are restricted to tremor, but occasionally vestibular or cerebellar ataxia, nystagmus, or loss of menace response can accompany the tremor.

Diagnosis should be suspected based on signalment, history, and clinical signs. Lack of access to tremorgenic toxins and failure to progress to more severe signs like seizures make intoxication unlikely. Normal metabolic testing (glucose, liver function) and normal mentation are expected. MR imaging is usually normal. CSF can be normal, but most often there is a slight increase in protein and a lymphocytic pleocytosis. Testing for infectious causes of CNS inflammation, including neosporosis, canine distemper, West Nile virus, and tick-borne pathogens, should be performed where appropriate, and treatment for 1 to 2 weeks with clindamycin or doxycycline may be considered. Signs usually persist until prednisone therapy is initiated (1-2 mg/kg PO q12h for 14 days). Tremors usually improve or resolve within the first week or two after initiating therapy. Once the tremors have resolved, the prednisone dose can be tapered gradually over 3 to 6 months to the lowest effective dose (usually 0.25 mg/kg q48h) and then can usually be discontinued. If the tremors return, immunosuppressive prednisone therapy is reinitiated, with more gradual tapering. Some dogs require additional immunosuppressive treatment with cyclosporine or azathioprine to taper the prednisone dose to acceptable levels and prevent relapses. The prognosis is good for recovery, but occasionally dogs will require lifelong continuous or intermittent therapy. Histologically, some affected dogs have had a mild nonsuppurative meningoencephalitis with perivascular cuffing that is most severe in the cerebellum.

CANINE EOSINOPHILIC MENINGITIS/ MENINGOENCEPHALITIS

Eosinophilic meningitis and meningoencephalitis occur uncommonly in dogs. Eosinophilic inflammation can be the response to migrating helminths, protozoal or fungal infection, or rarely viral infection of the CNS. There is also a primary allergic or immune-mediated disorder of dogs characterized by eosinophilic inflammation of the CNS and known as *idiopathic eosinophilic meningoencephalitis* (EME). This idiopathic disorder is most common in young (8-month to 3-year-old) large-breed dogs, particularly Golden Retrievers and Rottweilers. Neurologic signs of EME reflect cerebral cortical involvement and include behavior change, circling, and pacing. Ataxia and proprioceptive deficits are uncommon. Some dogs (10%-20%) also manifest systemic signs of diarrhea, vomiting, and abdominal pain. Peripheral eosinophilia is uncommon. MRI can be normal or reveal focal or multifocal patchy regions of T2 hyperintensity with variable contrast enhancement. CSF analysis reveals increased cellularity, with 20% to 99% eosinophils (often >80%). It is important to rule out or treat parasitic and infectious disease before initiating treatment for EME. If testing is negative for heartworm disease, fungal and protozoal pathogens, and *Baylisascaris* (serology), broad-spectrum deworming with fenbendazole and ivermectin is recommended, followed by 2 to 4 weeks of oral clindamycin and immunosuppressive doses of prednisone. Some dogs recover without treatment. Most dogs (75%) have a good response to treatment and can be weaned off oral prednisone after 3 to 4 months.

FELINE POLIOENCEPHALITIS

A nonsuppurative encephalomyelitis with no etiologic agent identified (viral non-FIP encephalitis) occasionally causes progressive seizures or brainstem and spinal cord signs in young adult cats. Affected cats range from 3 months to 6 years of age, but most are younger than 2 years. Affected animals have a subacute to chronic course with neurologic signs progressing over 3 to 5 weeks. Ataxia, paresis, and proprioceptive deficits affecting the pelvic limbs or the pelvic and thoracic limbs are common. When inflammation

extends to the nerve roots, LMN signs of hyporeflexia and muscle atrophy are apparent. Seizures, circling, behavior change, blindness, intention tremor, and nystagmus are observed in some cats.

Clinicopathologic findings are normal in most affected cats. CSF analysis is normal or reveals a mild increase in mononuclear cells and slightly increased protein concentration. Definitive diagnosis can only be confirmed at necropsy. Lesions are confined to the CNS and include meningitis, neuronal degeneration, and variable lymphohistiocytic perivascular infiltrates with characteristics suggesting a viral etiology. Routine testing for a wide variety of infectious agents has been negative. The prognosis is poor, although reports exist of spontaneous recovery from a clinically similar disorder in a few cats.

INFECTIOUS INFLAMMATORY DISORDERS

FELINE IMMUNODEFICIENCY VIRUS ENCEPHALOPATHY

Neurologic abnormalities associated with feline immunodeficiency virus (FIV) encephalopathy in cats include behavioral and mood changes, altered sleep patterns, depression, persistent staring, inappropriate elimination, seizures, twitching of the face and tongue, and occasionally paresis. A presumptive diagnosis of FIV encephalopathy is made on the basis of suggestive clinical signs and positive FIV serology, but because FIV-infected cats have increased susceptibility to numerous neoplastic and infectious causes of encephalitis, it is important to carefully exclude other neurologic diseases. CSF analysis reveals an increase in lymphocytes and normal or only slightly increased CSF protein concentration. FIV antibodies can be demonstrated in the CSF of most affected cats. Care must be taken to keep from contaminating the CSF with blood during collection, because serum antibody titers are higher than those in the CSF. Culture of freshly collected CSF may yield the virus. Administration of the reverse transcriptase inhibitor Zidovudine (AZT: 5 mg/kg PO q12h) may reduce the severity of neurologic impairment in some cats.

BACTERIAL MENINGOENCEPHALOMYELITIS

Bacterial infection of the CNS is uncommon in dogs and cats. It may result from direct extension of infection from an extraneural site such as the middle/inner ear, eye, retrobulbar space, sinus, or nose or because of a penetrating injury to the skull or a migrating foreign body. Hematogenous dissemination from extracranial infected foci occurs less frequently, except in neonates with omphalophlebitis and dogs and cats with severe immunodeficiency or overwhelming sepsis. Dogs with highly vascular septic pleuritis, prostatitis, endocarditis, pyelonephritis, osteomyelitis, and diskospondylitis may be at risk. Bacterial meningitis and meningoencephalomyelitis in dogs and cats, unlike in humans, are not caused by microorganisms having a specific predilection for the nervous system. Bacterial infections of the CNS are instead associated with the wide variety of organisms infecting extraneural sites.

Clinical signs of bacterial infection of the CNS commonly include pyrexia, neck pain, and severe systemic illness. Many affected animals either have an obvious site of infection adjacent to the CNS or they are bacteremic and systemically severely ill at the time of presentation. Rarely, affected animals are systemically normal. Neurologic abnormalities in dogs and cats with bacterial infections of the CNS reflect the location of damaged parenchyma and may include seizures, coma, blindness, nystagmus, head tilt, cranial nerve deficits, severe neck pain and progressive paresis, or paralysis. The clinical course is usually rapidly progressive and frequently fatal. Shock, hypotension, and disseminated intravascular coagulation are common, and routine laboratory tests may reflect the underlying inflammatory process. Advanced imaging typically reveals the site of original infection and confirms inflammation of the meninges and brain parenchyma. Spinal epidural empyema and abscessation are rarely identified.

CSF analysis may reveal an increased protein concentration and a severe neutrophilic pleocytosis in acute and severe cases but less pronounced changes or normal CSF in chronic low-grade cases. Neutrophils in the CSF only occasionally appear toxic or degenerate, and intracellular bacteria are rarely seen (Fig. 64.3). Treatment with antibiotics before CSF is collected may lower the CSF cell count and result in a predominance of mononuclear cells. The rate of organism recovery by CSF culture can be improved by inoculation of CSF into broth enrichment media, but fewer than 40% of dogs with bacterial meningitis will have positive CSF cultures. Because it is so difficult to document and characterize infection within the CNS, it is very important to evaluate the patient systemically whenever bacterial meningitis is suspected. Diagnostic evaluation should include blood and urine bacterial cultures, ophthalmologic and otic examinations, abdominal and cardiac ultrasound examinations, screening radiographs or CT of the spine and thorax, as well as CSF cytologic analysis and CSF anaerobic and aerobic bacterial culture. MR imaging of the affected region should also be considered. The presence of systemic bacterial illness or identification of an extraneural focus of infection in a dog or cat with neurologic signs and inflammatory CSF should prompt immediate treatment for suspected bacterial CNS infection. If the focus of underlying infection can be determined, that site should be cultured. Therapy is usually initiated before culture results are available.

Bacterial meningitis can be a life-threatening infection requiring rapid and aggressive treatment. Appropriate therapy of CNS infections is based on identifying the causative organism and selecting an effective antimicrobial agent that will reach high concentrations in the CSF and CNS tissues. Enrofloxacin, marbofloxacin, third-generation cephalosporins (e.g., ceftriaxone, cefotaxime), and the second-generation cephalosporin cefuroxime are good choices for

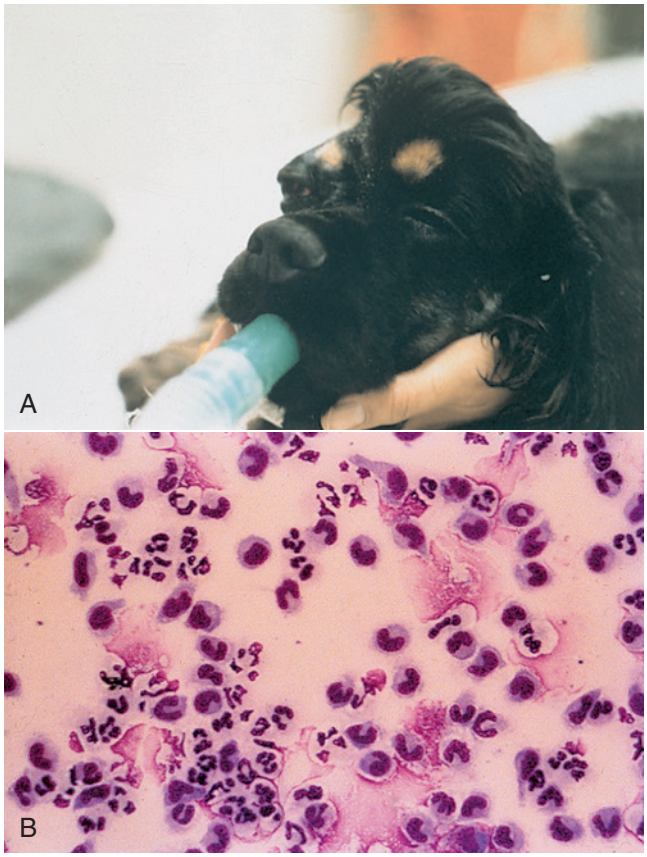


FIG 64.3
(A) This 4-year-old Cocker Spaniel with a chronic retrobulbar abscess developed fever and severe depression. **(B)** Cerebrospinal fluid from the dog revealed septic inflammation. Postmortem examination confirmed communication between the retrobulbar abscess and central nervous system.

gram-negative infections, and metronidazole can be used for anaerobic infections. Doxycycline, trimethoprim-sulfa, and chloramphenicol may also reach therapeutic concentrations in the CNS. While inflammation persists, ampicillin and amoxicillin with clavulanic acid are also effective and may be the best choice for gram-positive infections. Initial treatment with a combination of intravenous (IV) ampicillin (22 mg/kg IV q6h), enrofloxacin (2.5 mg/kg IV q12h), and metronidazole (15 mg/kg IV × 1, then 7.5 mg/kg IV q8h) may be warranted if the infectious agent is unknown. Whenever possible, antibiotics should be administered intravenously for 3 to 5 days to achieve high CSF concentrations, and then oral therapy should be continued for 4 to 8 weeks after recovery. Concurrent IV fluids and systemic support are important, and anticonvulsants should be administered to patients having seizures (see discussion of status epilepticus in Chapter 62). Antiinflammatory drugs or glucocorticoids (dexamethasone, 0.2 mg/kg IV q12h) are sometimes administered for the first 2 days of antibiotic treatment to minimize the inflammatory consequences of antibiotic-induced bacterial lysis. When imaging reveals significant spinal cord compression by an epidural abscess, surgery may be required.

The response to antibiotic therapy is variable, and relapses are common, particularly if the underlying source of the bacterial infection cannot be resolved. The prognosis should be considered guarded in most cases, because even with appropriate therapy many animals die. An exception may be otogenic intracranial infections in dogs and cats, where a good success rate after treatment with surgical drainage and antibiotics has been reported.

CANINE DISTEMPER VIRUS

Canine distemper virus (CDV) is a paramyxovirus that affects the CNS of dogs. Widespread vaccination has substantially decreased the incidence of clinically apparent CDV infections in many regions, but outbreaks still occur among unvaccinated dogs and sporadically in vaccinated dogs. Clinical signs vary depending on virulence of the virus strain, environmental conditions, and host age and immune status. Most CDV infections are probably subclinical or are associated with mild signs of upper respiratory tract infection that resolve without therapy. Young, immunocompromised, and unvaccinated dogs are most likely to develop severe generalized distemper.

Progressive generalized infection with CDV most commonly affects unvaccinated puppies between 12 and 16 weeks of age. The first sign of infection is a mild serous to mucopurulent ocular and nasal discharge followed by a dry cough and sometimes tonsillitis. The cough becomes moist and productive as pneumonia develops. Affected dogs are depressed, inappetent, and often febrile. Diarrhea develops in some puppies and may be mild or severe. Hyperkeratosis of the footpads and nose, pustular dermatitis affecting the unhaired skin on the ventral abdomen, and severe moist otitis externa may also be seen. Neurologic signs typically begin 1 to 3 weeks after recovery from the initial systemic illness and may include forebrain, vestibulocerebellar, brainstem, or spinal cord signs. Some of the most common neurologic signs reported include dementia, disorientation, altered mentation, seizures, circling, head tilt, nystagmus, cranial nerve deficits, hypermetria, tetraparesis, and ataxia. Seizures can be of any type, depending on the region of the forebrain that is affected, but "chewing gum" seizures caused by polioencephalomalacia of the temporal lobes are commonly described. Myoclonus, a repetitive rhythmic contraction of a group of muscles resulting in repetitive flexion of a limb or contractions of the muscles of mastication, is often referred to as *distemper chorea* and is very common in dogs with distemper encephalomyelitis. Anterior uveitis, optic neuritis, or chorioretinitis may be detected during an ophthalmologic examination in some infected dogs. Dogs surviving mild CDV infection before eruption of their permanent teeth will often have irregular dental surfaces and brown discoloration of their teeth subsequent to virus-induced enamel hypoplasia. Older animals occasionally develop chronic encephalomyelitis months to years after prior CDV infection and recovery (old dog encephalitis),

with neurologic abnormalities that include progressive tetraparesis or vestibular dysfunction in the absence of systemic signs.

CDV is diagnosed on the basis of history, physical examination, and laboratory findings. In most young dogs a history of mild to severe gastrointestinal and respiratory illness precedes the onset of neurologic signs. Results of a CBC may be normal or may reveal a persistent lymphopenia; distemper inclusions can sometimes be found in the circulating lymphocytes and erythrocytes. Optic neuritis, chorioretinitis, and retinal detachment are occasionally seen.

Early in an infection (first 3 weeks), immunofluorescent or immunohistochemical techniques using anti-CDV antibodies may reveal CDV in cytologic smears prepared from conjunctival, tonsilar, or nasal epithelium. Virus may be detected past these initial stages in epithelial cells and macrophages obtained from the lower respiratory tract by tracheal wash or in histologic samples of the skin, footpads, and CNS; thus immunohistochemical techniques can be applied to biopsy or necropsy specimens for diagnosis. Biopsy of the haired skin of the dorsal neck can be used for antemortem immunohistochemical testing to confirm acute and subacute infection with CDV. Reverse transcriptase–polymerase chain reaction (RT-PCR) can also be used as a sensitive and specific test to detect CDV RNA in whole blood, buffy coat preparations, CSF, and tissues of affected dogs.

MRI findings include poorly demarcated focal or multifocal hyperintense lesions on T2W in the forebrain, brainstem, cerebellum, or spinal cord. Distemper meningoencephalitis characteristically causes an increase in protein concentration and a mild lymphocytic pleocytosis in the CSF; occasionally the CSF is normal or more indicative of an inflammatory process (increased neutrophils). Increased protein concentration in the CSF has been identified primarily as anti-CDV antibody. Measured CDV antibody titer in the CSF may be increased relative to the serum titer.

Treatment of acute CDV meningoencephalomyelitis is supportive, nonspecific, and frequently unrewarding. Progressive neurologic dysfunction usually necessitates euthanasia. Anticonvulsant therapy has been recommended to control seizures. Antiinflammatory doses of glucocorticoids (predisone 0.5 mg/kg q12h PO for 10 days, then taper) may be used to control other neurologic signs in the absence of systemic disease, but their beneficial effects are not well documented.

Prevention of CDV infection through routine vaccination is usually very effective. CDV can, however, develop with exposure after stress, illness, or immunosuppression, even in a currently vaccinated dog. Meningoencephalitis that was presumed to be vaccine-induced distemper was reported in a few immunosuppressed puppies 7 to 14 days after vaccination with modified-live virus–canine distemper vaccines (MLV-CDV). Although this was likely a historical problem with particular batches of vaccines produced using old technology, vaccination of immunosuppressed neonates, particularly those with a known or suspected parvoviral infection, should be avoided.

RABIES

Rabies virus infection in dogs and cats is almost always the result of a bite from an infected animal with rabies virus in its saliva. Most dogs and cats are infected through contact with wildlife vectors (e.g., skunks, raccoons, foxes, bats). Although the prevalence of wildlife rabies has been increasing, cases of rabies in pet dogs and cats have been decreasing thanks to routine vaccination protocols. The incubation period from the time of the bite to the onset of clinical signs is extremely variable (1 week to 8 months), with average incubation 3 to 8 weeks. Once neurologic signs develop, the disease is rapidly progressive, with death occurring within 7 days in most animals.

Rabies can have a wide range of clinical signs, which makes it difficult to differentiate from other acute progressive encephalomyelitis syndromes. Because of its public health significance, rabies should be on the list of differential diagnoses considered in every animal with rapidly progressing neurologic dysfunction, and precautions should be taken to minimize human exposure. Rabies infection has classically been divided into two major types: furious and paralytic. Dogs and cats typically undergo an early prodromal phase lasting 2 to 3 days during which they may be apprehensive or nervous and may lick or chew at the site of inoculation. This can be followed by a furious or psychotic phase (1-7 days) in which animals are increasingly irritable and excitable, often snapping at imaginary objects and biting at their cage or surroundings. They become uncoordinated and may exhibit generalized seizures progressing to death. Animals that develop the paralytic or dumb type of rabies develop generalized LMN paralysis progressing from the site of inoculation to involve the entire CNS within a few (range, 1-10) days. Cranial nerve paralysis may be the first sign seen (especially if the bite was on the face). Difficulty swallowing, excessive drooling, hoarse vocalization, diminished facial sensation, and dropped jaw occur, usually progressing to respiratory paralysis and death.

Any inadequately vaccinated animal with an acute, rapidly progressive course of neurologic disease should be suspected of having rabies. Ancillary testing should be performed with caution, minimizing exposure of personnel. CSF analysis reveals increased mononuclear cells and protein concentration, as might be expected with any viral encephalomyelitis. Rabies antibody may be increased in CSF compared with serum. Biopsies obtained from the dorsal skin at the nape of the neck or the maxillary sensory vibrissae may be positive for rabies virus antigen, but although positive results are reliable, negative results are not. Definitive diagnosis of rabies encephalitis is through postmortem demonstration of rabies virus antigen by immunohistochemical techniques in the brain tissue (thalamus, pons, medulla) of an infected animal. Because of the risk associated with inadvertent human exposure, it is recommended that all inadequately vaccinated animals euthanized or dying with progressive neurologic dysfunction of unknown origin undergo postmortem evaluation, and persons performing these examinations should be advised to take precautions to prevent rabies exposure.

Fortunately, vaccinations have been extremely effective in reducing the prevalence of rabies in pet dogs and cats, and in decreasing the incidence of rabies infection in humans. Inactivated products and recombinant vaccines are available and are relatively safe and effective when used as directed. Dogs and cats should receive their first rabies vaccine after 12 weeks of age and then again at 1 year of age. Subsequent boosters are administered every 1 to 3 years, depending on the vaccine used and local public health regulations. Rarely, soft tissue sarcomas have developed in cats at the site of rabies virus prophylactic inoculation. Postvaccinal polyradiculoneuritis causing an ascending LMN tetraparesis has also been reported occasionally in dogs and cats.

FELINE INFECTIOUS PERITONITIS

Progressive neurologic signs occur in approximately 30% of cats affected with the dry form of feline infectious peritonitis (FIP). Neurologic FIP is the most common single cause of inflammatory brain disease and the most common cause of progressive spinal cord signs in cats. Neural FIP is most common in male cats younger than 2 years of age from multi-cat households.

The most common neurologic signs of FIP include seizures, behavior change, vestibular dysfunction, tremors, hypermetria, cranial nerve deficits, and UMN paresis. Most affected cats have a fever and systemic signs such as anorexia and weight loss. Concurrent anterior uveitis, iritis, keratic precipitates, and chorioretinitis are common and should raise suspicion of this disease. Careful abdominal palpation will reveal organ distortion caused by concurrent granulomas in the abdominal viscera in over 50% of cats with CNS FIP.

Typically, the CBC is inflammatory, and serum globulin concentrations may be very high. Results of serum tests for anticoronavirus antibodies are variable. MRI typically reveals inflammation of the ventricular lining and meninges, secondary hydrocephalus, and occasionally focal or multifocal granulomatous lesions in the brain or spinal cord parenchyma. CSF analysis reveals a marked neutrophilic or pyogranulomatous pleocytosis (>100 cells/μL; >70% neutrophils) and an increase in CSF protein concentration (>200 mg/dL) in most cases, but occasionally CSF will be normal or only slightly inflammatory. Coronavirus can sometimes be detected in the CSF and other affected tissues using RT-PCR. The prognosis for cats with CNS FIP is very poor. Some palliation may be achieved with immunosuppressive and antiinflammatory medications (see Chapter 96 for more information on FIP).

TOXOPLASMOSIS

Toxoplasma gondii infections can be acquired transplacentally, through ingestion of raw meat containing encysted organisms, or through ingestion of food or water contaminated by cat feces containing oocysts. Most infections are asymptomatic. Transplacentally infected kittens may develop acute fulminating signs of liver, lung, CNS, and ocular involvement. Disease in older animals results from reactivation of a chronic encysted infection. Infection is evident in the lung, CNS, muscle, liver, pancreas, heart, and eye in cats. In dogs, lung, CNS, and muscle infections predominate, but ocular infections may also occur.

CNS toxoplasmosis can cause a variety of signs, including behavioral change, blindness, seizures, circling, tremors, ataxia, paresis, and paralysis. Muscle pain and weakness caused by *Toxoplasma* myositis is discussed in Chapter 67.

Routine laboratory work may be normal in dogs and cats with CNS toxoplasmosis, or a neutrophilic leukocytosis and eosinophilia may be seen. Serum globulins may be increased. Liver enzymes are increased when there is hepatic infection, and CK is increased in animals with myositis. CSF analysis typically reveals increased protein concentration and a mild to moderately increased nucleated cell count. Lymphocytes and monocytes usually predominate, but occasionally the pleocytosis is neutrophilic or eosinophilic. The CSF concentration of antibodies directed against *T. gondii* may be increased relative to serum concentration, suggesting local production of specific antibodies. Rarely, CSF cytologic examination reveals *T. gondii* organisms within host cells, allowing a definitive diagnosis of toxoplasmosis.

Antemortem diagnosis of CNS toxoplasmosis may be difficult because *T. gondii*-specific antibodies and antigen can be detected in the serum of normal cats. If other organ systems are involved, finding organisms in samples from affected extraneural tissues allows definitive diagnosis. In patients with myositis, immunohistochemistry can be used to identify organisms in muscle biopsies. A fourfold rise in IgG titer in two serum samples taken 3 weeks apart or a single elevated IgM titer in a patient with neurologic signs supports a diagnosis of toxoplasmosis, but antibody titers are negative in some animals with severe disease (see Chapter 98). Identification of *T. gondii*-specific IgM antibody and organism DNA (by PCR) in CSF or aqueous humor of symptomatic animals suggests *T. gondii* meningoencephalomyelitis.

Recommended treatment for meningoencephalomyelitis caused by toxoplasmosis in dogs and cats consists of clindamycin hydrochloride (10 mg/kg PO q8h or 15 mg/kg PO q12h for at least 4-8 weeks). This drug has been shown to cross the blood-brain barrier and has been used with success in a limited number of animals. Trimethoprim-sulfadiazine (15 mg/kg PO q12h) can be used as an alternate anti-*Toxoplasma* drug, especially in combination with pyrimethamine (1 mg/kg/day), but if this is used for long-term treatment, folic acid supplementation should be considered; there may be some toxicity in cats. Azithromycin (10 mg/kg PO q24h) has been used successfully in some cats. Regardless of therapy, prognosis for recovery is grave in animals with profound neurologic dysfunction. Affected cats should be routinely tested for concurrent feline leukemia virus (FeLV) and FIV infections. Neurologic, ocular, and muscular manifestations of toxoplasmosis are not usually associated with patent infection and oocyte shedding in cats, so isolation of affected animals is not necessary.

NEOSPOROSIS

Neospora caninum is a protozoan parasite that causes neuromuscular and CNS disease in dogs. Clinical disease in naturally infected cats has not been reported. Domestic dogs and coyotes are definitive hosts, shedding oocysts in their stool after ingestion of *N. caninum* cysts in muscle from intermediate hosts (primarily deer and cattle). The predominant route of transmission is transplacental, causing acute symptomatic infection in some puppies and subclinical infection leading to encystment in neural and muscle tissues in others.

Congenitally infected puppies 6 weeks to 6 months of age typically develop rear limb weakness, loss of patellar reflexes, quadriceps muscle atrophy, and finally LMN paralysis of the rear limbs as a result of inflammation of the muscles and nerve roots (Fig. 64.4). Multiple puppies from a litter may be affected. If treatment is not initiated promptly, severe denervation atrophy of the muscles and myositis leads to irreversible fibrous contracture of the quadriceps and gracilis muscles fixing the rear limbs in rigid extension (Fig. 64.5). Most affected puppies are bright and alert and otherwise normal. Rarely, untreated dogs develop similar progressive signs involving the forelimbs or even brain signs.

Serum CK may be mildly to moderately increased in affected puppies. Serology can be used to support the diagnosis of neosporosis, but negative results are common in acute disease. Organisms can sometimes be detected using immunohistochemical stains in areas of lymphoplasmacytic inflammation in muscle biopsies. CSF may be normal or there may be a mild mixed inflammatory pleocytosis. A presumptive diagnosis of pediatric neosporosis is usually made based on the characteristic signs of rear limb weakness, quadriceps muscle weakness and atrophy, and loss of the patellar reflex. Treatment is initiated while test results are still pending. Clindamycin hydrochloride 10 mg/kg q8h is administered for 4 to 12 weeks. Rapidly progressive signs, delayed treatment, and pelvic limb hyperextension are associated with a poor prognosis for recovery.

Disease in older animals usually results from reactivation of a chronic encysted infection acquired congenitally or through ingestion of tissue cysts. These dogs commonly have signs of CNS involvement, with progressive cerebellar signs of hypermetria, cerebellar ataxia, and intention tremor most common. Paraparesis, tetraparesis, seizures, vestibular signs, and cranial nerve abnormalities have all been reported, and some dogs have concurrent myositis. Most affected dogs are systemically normal, but occasionally systemic neosporosis will occur, causing fever, pneumonia, hepatitis, pancreatitis, esophagitis, or pyogranulomatous dermatitis.

Hematologic and biochemical findings vary and depend on the organ systems involved. In dogs with myositis, serum CK and aspartate aminotransferase (AST) activities may be increased. Some puppies with clinically evident neosporosis will have negative serology, but most affected adult dogs have positive titers. Adult dogs with CNS neosporosis may have normal CSF or may have mild increases in protein concentration and leukocyte count, with monocytes, lymphocytes, and neutrophils predominating and rarely eosinophils. Inflammatory CSF should always prompt serologic and CSF testing for a variety of infectious agents including *Neospora* before initiating treatment for a presumed noninfectious inflammatory disorder. *Neospora*-specific antibodies or organism DNA (PCR) may be detected in the CSF from adult dogs with neosporosis. Immunocytochemical staining can be used to identify *Neospora* and differentiate it from *Toxoplasma* in muscle biopsies from dogs with myositis. When there is a high clinical suspicion for neosporosis because of typical signs in a young dog, treatment should be initiated promptly instead of waiting for test results.

Treatment with clindamycin hydrochloride (10 mg/kg PO q8h or 15 mg/kg PO q12h for at least 4-8 weeks) is most



FIG 64.4
Ten-week-old Irish Wolfhound puppy with crouched rear limb stance, quadriceps muscle weakness, and atrophy and patellar areflexia caused by *Neospora caninum* myositis and lumbar radiculoneuritis. This dog recovered after clindamycin treatment.



FIG 64.5
Young Labrador Retriever with rigid extension of the rear limbs caused by pediatric neosporosis.

effective in puppies and dogs without severe neurologic signs. Multifocal signs, rapid progression of signs, pelvic limb rigid hyperextension, and delayed treatment are all associated with a poor prognosis for recovery.

LYME DISEASE

Lyme neuroborreliosis resulting from CNS infection by the spirochete *Borrelia burgdorferi* has been well documented in people, but there are few reports of dogs with neurologic signs convincingly caused by Lyme disease. Most affected dogs have had concurrent polyarthritis, lymphadenopathy, and fever. Reported signs of neurologic system involvement include aggression, other behavior changes, and seizures. CSF may be normal or only slightly inflammatory, and there may be an increase in anti–*B. burgdorferi* antibody in the CSF compared with serum. Although it is rare, Lyme neuroborreliosis should be considered in the differential diagnosis of disease involving the CNS in dogs from endemic regions. Early antibiotic treatment may be effective, but it is important to select an effective antibiotic capable of reaching high concentrations in the CSF. Subcutaneous (SC) or IV ceftriaxone (25 mg/kg q24h for 14-30 days), oral doxycycline (10 mg/kg PO q12h for 30 days), and oral amoxicillin (20 mg/kg PO q8h for 30 days) have all been recommended.

MYCOTIC INFECTIONS

Disseminated systemic mycotic infections may occasionally involve the CNS and eyes. Clinical findings depend on the fungus involved and typically include fever, weight loss, severe respiratory or gastrointestinal signs, lymphadenopathy, or lameness in patients with neurologic and ocular signs. The most common neurologic signs are depressed mentation, behavior change, seizures, circling, and paresis. Ocular examination may reveal uveitis, chorioretinitis, retinal detachment, or optic neuritis. Typical abnormalities on CSF analysis include a neutrophilic pleocytosis and increased protein content. Diagnosis usually relies on finding the organism in extraneural infected tissues. Therapy may be attempted, but the prognosis is poor when the nervous system is involved. Fluconazole (5 mg/kg PO q12h for 3-4 months) or voriconazole (6 mg/kg PO q24h) may be the most effective antifungal drugs for most CNS or ocular fungal infections.

It is uncommon for systemic mycoses to present with neurologic signs alone. The exception is infection caused by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gatti*. These organisms have a predilection for the CNS in the dog and cat. Infection occurs via inhalation, and CNS infection occurs by extension from the nose through the cribriform plate and via hematogenous dissemination. Cats are often presented for signs of nasal and sinus infection that progresses to neurologic, ocular, and sometimes cutaneous involvement. Dogs are more often presented for neurologic signs without clinical signs related to systemic infection. Neurologic signs seen in both species include mentation change, blindness, seizures, vestibular signs, paresis, ataxia, and neck or spinal pain.

MRI in most dogs and some cats with CNS *Cryptococcus* reveals focal or multifocal ill-defined contrast enhancing inflammatory parenchymal lesions and meningeal enhancement. A few cats have normal MRI images, and others have multifocal parenchymal mass lesions that enhance only peripherally, representing accumulations of fungal organisms and capsular material without much inflammation—gelatinous pseudocysts.

In most dogs and cats with cryptococcal meningoencephalitis, CSF analysis reveals increased protein concentration and cell counts. A neutrophilic pleocytosis is most common, but mononuclear cells and eosinophils have been reported. Organisms can be visualized in the CSF in up to 60% of cases. Fungal culture of the CSF should be considered in animals with inflammatory CSF in which no organisms are visible. Cytologic examination of nasal exudate, draining tracts, enlarged lymph nodes, and granulomas located extraneurally usually yields the diagnosis. The organism is readily visible using Gram stain, India ink, or Wright stain. Detection of capsular antigen in the CSF or serum of affected animals using cryptococcal antigen latex agglutination serology (CALAS) is a sensitive and specific test in dogs and cats. Treatment of CNS cryptococcal infection is usually attempted using amphotericin B or fluconazole, both of which penetrate the CNS. Mortality is high during the first few weeks of treatment. Long-term survival is possible but may require intermittent or continuous lifelong therapy. Prognosis is related to the extent and severity of neurologic involvement (see Chapter 97 for more information).

RICKETTSIAL DISEASES

A number of tick-borne rickettsial diseases can cause neurologic abnormalities in dogs. Rocky Mountain spotted fever (RMSF), caused by infection with *Rickettsia rickettsii,* is the most likely to cause severe neurologic signs, but infection with *Ehrlichia canis, Anaplasma phagocytophilum,* and *Ehrlichia ewingii* have also been reported to cause neurologic signs in dogs. Neurologic signs with each of these diseases may be associated with vasculitis and include depression, altered mentation, neck or spinal pain, paresis, ataxia, tremors, vestibular signs, and seizures. Neurologic abnormalities have not been recognized in dogs without concurrent systemic disease. Signs of systemic disease depend on the organism involved and the degree of involvement of other organ systems but may include fever, anorexia, depression, vomiting, oculonasal discharge, cough, dyspnea, lameness, and lymphadenopathy.

Although the number of cases reported is small, neutrophils seem to predominate in the CSF of dogs with RMSF, whereas lymphocytes or neutrophils predominate in ehrlichiosis; CSF is normal in some dogs with each disease. In some dogs with acute *A. phagocytophilum* and *E. ewingii* infections, neutrophils in the blood, synovial fluid, or CSF may contain morulae. Serologic testing or PCR (blood or CSF) is essential to confirm the diagnosis of rickettsial infection and differentiate between these diseases. Treatment with doxycycline (5-10 mg/kg PO or IV q12h) is effective in most

cases. Short-term treatment with corticosteroids may also be warranted. Dramatic clinical improvement should be expected within 24 to 48 hours of initiating treatment. The presence of neurologic signs may slow recovery, and in some cases the neurologic damage is irreversible (see Chapter 97 for more information on rickettsial diseases).

PARASITIC MENINGITIS, MYELITIS, AND ENCEPHALITIS

Meningitis and meningoencephalitis caused by aberrant parasite migration have been reported in the dog and cat. In these diseases, migration and growth of parasites can result in extensive damage to the neural parenchyma. An eosinophilic CSF pleocytosis should prompt consideration of parasitic migration through the CNS, although several more common neurologic disorders should also be considered, including intracranial neoplasia, toxoplasmosis, neosporosis, GME, and idiopathic EME. Diagnostic evaluation of animals with eosinophilic CSF should include a fundic examination, CBC, serum biochemistry profile, urinalysis, serum and CSF titers for *Toxoplasma* and *Neospora,* thoracic and abdominal radiographs, abdominal ultrasound, fecal flotation, and heartworm antigen testing. CT and MRI may document necrosis along the path of parasite migration within the CNS. Definitive diagnosis of parasitic CNS disease requires pathologic demonstration of the parasite in the CNS. Empirical treatment with ivermectin should be considered if parasite migration is likely (200-300 µg/kg PO or SC every 2 weeks for 3 treatments). Antiinflammatory treatment with prednisone may also be indicated.

Suggested Readings

Adamo PF, Adams WM, Steinberg H. Granulomatous meningoencephalitis in dogs. *Compend Contin Educ Vet*. 2007;29:679.

Cizinauskas S, Jaggy A, Tipold A. Long-term treatment of dogs with steroid-responsive meningitis-arteritis: clinical, laboratory and therapeutic results. *J Small Anim Pract*. 2000;41:295.

Crookshanks JL, et al. Treatment of canine pediatric *Neospora caninum* myositis following immunohistochemical identification of tachyzoites in muscle biopsies. *Can Vet J*. 2007;48:506.

Dubey JP, Lappin MR. Toxoplasmosis and neosporosis. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 3rd ed. St Louis: Elsevier; 2006.

Greene CE, Appel MJ. Canine distemper. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 3rd ed. St Louis: Elsevier; 2006.

Greene CE, Rupprecht CE. Rabies and other *Lyssavirus* infections. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 3rd ed. St Louis: Elsevier; 2006.

Higginbotham MJ, Kent M, Glass EN. Noninfectious inflammatory central nervous system diseases in dogs. *Compend Contin Educ Vet*. 2007;29:488.

Kent M. Bacterial infections of the central nervous system. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 3rd ed. St Louis: Elsevier; 2006.

Lowrie M, et al. Steroid responsive meningitis arteritis: a prospective study of potential disease markers, prednisolone treatment, and long-term outcome in 20 dogs (2006-8). *J Vet Intern Med*. 2009;23:862.

Munana KR. Head tilt and nystagmus. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2004.

Radaelli ST, Platt SR. Bacterial meningoencephalomyelitis in dogs: a retrospective study of 23 cases (1990-1999). *J Vet Intern Med*. 2002;16:159.

Syke JE, et al. Clinical signs, imaging features, neuropathology, and outcome in cats and dogs with central nervous system cryptococcosis from California. *J Vet Intern Med*. 2010;24:1427.

Talarico LR, Schatzberg SJ. Idiopathic granulomatous and necrotizing inflammatory disorders of the canine nervous system: a review and future perspectives. *J Small Anim Pract*. 2009;51:138.

Windsor RC, et al. Cerebrospinal eosinophilia in dogs. *J Vet Intern Med*. 2009;23:275.

CHAPTER 65

Disorders of the Spinal Cord



GENERAL CONSIDERATIONS

Spinal cord disorders can be caused by anomalies, degeneration, neoplasia, inflammatory conditions, external trauma, internal trauma from disk extrusion, hemorrhage, or infarction (Box 65.1). Clinical signs depend on lesion location and severity and frequently include focal or generalized pain, paresis, ataxia, paralysis, and occasionally an inability to urinate. Examination of the signalment, history, onset, and progression of the disease can provide valuable information necessary for establishing a likely cause. Neoplasia and type II intervertebral disk (IVD) protrusion occur most commonly in middle-aged and older dogs. Congenital malformations are present at birth, generally do not progress, and are often breed-associated. Type I disk extrusions primarily occur in chondrodystrophic small breeds of dogs, whereas Cavalier King Charles Spaniels are predisposed to Chiari-like malformations and syringomyelia. External trauma, traumatic IVD extrusions, vascular disorders (hemorrhage or infarction), and most type I IVD extrusions are associated with peracute or acute nonprogressive signs of spinal cord dysfunction (see Box 65.1). Infectious and noninfectious inflammatory disorders typically have a subacute and progressive course, whereas tumors and degenerative processes are most often slowly progressive.

LOCALIZING SPINAL CORD LESIONS

Once a complete neurologic examination has been performed and gait, postural reactions, proprioception, strength, muscle tone, spinal reflexes, and painfulness have all been assessed, it is possible to identify the location of a spinal cord lesion. Functionally, the spinal cord can be divided into four regions: the cranial cervical spinal cord (C1-C5), cervical intumescence (C6-T2), thoracolumbar region (T3-L3), and lumbar intumescence (L4-S3). Signs allowing localization of spinal cord lesion to each site are listed in Table 65.1.

C1-C5 LESIONS

Lesions of the cranial cervical spinal cord cause upper motor neuron (UMN) paresis in all four limbs. Because the spinal cord pathways to the rear limbs are longer and more superficially located in the cord than those to the forelimbs, rear limb UMN deficits are almost always worse than forelimb deficits in patients with mild compressive lesions of the C1-C5 spinal cord segments. Most lesions of the C1-C5 spinal cord cause a classical UMN gait in all four limbs, including a long-strided ataxic gait, postural reaction deficits, decreased proprioception (slow knuckling, toe scuffing), increased extensor muscle tone, and normal to increased spinal reflexes in all four limbs. Animals with C1-C5 lesions often exhibit overextension of their thoracic limbs as they move, resulting in an overreaching or floating forelimb gait that should not be confused with the hypermetria associated with cerebellar disease, where each limb is overflexed on protraction. Unilateral lesions of the cervical cord cause hemiparesis and UMN signs affecting the ipsilateral rear limbs and forelimbs. Cervical lesions are rarely severe enough to cause loss of deep pain sensation; such a severe injury would be expected to cause complete respiratory paralysis and rapid death. Central cord lesions (e.g., intramedullary neoplasia, infarcts, hydromyelia) in the C1-C5 region occasionally cause severe UMN deficits in the forelimbs but nearly normal rear limbs (central cord syndrome) because the more superficially located white matter tracts to the rear limbs are spared, whereas the more centrally located ascending and descending tracts to the forelimbs are affected.

C6-T2 LESIONS

Spinal cord lesions between segments C6 and T2 result in paresis of all four limbs and GP ataxia in the rear limbs. The C6-T2 spinal cord segments contain the cell bodies of the nerves of the brachial plexus, so lower motor neuron (LMN) signs of weakness, a short-strided "choppy" gait, rapid muscle atrophy, and hyporeflexia predominate in the forelimbs. The ascending and descending spinal cord tracts to the pelvic limbs pass through this region, so C6-T2 lesions cause UMN deficits in the rear limbs including ataxia, a long stride, loss

BOX 65.1

Common Spinal Cord Disorders

Acute (Minutes to Hours)

External trauma
Hemorrhage/vascular infarction
Type I intervertebral disk extrusion
Traumatic disk extrusion
Fibrocartilaginous embolism
Atlantoaxial subluxation*

Subacute Progressive (Days to Weeks)

Infectious meningoencephalomyelitis
Noninfectious inflammatory disease
  Granulomatous meningoencephalitis (GME), others
  Aseptic meningitis (usually painful, normal neurologic exam)
Diskospondylitis (usually painful, normal neurologic exam)
Type I intervertebral disk extrusion*
Rapidly growing tumors (lymphoma, metastatic neoplasia)

Chronic Progressive (Months)

Neoplasia
Spinal articular cysts
Spinal arachnoid diverticula
Type II intervertebral disk protrusion
Degenerative myelopathy
Cauda equina syndrome
Cervical spondylomyelopathy

Progressive in Young Animals

Neuronal abiotrophies and degenerations
Metabolic storage diseases
Atlantoaxial instability
Syringomyelia/hydromyelia

Congenital (Constant)

Spina bifida
Caudal dysgenesis of Manx cats
Spinal dysraphism

**Atypical onset/progression for this disorder.*

TABLE 65.1

Neurologic Findings in Dogs and Cats With Spinal Cord Lesions

SITE OF LESION	THORACIC LIMBS	PELVIC LIMBS
C1-C5	UMN	UMN
C6-T2	LMN	UMN
T3-L3	Normal	UMN
L4-S3	Normal	LMN

LMN, Lower motor neuron signs; *UMN,* upper motor neuron signs.

of proprioception, delayed postural reactions, increased extensor muscle tone, and normal to increased reflexes. When C6-T2 lesions are unilateral, ipsilateral forelimbs and rear limbs will be affected. Horner syndrome may be seen if the T1-T2 spinal cord segments or nerve roots are involved (see Chapter 61), and the ipsilateral cutaneous trunci reflex may be lost if the C8-T1 spinal cord segments or nerve roots are damaged. Because the phrenic nerve originates at C5-C7, a severe lesion in this region could also cause diaphragmatic paralysis. When C6-T2 lesions affect only the central cord, the superficially located long tracts to the rear limbs are spared, so the forelimb LMN signs may be much more pronounced than the rear limb UMN signs.

T3-L3 LESIONS

Spinal cord lesions between segments T3 and L3 cause UMN paresis and ataxia affecting the rear limbs (see Table 65.1), but forelimbs are normal. Examination of the rear limbs reveals a long uncoordinated stride, loss of proprioception, delayed postural reactions, increased extensor muscle tone, and normal to increased reflexes. As compressive spinal cord lesions in this region become more severe, a predictable worsening of neurologic deficits (Fig. 65.1) and gait deterioration follow. With severe focal lesions in this region, there may be a loss of superficial sensation and the cutaneous trunci reflex caudal to the lesion site. Identification of the spinal location caudal to which the cutaneous trunci reflex (panniculus) disappears and demonstration of a focal site of hyperpathia (painfulness) can greatly assist in the localization of severe T3-L3 spinal cord lesions.

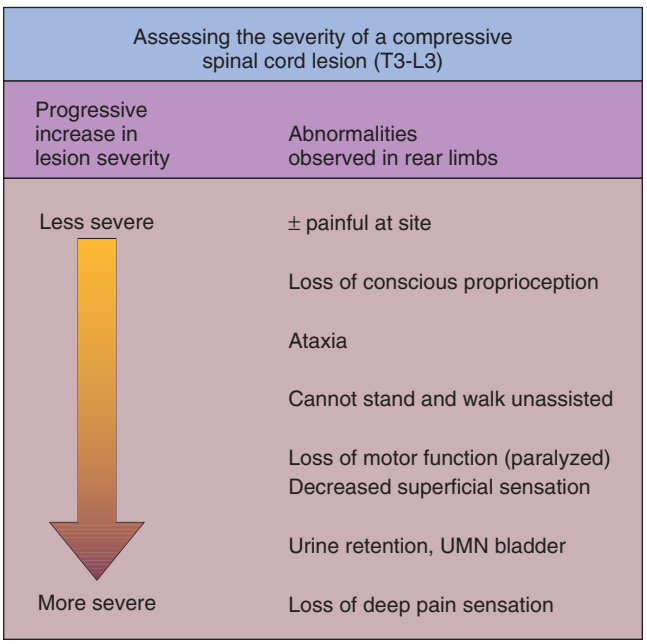


FIG 65.1
Assessing severity of a compressive lesion of the T3-L3 spinal cord.

L4-S3 LESIONS

Lesions affecting the lumbar intumescence cause LMN signs in the rear limbs. Severe weakness, muscle atrophy, and loss of reflexes are apparent in the rear limbs, whereas the forelimbs are normal. Animals that can still walk exhibit a weak, short-strided rear limb gait. Bladder dysfunction and paresis or paralysis of the anal sphincter and tail are also common with severe lesions affecting the sacral cord segments. Lesions that compress the lumbar, sacral, and caudal nerve roots as they extend caudally from the end of the spinal cord within the vertebral canal (cauda equina) typically cause pain at the site and, when severe, cause LMN dysfunction as well.

DIAGNOSTIC APPROACH

Lesions should be localized to a spinal cord region on the basis of the neurologic examination. It is important to recognize that spinal cord segments do not correlate directly with vertebral location in the dog and cat (Table 65.2; Fig. 65.2). The C6-T2 spinal cord segments of the cervical intumescence are located within vertebrae C4-T2. The L4-S3 spinal cord segments of the lumbar intumescence are located within vertebrae L3-L5 in dogs and L3-L6 in cats. The spinal cord is shorter than the vertebral canal, with the caudal segments ending at approximately the L6 vertebra in dogs and the L7 vertebra in cats. The nerve roots arising from the L7, sacral, and caudal spinal cord segments (cauda equina) course caudally within the vertebral canal to their site of exit immediately caudal to the vertebra of the same number and are susceptible to compressive damage in the lumbosacral region (see discussion of cauda equina syndrome).

Once spinal cord lesions are localized to the proper regional spinal cord segments and vertebrae, imaging and further diagnostic testing will usually be necessary to establish a diagnosis. Radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) of the vertebral bodies that house the affected spinal cord segments may be useful. Vertebral radiographs can be used to identify vertebral

TABLE 65.2

Localization of Spinal Cord Segments Within Vertebral Bodies in the Dog

SPINAL CORD SEGMENT	VERTEBRAL BODY
C1-C5	C1-C4
C6-T2	C4-T2
T3-L3	T2-L3
L4	L3-L4
L5, L6, L7	L4-L5
S1-S3	L5
Caudal	L6-L7
Cauda equina spinal nerves	L5-sacrum

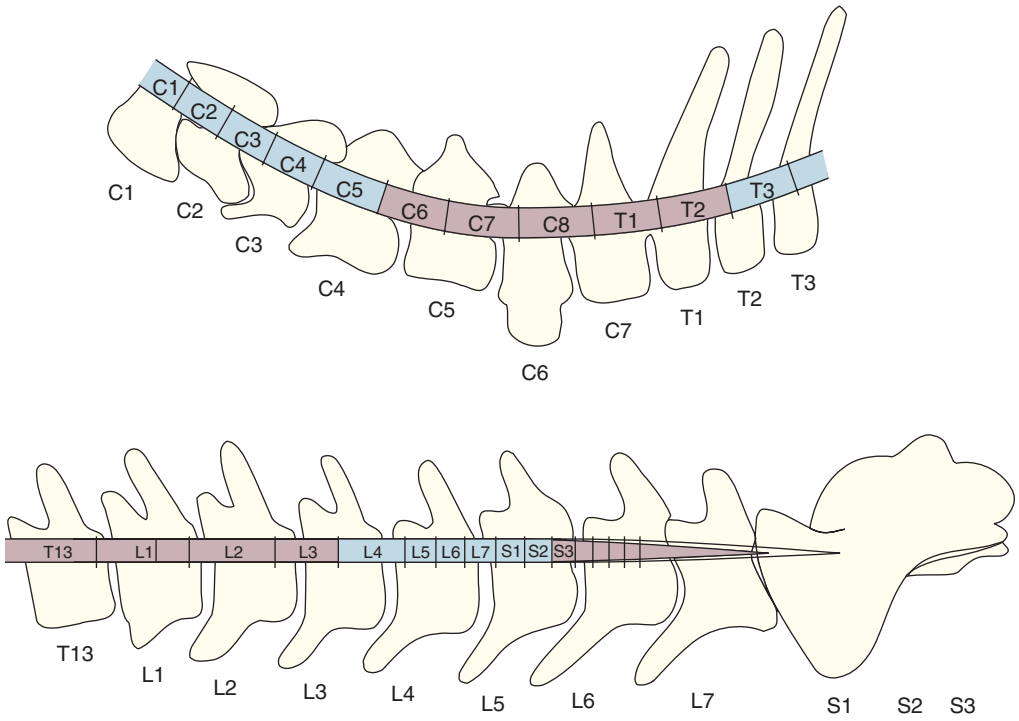


FIG 65.2
Position of spinal cord segments within the cervical, cranial thoracic, and lumbar vertebrae. Cervical intumescence (C6-T2) and lumbar intumescence (L4-S3) are highlighted.

malformations, subluxation caused by trauma, diskospondylitis, vertebral fractures, intervertebral disk disease (IVDD), and lytic vertebral neoplasms. CT is a good imaging modality for all of these same lesions affecting bone and for identification and localization of calcified IVD extrusions. Myelography can be used to localize compressive spinal cord lesions either alone or with CT. MR imaging is the best tool for evaluating the spinal cord as it allows identification of compressive, expansive, or infiltrative lesions within the spinal canal and allows assessment of spinal cord parenchyma. Cerebrospinal fluid (CSF) analysis can be performed to look for evidence of neoplasia or inflammation. When infectious or neoplastic disorders are considered as differentials for a myelopathy, systemic screening tests such as thoracic and abdominal radiographs, abdominal ultrasound, lymph node aspirates, complete ophthalmic examination, infectious disease serology, and tissue biopsies should be considered to help determine the diagnosis. Rarely, surgical exploration or biopsy of the spinal cord at the affected site will be required to achieve a diagnosis, gauge prognosis, and recommend treatment.

PERACUTE OR ACUTE SPINAL CORD DYSFUNCTION

TRAUMA

Traumatic injuries to the spinal canal are common, with fractures and luxations of the spine and traumatic disk extrusion being the most frequent consequences. Severe spinal cord bruising and edema can occur secondary to trauma, even without disruption of the bony spinal canal.

Clinical Features

Clinical signs associated with spinal trauma are acute and generally nonprogressive. Animals are usually in pain, and other evidence of trauma (e.g., shock, lacerations, abrasions, fractures) may be present. Neurologic findings depend on lesion location and severity. Neurologic examination should determine the location and extent of the spinal injury. Excessive manipulation or rotation of the animal should be avoided until the vertebral column is determined to be stable.

Diagnosis

A diagnosis of trauma is readily made on the basis of the history and physical examination findings. A thorough and rapid physical examination is important to determine whether the animal has life-threatening nonneurologic injuries that should be addressed immediately. Concurrent problems may include shock, pneumothorax, pulmonary contusions, diaphragmatic rupture, ruptured biliary system, ruptured bladder, orthopedic injuries, and head trauma. Concern that the animal may have vertebral column instability warrants use of a stretcher or board to restrain, examine, and transport the dog or cat in lateral recumbency.

The neurologic examination can be performed with the animal in lateral recumbency but will be limited to evaluation of mental status, cranial nerves, posture, muscle tone, voluntary movement, spinal reflexes, the cutaneous trunci reflex, and pain perception. Dogs with severe thoracic spinal cord lesions may exhibit the Schiff-Sherrington posture (see Fig. 58.8). The most important prognostic indicator after spinal trauma is the presence or absence of nociception or deep pain sensation. If deep pain is absent caudal to a traumatic thoracolumbar spinal cord lesion, the prognosis for functional recovery is poor, and, regardless of treatment, about 20% of dogs will develop ascending descending myelomalacia (see p. 1142) in the hours or days after injury.

The neurologic examination allows determination of the neuroanatomic site of the lesion. Survey radiographs or CT can then be used to more specifically localize the lesion, assess the degree of vertebral damage and displacement, and aid in prognosis. Manipulation or twisting of unstable areas of the spine must be avoided during imaging. If the animal is recumbent or restrained on a board, lateral and cross-table ventrodorsal radiographs allow assessment for the presence or absence of fractures or an unstable vertebral column. CT is a much more accurate means to assess vertebral damage than radiography, whereas MRI is superior for evaluating spinal cord parenchyma.

The *entire* spine should be assessed. Most spinal fractures and luxations occur at the junction of mobile and immobile regions of the spine, such as the lumbosacral junction or the thoracolumbar, cervicothoracic, atlantoaxial, or atlantooccipital regions. Multiple fractures occur in some 10% of trauma patients and are easily missed. Neurologic signs caused by LMN lesions at an intumescence can mask UMN lesions located more cranially in the spinal cord, so imaging and clinical evaluation of all spinal regions are important. When lesions identified using imaging do not correspond completely with clinical neuroanatomic localization, further investigation is required.

Various classification schemes exist to determine the stability of vertebral injuries and the need for surgery. The vertebral body can be divided into three compartments and each assessed using radiographs or CT for damage (Fig. 65.3). When two of the three compartments are damaged or displaced, the fracture is considered unstable. Unstable fractures generally require surgical intervention or splinting, whereas stable fractures without significant ongoing spinal cord compression can usually be managed conservatively. Splints are most effective when deep pain sensation is present, ventral and middle compartments are intact, and associated soft tissue injuries are minimal. Most dogs with cervical or lumbosacral injury are managed nonsurgically unless the patient deteriorates neurologically or remains in a great deal of pain 72 hours after injury, which suggests nerve root entrapment. Surgery is preferred for unstable thoracic and lumbar spinal injuries.

Treatment

Primary treatment of animals with acute spinal injury involves evaluation for and treatment of other life-threatening

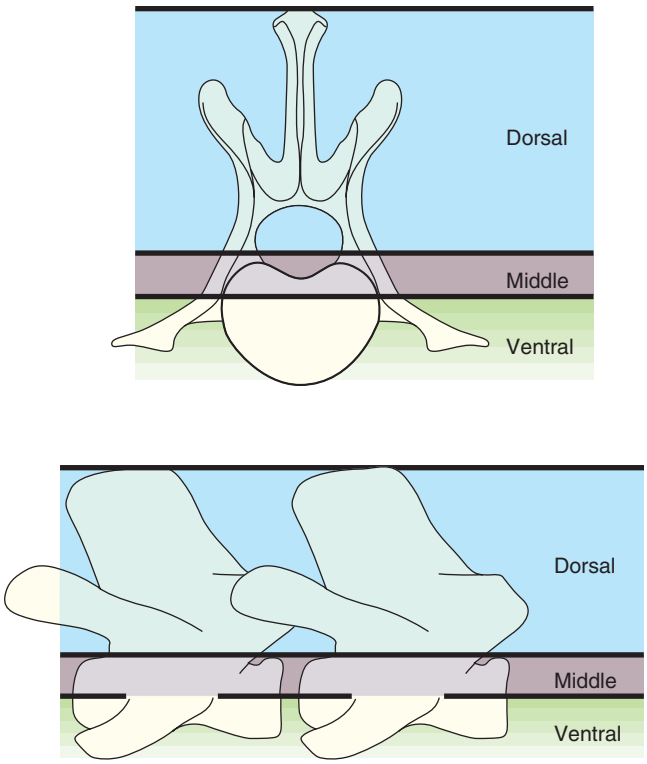


FIG 65.3
Illustration of the three-compartment model for radiographic evaluation of spinal fractures. Dorsal compartment includes articular facets, laminae, pedicles, spinous processes, and supporting ligaments. Middle compartment contains the dorsal longitudinal ligament, dorsal annulus, and the floor of the spinal canal. Ventral compartment consists of the remainder of the vertebral body and the annulus, nucleus pulposus, and ventral longitudinal ligament. When two or three of the compartments are damaged or displaced, surgical stabilization is indicated.

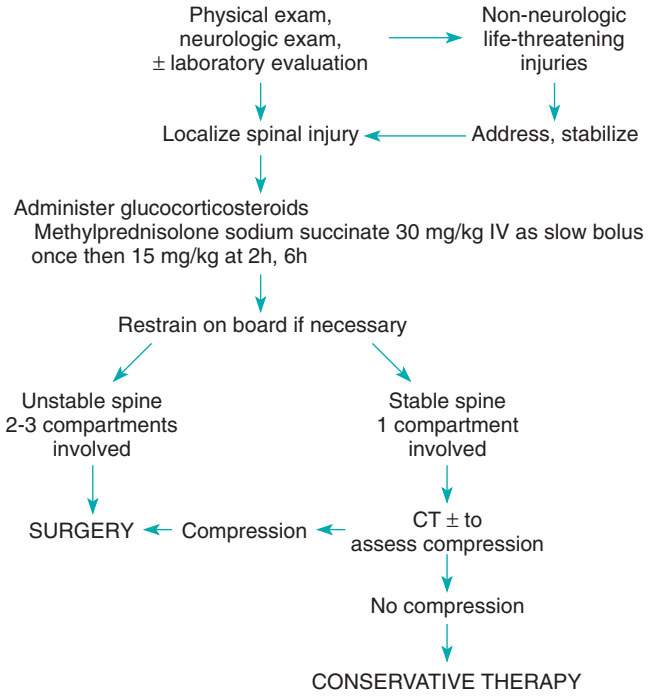


FIG 65.4
Algorithm for management of acute spinal trauma.

injuries and maintenance of patient blood pressure, perfusion, and oxygenation. There is weak experimental evidence that intravenous (IV) administration of methylprednisolone sodium succinate (MPSS), a highly soluble corticosteroid with neuroprotective effects exerted primarily by its actions as a free-radical scavenger, within 8 hours of trauma may be beneficial (Fig. 65.4). Unfortunately, a few dogs treated according to this protocol suffer from serious gastrointestinal complications. Adverse effects should be monitored and may be decreased by concurrent administration of an H_2-receptor blocker (oral [PO] or IV ranitidine, 2 mg/kg q8h; or famotidine, 0.5 mg/kg PO or IV q24h), a proton pump inhibitor (omeprazole, 0.7-1.5 mg/kg/day) or a synthetic prostaglandin E_1 analog (misoprostol, 2-5 µg/kg PO q8h), and a mucosal protectant (sucralfate, 0.25-1 g PO q8h; see Chapter 28).

Intensive nursing care is critically important in dogs and cats managed conservatively or surgically. Narcotic analgesics may be administered as needed (Table 65.3). Thickly padded, clean, dry cages and frequent turning of the patient will help prevent pressure sores. All impaired limbs should be moved repeatedly through a full range of motion many times each day. Maintenance of an indwelling urinary catheter ensures a dry animal but may increase the risk of urinary tract infection, particularly when kept in place for longer than 3 days. When long-term care is necessary, the bladder should be gently expressed or catheterized and emptied four to six times daily and urinary tract infections treated as they occur. In animals with UMN bladders (see Chapter 58) or those with urethral spasm, medical therapy (phenoxybenzamine, 0.25-0.5 mg/kg PO q8h, and diazepam, 0.5 mg/kg q8h) may help relax the urethral sphincter, making bladder expression easier and less traumatic. When an animal starts to regain voluntary motion in the limbs, physical therapy is increased; hydrotherapy or swimming stimulates voluntary movement, improves circulation to the limbs, and cleans the skin.

TABLE 65.3

Narcotic Analgesics Used to Treat Spinal Pain in Dogs

DRUG	DOSAGE
Oxymorphone	0.05 mg/kg IM
Morphine	0.3-2.2 mg/kg, SC or IM
Butorphanol	0.4-0.8 mg/kg SC
Buprenorphine	0.02-0.06 mg/kg, IM or SC

IM, Intramuscular; *SC,* subcutaneous.

Prognosis

Prognosis for recovery depends on the site and severity of injury. Unstable cervical vertebral fractures are associated with very high mortality at the time of trauma and also in the perioperative period. Prognosis for recovery is good if affected animals do not die acutely from respiratory dysfunction. Animals with thoracic and lumbar spinal cord injury and intact voluntary motion have a good prognosis for return of full function. Animals that are paralyzed but retain deep pain and normal bladder function have a fair prognosis for recovery, although they may have residual neurologic deficits. Animals presenting after spinal trauma with no deep pain sensation rarely recover. Lesions of the white matter producing strictly UMN signs may have a better prognosis for full recovery than lesions affecting clinically important LMNs at the cervical or lumbar intumescence. In any animal with paralysis caused by a spinal cord injury, if no signs of improvement are evident by 21 days after injury, the prognosis for recovery is poor.

HEMORRHAGE/INFARCTION

Nontraumatic hemorrhage into the spinal canal causing acute neurologic deficits and sometimes pain (i.e., hyperesthesia) has been recognized in young dogs with hemophilia A, dogs of any age with von Willebrand disease, dogs and cats with acquired bleeding disorders (i.e., warfarin intoxication, thrombocytopenia, disseminated intravascular coagulation), dogs with vascular anomalies (i.e., aneurysms, arteriovenous fistulas), and dogs and cats with primary or metastatic spinal neoplasia that bleeds (i.e., lymphoma, hemangiosarcoma). Signs occur acutely and are minimally progressive, with neurologic signs reflecting the site and severity of spinal cord damage or compression. Bleeding into the subarachnoid space can cause inflammation (meningitis) and pain. Antemortem diagnosis usually requires advanced diagnostic imaging (i.e., MRI), although identification of a systemic bleeding disorder or neoplasia can suggest the diagnosis. Treatment should be initiated to resolve the cause of bleeding, and surgical decompression of the spinal cord will rarely be required.

Spinal cord infarction by a blood clot is a rare cause of peracute neurologic dysfunction in dogs and cats. Signs are referable to the site and severity of the vascular compromise. Blood stasis, endothelial irregularity, hypercoagulability, and impaired fibrinolysis are all known predisposing factors for thromboembolism (see Chapter 12). Cardiomyopathy, hyperadrenocorticism, protein-losing nephropathy, immune-mediated hemolytic anemia, heartworm disease, vasculitis, and disseminated intravascular coagulation have all been associated with an increased risk of systemic thrombosis and can occasionally result in regional spinal cord infarction. Treatment consists of general supportive care and anticoagulant medications to decrease the risk of further infarction, but antemortem definitive diagnosis is difficult and prognosis for recovery is poor.

ACUTE INTERVERTEBRAL DISK EXTRUSION

The intervertebral disks are composed of an outer fibrous layer (annulus fibrosus) and a gelatinous center (nucleus pulposus). With normal aging the nucleus is gradually replaced by fibrocartilage. In some dogs, particularly the chondrodystrophoid breeds, the nucleus matrix degenerates, dehydrates, and mineralizes, making these dogs prone to acute disk rupture. Acute extrusion of mineralized nucleus pulposus into the spinal canal through the dorsal annulus causing bruising or compression of the spinal cord is classified as a Hansen type I IVD extrusion (Fig. 65.5). This type

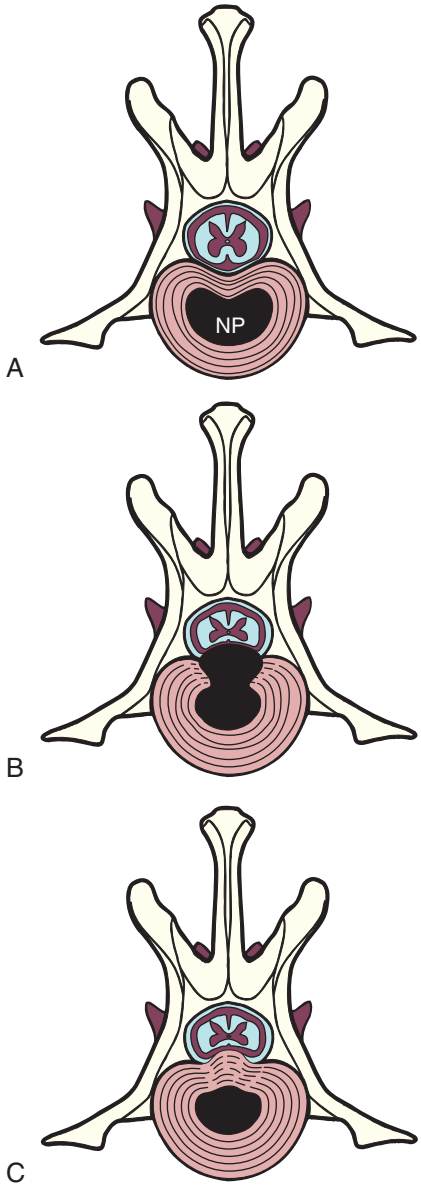


FIG 65.5
(A) Normal relationship between the intervertebral disk and spinal cord. **(B)** Hansen type I disk extrusion, wherein the NP herniated into the vertebral canal through a ruptured annulus fibrosus. **(C)** Hansen type II disk protrusion, with bulging of the thickened annulus into the vertebral canal. *NP,* Nucleus pulposus.

of disk injury is most common in small-breed dogs like the Dachshund, Toy Poodle, Pekingese, Beagle, Welsh Corgi, Lhasa Apso, Shih Tzu, Chihuahua, and Cocker Spaniel, with a peak incidence between 3 and 6 years of age. Dachshunds are the breed most often presented for thoracolumbar IVD extrusions, whereas cervical IVD extrusions are most common in Beagles. Acute type I IVD extrusions also occasionally occur in middle-aged and older large-breed dogs, particularly in Basset Hounds, Labrador Retrievers, Dalmatians, Shar Peis, Border Collies, Rottweilers, Doberman Pinschers with caudal cervical spondylomyelopathy (CSM), and German Shepherd dogs. Intervertebral disk extrusion is a rare cause of clinically evident spinal cord compression in the cat, occurring in older cats (mean age, 9.8 years) and typically affecting the lower thoracic and lumbar regions (most commonly, L4/L5).

Clinical Features

Pain is a prominent feature in most dogs with acute IVD extrusion. The extruded material compresses the highly innervated nerve roots and meninges, causing pain. Some dogs with acute IVD extrusion are presented with spinal pain and no accompanying neurologic deficits. Others suffer concussive or compressive injury to the spinal cord from the disk extrusion and are presented with varying degrees of spinal cord injury. Clinical signs depend on the location of the spinal injury, severity of cord bruising, and degree of spinal cord compression.

Cervical disk extrusions (C1-C5) most commonly cause neck pain without associated neurologic deficits, even when large masses of disk material extrude into the spinal canal. This is because the vertebral canal in the cervical region has a very wide diameter with space around the cord, making significant spinal cord compression uncommon. Affected dogs guard their neck from movement and may vocalize when they shift position. Many affected dogs will exhibit root signature—limping on one forelimb and holding it up when standing (Fig. 65.6) in response to muscle spasm. If significant spinal cord compression does occur in the cervical region, UMN signs will be seen in all four legs.

Acute disk extrusion in the thoracolumbar (T3-L3) region also causes pain, but there is less room in the vertebral canal around the spinal cord in this region, so T3-L3 disk extrusions often cause significant spinal cord compression as well as back pain. Mildly affected dogs may be neurologically normal but stand with an arched back and exhibit pain on movement, spinal palpation, or being picked up. The severity of neurologic signs can be related to the force of disk extrusion and the extent of cord bruising, but in most cases there will be a typical progression of UMN signs in the pelvic limbs as the degree of T3-L3 spinal cord compression worsens (see Fig. 65.1). Proprioception is lost first, then the ability to rise and walk, then the ability to voluntarily move the rear legs, then bladder control, followed by the ability to feel deep pain. Most IVD extrusions in the T3-L3 region occur at the T11/12, T12/13, T13/L1, and L1/2 sites. Cranial thoracic IVD extrusions are relatively uncommon owing to dorsal stabilization by the intercapital ligaments, but they do occasionally occur, particularly in German Shepherd dogs and Cocker Spaniels. Disk extrusion in the lower lumbar region between the L3/4 and L6/7 disks is less common (10%-15% of dogs) than T3-L3 extrusions, damaging the spinal cord at the lumbar intumescence and resulting in LMN signs. The neurologic signs that occur with spinal cord compression by type I IVD extrusions are usually symmetric, although lateralized disk extrusions can result in asymmetric signs.



FIG 65.6
Adult Beagle with neck and shoulder pain secondary to cervical intervertebral disk prolapse. Lifting of the limb has been referred to as *root signature*.

Diagnostic Approach

Acute IVD extrusion should be suspected as the cause of neurologic dysfunction based upon the signalment, history, physical examination, and neurologic findings. Neurologic examination and detection of a specific area of spinal pain are used to localize the lesion to a particular region of the spinal cord. Animals with IVD extrusion should have no systemic signs of illness (e.g., fever, weight loss) and no specific neurologic abnormalities suggesting intracranial disease. Acute neurologic dysfunction caused by IVD extrusion must be distinguished from fracture/luxation, hemorrhage, or fibrocartilaginous embolism (FCE) through clinical findings and testing.

The amount of workup recommended at the time of presentation will vary. When the diagnosis is fairly certain based upon signalment and history, and clinical findings and neurologic assessment suggest that nonsurgical treatment is warranted, medical management can be recommended without further testing or definitive diagnosis. When clinical findings, history, or signalment make acute IVD extrusion a less likely diagnosis, screening radiographs or CT are indicated. Spinal radiographs can be taken in an awake animal

to look for characteristic features of disk disease and to rule out other diseases (e.g., diskospondylitis, lytic vertebral tumor, fracture, atlantoaxial luxation).

Radiographic observation of calcified disks confirms the presence of generalized IVDD, but, unless there is dorsal displacement of mineralized disk material into the spinal canal, this does not necessarily implicate the disk extrusion as the cause of neurologic dysfunction. Radiographic changes consistent with extrusion of a disk in the thoracolumbar region include a narrowed or wedged disk space, a small or cloudy intervertebral foramen ("horse's head"), narrowing of the facetal joints, and a calcified density in the spinal canal above the involved disk (Figs. 65.7 and 65.8). Many dogs with disk extrusion have multiple abnormal sites, however, and radiographs cannot determine which is the active site causing the current problem. Myelography or advanced diagnostic imaging (i.e., CT, MRI) will be required to definitively localize the site of an extruded disk causing spinal cord compression in animals in which surgical treatment is being considered.

Myelography was once the standard imaging modality for diagnosing and localizing acute disk extrusion in dogs, but this has largely been replaced with the less invasive and more diagnostic CT and MRI (Fig. 65.9). Myelography is a good test to demonstrate the site of disk extrusion but does not (without concurrent CT) reliably determine whether more of the disk material is located on the left or right side of the cord—important information for surgical planning. Collection and analysis of CSF should always be recommended before proceeding with a myelogram, because inflammatory CNS disorders (granulomatous meningoencephalitis [GME], others) can be clinically very similar to disk extrusion and can be very difficult to diagnose once CSF has been altered by instilling myelographic contrast material into the subarachnoid space (see discussion of myelography, Chapter 59).

CT can be used as an adjunct to myelography or as the sole diagnostic procedure to demonstrate spinal cord compression by an extruded disk and to eliminate other bone-related reasons for spinal cord signs (fracture, luxation, vertebral lysis). CT is very quick, can often be performed under sedation instead of general anesthesia, and has diagnostic accuracy similar to myelography for diagnosis and localization of calcified extruded disks. CT myelography may be necessary to determine lateralization of IVD herniation when the extruded disk is not calcified or severe spinal cord swelling is present.

MRI is the best diagnostic method for localizing the site and the side of extruded disks with nearly 100% accuracy (Fig. 65.10). MRI also allows evaluation of the cord parenchyma for injury and edema, which may be associated with prognosis for recovery in patients with loss of deep pain sensation. However, MRI is slower than CT, less readily available, and more expensive, requiring general anesthesia.

Treatment Recommendations

Treatment recommendations for dogs with acute IVD extrusion are based on location of the spinal cord injury and severity of signs noted at the time of presentation (Tables 65.4 and 65.5). Treatment options are conservative (medical) and surgical. Surgery should be recommended when decompression will significantly increase the likelihood, speed, and completeness of recovery.

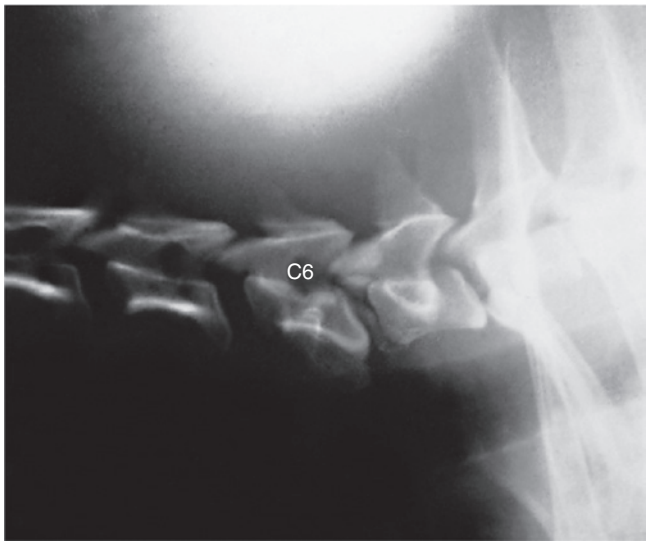


FIG 65.7
Lateral radiograph of the cervical vertebral column of an adult dog showing acute intervertebral disk prolapse at the C6-C7 site. The intervertebral space is narrowed, and a calcified density can be seen in the spinal canal above the disk space.

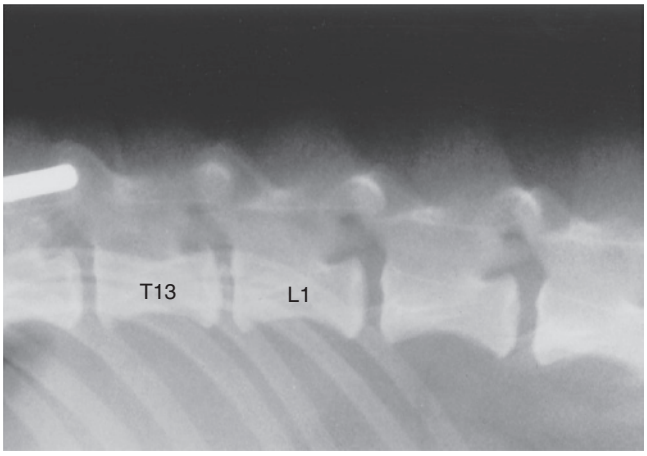


FIG 65.8
Lateral plain radiograph of vertebral column of a 4-year-old Pekingese with acute intervertebral disk prolapse. The intervertebral space between T13 and L1 is narrowed, the intervertebral foramen ("horse's head") is small, and a calcified density can be seen in the spinal canal above the T13-L1 disk space.

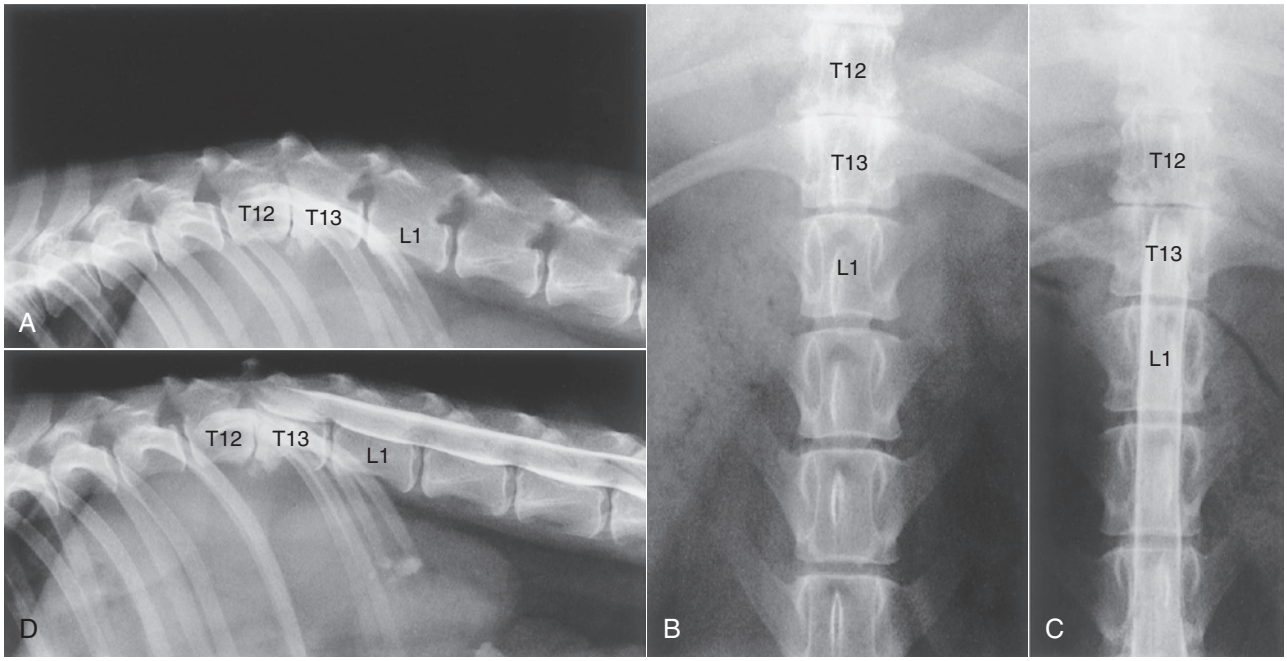


FIG 65.9
Lateral **(A)** and ventrodorsal **(B)** plain radiographs of the vertebral column of an 8-year-old Miniature Schnauzer with acute paralysis after a chronic history of intermittent back pain. Marked collapse of the intervertebral space at T12-T13, a small intervertebral foramen, and clouding of the foramen is evident. The T13-L1 space is also slightly narrowed. **(C)** and **(D)** Myelography confirms the presence of a significant extradural mass at T12-T13 located ventrally and on the right, causing considerable cord compression and displacement. A minimal extradural mass effect also exists at T13-L1, without significant compression. Surgery confirmed spinal cord compression by the disk material at T12-T13.

TABLE 65.4

Classification of Dysfunction and Treatment Recommendations: Canine Cervical Disk Extrusion

GRADE	CLINICAL FINDINGS	TREATMENT
1	Single episode of pain Normal neurologic exam	Cage rest ± analgesics
2	Intractable pain or recurrent pain	Surgical decompression
3	Neurologic deficits ± pain	Surgical decompression

TABLE 65.5

Classification of Dysfunction and Treatment Recommendations: Canine Thoracolumbar Disk Extrusion

CLINICAL FINDINGS	TREATMENT
Single episode of pain Normal neurologic exam	Cage rest ± analgesics
Intractable pain *or* Recurrent pain *or* Deterioration in neurologic status	Surgical decompression
Ataxia, proprioceptive deficits Paraparesis, able to stand and walk	Cage rest ± analgesics
Severe paraparesis, unable to stand and walk	Surgical decompression
Paralyzed	Surgical decompression

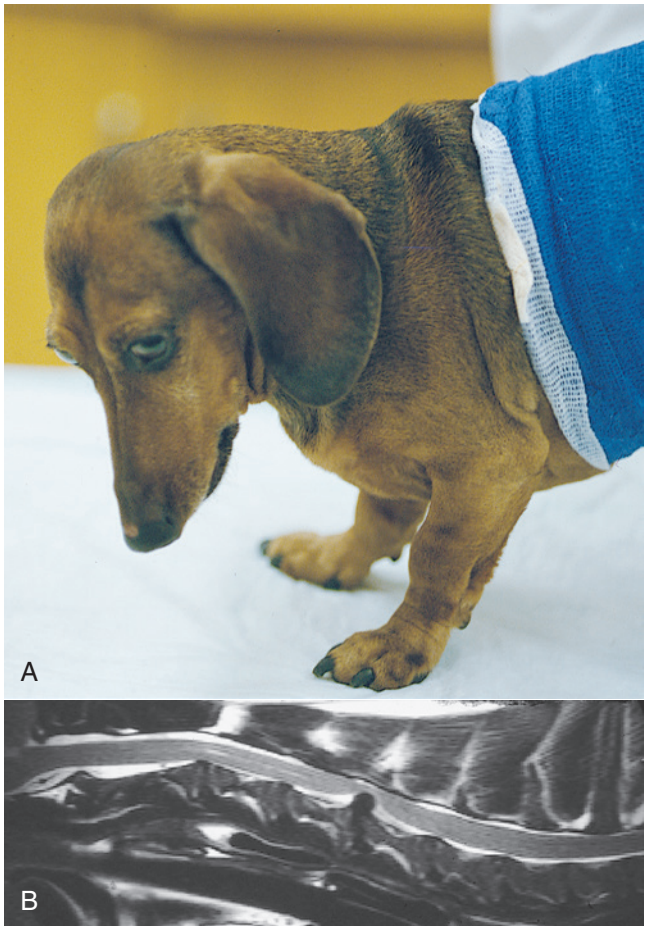


FIG 65.10
(A) This 7-year-old Dachshund had a 3-week history of severe neck pain and mild proprioceptive deficits in the left rear limb. **(B)** Magnetic resonance imaging revealed prolapse of the C3-C4 intervertebral disk, with significant spinal cord compression at that site.

Medical Management

Strict cage rest is the most important part of medical management and must be maintained for a minimum of 4 weeks to allow the annulus to repair. Animals should be kept in a small kennel crate or in the owner's arms at all times except when walked outside with a harness to urinate and defecate. Nonsteroidal antiinflammatory drugs (NSAIDs) or narcotic analgesics (see Table 65.3) can be administered for the first 3 to 5 days if strict confinement is likely to be enforced. Muscle relaxants (methocarbamol, 15-20 mg/kg PO q8h) may help to decrease painful muscle spasms in dogs with cervical disk extrusions, and gabapentin (10-20 mg/kg PO q8h) is sometimes administered when nerve root pain is suspected. Although many veterinarians routinely treat IVD extrusion dogs with glucocorticoids to decrease pain, there is no evidence that this improves the long-term outcome, and there is a high risk of gastrointestinal adverse effects even if low doses are used (prednisone, 0.1-0.2 mg/kg PO bid). Glucocorticoids and NSAIDs should never be administered concurrently. Animals being treated medically must be evaluated frequently for deterioration in neurologic status. After 4 weeks of strict crate confinement, 3 weeks of house confinement with no jumping or running and leash exercise only should be recommended, followed by a gradual increase in monitored exercise and (if necessary) a weight reduction program. Food and water dishes should be elevated and a chest harness should be used instead of a collar in dogs recovering from cervical disk extrusion.

Cervical Disk Extrusion

Approximately 15% of dogs with IVD extrusion have a cervical disk, with the cranial cervical sites (especially C2-3) most frequently affected in small-breed dogs. Dogs with a first episode of acute neck pain and no neurologic deficits are usually managed conservatively with strict cage confinement and analgesics. Most dogs respond at least transiently to conservative medical management, but a few will have intractable pain or recurrent episodes of pain days or weeks later. Dogs with cervical pain that does not resolve with 1 or 2 weeks of conservative management, dogs with severe pain that cannot be controlled short term, dogs with recurrent episodes of neck pain, and dogs that develop even mild UMN paresis or ataxia indicating cervical spinal cord compression should be treated surgically (see Table 65.4). Because the spinal canal is so much larger than the spinal cord in the cervical region, any neurologic evidence of spinal cord compression suggests there is a large amount of disk material within the spinal canal, so recovery will be more complete and rapid if surgery is performed.

When surgery is recommended for cervical IVD extrusion, imaging must be performed to precisely locate the lesion, and surgical decompression is performed using a ventral slot procedure. A small rectangular window of bone is removed from the ventral aspect of the vertebral bodies adjacent to the extruded disk, and the disk material is removed from the spinal canal. Most dogs are in a great deal less pain within 24 to 36 hours after decompressive surgery, and resolution of neurologic deficits usually occurs gradually over 1 to 4 weeks. Exercise should be restricted for 2 weeks, followed by physiotherapy to enhance recovery. The prognosis for full recovery in dogs with neck pain alone or neck pain plus moderately severe tetraparesis is 80% to 90% at 4 weeks. Dogs with paralysis are more likely to have residual deficits, but roughly 80% of these dogs will become ambulatory.

Thoracolumbar Disk Extrusions

Nearly 70% of type I IVD extrusions occur in the T3-L3 region of the spine. Medical management is recommended when there is pain only with no neurologic deficits or when there are mild rear limb neurologic deficits but the dog has good voluntary motion bilaterally and is still able to rise and walk unassisted (see Table 65.5). Dogs should be monitored closely during medical management, because neurologic deterioration or failure to improve within 5 to 7 days should prompt recommendations for surgical intervention. Dogs with thoracolumbar IVD extrusions occasionally have

uncontrollable pain or recurrent episodes of pain that should also prompt a recommendation for surgery.

Surgical treatment is recommended for all patients with thoracolumbar IVD extrusion that are unable to walk at the time of presentation because their rate of recovery will be faster after decompression than after nonsurgical treatment, and the likelihood that they will have residual neurologic deficits is decreased. Surgery may also be recommended in fully ambulatory dogs with less severe spinal cord compression if the owners do not wish to attempt medical treatment or if the neurologic signs or pain do not rapidly resolve with medical therapy.

Whenever surgical treatment is anticipated, preoperative imaging is essential to identify the affected interspace and determine which side to decompress to gain access to disk material. Decompression is usually accomplished through a hemilaminectomy, and disk material is removed from the spinal canal. In addition to surgical decompression, many surgeons recommend concurrent fenestration of the affected site and adjacent high-risk sites (T11-L3) to help decrease the likelihood of subsequent herniations.

Postsurgically, animals must be kept clean and confined. Padded bedding and frequent turning can prevent pressure sores. Complete bladder emptying at least four times daily by manual expression, an indwelling catheter, or intermittent aseptic catheterization is necessary in dogs that have lost bladder function. In dogs with UMN bladders, medical treatment with phenoxybenzamine and diazepam can lower sphincter pressure, facilitating manual expression and attempts by the animal to void. Massage of the limbs and passive physiotherapy, including limb abduction, may help prevent neurogenic atrophy and muscle fibrosis and may lead to a more complete recovery. Towel walking of paraparetic dogs can improve attitude and promote early use of the affected limbs. Once the skin incision has healed, swimming may be instituted to encourage movement. In dogs with a prolonged anticipated recovery period, use of a paraplegic cart can provide a stimulus for recovery (Fig. 65.11). Improvement in neurologic function usually occurs within 1 week of surgery. No improvement after 28 days signals that the prognosis for recovery is poor.

More than 95% of dogs with deep pain perception at the time of evaluation recover fully after effective decompression, with most becoming ambulatory within 14 days after surgery (Table 65.6). Dogs with loss of deep pain perception (grade 5) are very unlikely to recover without surgical intervention, but with rapid decompression (within 12-72 hours), approximately 60% of small-breed dogs and 25% of large-breed dogs will make a functional recovery. If deep pain does not return within 4 weeks, the prognosis for recovery is very poor.

Acute, forceful, IVD extrusions sometimes cause considerable intramedullary hemorrhage and edema as well as spinal cord compression. In approximately 10% of dogs with



FIG 65.11
A paraplegic cart can provide a stimulus for recovery and improve mobility and attitude in paralyzed dogs recovering from thoracolumbar disk surgery.

TABLE 65.6

Results of Treatment for Thoracolumbar Disk Disease

NEUROLOGIC GRADE	CONSERVATIVE % SUCCESS	CONSERVATIVE RECOVERY TIME (WEEKS)	DECOMPRESSION % SUCCESS	DECOMPRESSION RECOVERY TIME (WEEKS)
1 No deficits	>95%	3	>95%	<2
2 Paresis (walking)	84%	6	95%	<2
3 Paresis (not walking)	84%	6	95%	<2
4 Paraplegia	81%	9-12	95%	1-4
5 No deep pain	<10%	—	64%	5-10

thoracolumbar IVD extrusion presenting with complete paralysis and loss of deep pain perception, focal spinal cord damage and swelling result in spinal cord ischemia and progressive myelomalacia of the cord cranial and caudal to the original lesion (i.e., *ascending descending myelomalacia, progressive hemorrhagic malacia*). This condition usually develops within 5 days of the original disk extrusion. Myelomalacia should be suspected when the line demarcating the presence of the cutaneous trunci reflex moves cranially or the patellar and withdrawal reflexes are lost (LMN signs) in the rear limbs of a dog that had UMN paralysis in the rear limbs when first evaluated. Most affected dogs are also very anxious and experience a great deal of pain. When ascending descending myelomalacia is recognized, euthanasia should be recommended; no chance for recovery exists, and most affected dogs will die within a few days of respiratory paralysis.

TRAUMATIC DISK EXTRUSIONS

Exercise or trauma-induced peracute disk extrusions (*Hansen's type III disk extrusion, acute noncompressive nucleus pulposus extrusion: ANNPE*) occur occasionally in dogs without preexisting degenerative disk disease. The sudden explosive rupture of the annulus in these dogs usually occurs during running or jumping or in association with a fall or motor vehicle accident. This results in an acute nucleus pulposus extrusion with neurologic signs caused by spinal cord bruising, hemorrhage, and edema. Predisposed breeds include Border Collies, Labrador Retrievers, Staffordshire Bull Terriers, Sighthounds, and other large-breed athletic dogs. The onset of signs is peracute and associated initially with discomfort, but within 12 to 24 hours there is no site of pain on spinal palpation. Neurologic signs reflect the location and severity of the spinal injury. Asymmetry is common. Spinal radiographs do not reveal evidence of chronic disk degeneration or mineralization, but mild IVD space narrowing is often evident at the site of disk extrusion. Advanced imaging typically reveals a focal area of T2 weighted (T2W) intramedullary spinal cord hyperintensity overlying an IVD space, a reduced volume of the T2W hyperintense nucleus pulposus signal at that site, mild narrowing of the associated disk space, and a variable amount of extradural material in the canal at that site with little or no spinal cord compression. The pathology in these dogs is related to cord bruising and hemorrhage from the force of the disk extrusion without significant spinal cord compression, so surgical decompression is not warranted. Traumatic disk extrusion in older dogs and chondrodystrophic dogs will occasionally (<30%) result in moderate to severe spinal cord compression by extruded disk material requiring surgical decompression so imaging should always be recommended. The recommended treatment for noncompressive traumatic disk extrusion is supportive care and physical therapy. Most dogs that have deep pain sensation will regain the ability to walk within 1 to 4 weeks, but some residual paresis is common. Urinary or fecal incontinence, when present, may take longer to recover from or may be permanent.

FIBROCARTILAGINOUS EMBOLISM

Acute infarction and ischemic necrosis of the spinal cord parenchyma occur when fibrocartilage presumably from the nucleus pulposus of the IVD is embolized into the very small arteries and veins supplying the spinal cord parenchyma and leptomeninges. This causes peracute nonprogressive signs of spinal cord dysfunction affecting any region of the spinal cord and results in paresis or paralysis. The cause of this disorder is unknown. It is most common in medium-sized and large-breed dogs. It has also been described in small-breed dogs, especially the Miniature Schnauzer, and in a few cats. Most affected dogs are young or middle-aged, with the majority of cases between 3 and 7 years of age. A few dogs younger than 1 year of age have been recognized with FCE, especially Irish Wolfhounds. No gender predilection exists.

Clinical Features

The onset of neurologic signs is very sudden. In about half of all cases, FCE occurs immediately after minor trauma or during exertion. Neurologic examination reflects a focal spinal cord lesion, and the deficits observed depend on the region of spinal cord affected and severity of cord involvement. The thoracolumbar cord (causing UMN signs in the rear limbs) and the lumbosacral intumescence (causing LMN signs in the rear limbs) are most often affected. The cervical cord is affected less frequently (10%), but it may be the site most often affected in small-breed dogs. Neurologic dysfunction may be mild or severe. Asymmetry is common, with the right and left sides affected to different degrees. Dogs may cry out as though in pain at the onset of signs, and dogs evaluated within 2 to 6 hours of onset sometimes exhibit focal spinal hyperpathia (i.e., painfulness); however, this resolves quickly, and most affected dogs do not exhibit pain by the time they are brought to a veterinarian, even on manipulation of their spine. The lack of pain and the asymmetry are very helpful in differentiating FCE from other disorders that cause peracute nonprogressive neurologic dysfunction, such as acute type I IVD extrusion and fracture/luxation. FCE typically causes peracute nonprogressive signs, but up to 30% of affected dogs can have some worsening of neurologic signs within minutes to hours of onset.

Diagnosis

FCE is suspected on the basis of signalment, history, and recognition of peracute, nonprogressive, nonpainful spinal cord dysfunction. Spinal radiographs are normal but assist in ruling out diskospondylitis, fractures, lytic vertebral neoplasia, and IVDD. CSF is usually normal, although an increase in protein (especially albumin) concentration may be observed in some (50%) cases, and neutrophil numbers may be slightly increased within the CSF in the first 24 hours after the onset of clinical signs. Myelography or spinal CT may be performed to rule out compressive lesions of the spinal cord for which emergency surgery might be indicated, such as fractures, disk extrusion, and neoplasia. MRI may reveal focal edema and T2W hyperintensity within the spinal



FIG 65.12
This adult Border Collie had an acute onset of lameness, flaccid paresis, decreased sensation, and hyporeflexia in the left rear limb while retrieving a Frisbee. The limb was not painful, and radiographs, cerebrospinal fluid analysis, and myelogram were all normal. A presumptive diagnosis of fibrocartilaginous embolism (FCE) involving the lumbar and sacral spinal cord segments on the left side was made. This dog recovered uneventfully within a 3-week period.

cord parenchyma in severely affected dogs, but mild lesions will not be evident. The location of spinal cord hyperintensity over a vertebral body rather than centered over a disk space helps differentiate FCE from traumatic disk based on MRI. The diagnosis of FCE is typically made on the basis of clinical findings and exclusion of acute compressive spinal cord disorders (Fig. 65.12).

Treatment

Treatment for FCE consists of nonspecific supportive measures, nursing care, and physiotherapy. Most affected dogs are large breeds, making this type of management difficult. In animals brought to the clinician during the first 6 hours of paralysis, it may be reasonable to treat aggressively with one dose of methylprednisolone sodium succinate, as is sometimes recommended for the initial treatment of acute spinal cord trauma, but there is no evidence that this treatment affects outcome (see Fig. 65.4). Cage rest is not required—in fact, early intervention with physiotherapy may help speed recovery. Most clinical improvement takes place within the first 7 to 10 days after the onset of neurologic signs, although it may take 6 to 8 weeks for a complete return to function. If no improvement is seen within 21 days, it is unlikely that the dog or cat will improve.

Prognosis

Recovery depends on the extent and location of spinal cord injury. Most affected dogs (85%) walk within 21 days, but permanent neurologic deficits are common. The prognosis is best for recovery in dogs and cats with UMN signs and intact deep pain sensation. Animals with LMN signs caused by damage at the brachial or lumbosacral intumescence (C6-T2 or L4-S3) are less likely to fully recover. Animals that have lost the ability to perceive painful stimuli in the affected limbs are unlikely to recover the ability to ambulate without assistance.

ATLANTOAXIAL INSTABILITY

Although some dogs with congenital atlantoaxial instability will be presented acutely for neck pain and tetraparesis, many affected dogs have slowly progressive waxing and waning tetraparesis due to repeated cervical spinal cord injury. This condition will be discussed with progressive spinal cord disorders affecting young animals. Traumatic fracture of the dens leading to subluxation can occur in any dog or cat and will result in acute UMN dysfunction in all limbs. Management should be as described for acute spinal trauma.

NEOPLASIA

Neoplasms usually cause neurologic signs by compressing or infiltrating the spinal cord parenchyma. Neoplastic conditions will be discussed in this chapter with chronic progressive spinal cord diseases. It is important to realize, however, that primary or metastatic neoplasia can cause acute nonprogressive neurologic signs as a result of intraparenchymal hemorrhage or lysis of vertebral bones, leading to fracture.

PROGRESSIVE SPINAL CORD DYSFUNCTION

Damage to the spinal cord that progresses over a few days to weeks (subacute) is most often caused by inflammatory (infectious or immune) processes or some type of neoplasia. Degenerative disorders and most cancers generally cause more slowly progressive spinal cord dysfunction. In all patients with progressive spinal cord dysfunction, complete patient evaluation, including systemic evaluation for extraneural disease, should be recommended. The lesion should be localized and ancillary tests performed to reach a diagnosis and determine appropriate treatment.

SUBACUTE PROGRESSIVE DISORDERS

Infectious Inflammatory Disease

Most of the infectious inflammatory diseases discussed in Chapter 64 can result in myelitis (i.e., spinal cord inflammation), leading to progressive neurologic signs suggesting multifocal or focal spinal cord damage. Canine distemper, Rocky Mountain spotted fever, and neosporosis in dogs and feline infectious peritonitis in cats are the infectious disorders most likely to cause spinal cord signs. Systemic evaluation will sometimes reveal the specific diagnosis. MR imaging can help to localize and characterize lesions. CSF analysis is used to confirm that inflammatory disease is present and to test for infectious agents. Additional

diagnostic testing is often necessary to identify an etiology (see Chapter 64).

Noninfectious Inflammatory Disease

Some of the noninfectious inflammatory diseases discussed in Chapter 64 can cause progressive spinal cord signs. Dogs with steroid responsive meningitis-arteritis (SRMA) are typically presented for cervical pain and fever with no neurologic deficits. Neurologic deficits are common with meningoencephalitis of unknown etiology (MUE) or focal or disseminated GME affecting the spinal cord. CSF analysis is necessary to confirm inflammatory myelitis, and additional tests are required to rule out infectious etiologies. See Chapter 64 for more information.

Diskospondylitis

Diskospondylitis is an infection of the intervertebral disks and adjacent cartilaginous vertebral end plates by bacterial or fungal organisms. Hematogenous spread of infection from infected foci in the body is implicated as the cause in most cases, but extension of infection from an infected local site and migration of foreign bodies (grass awns or porcupine quills) to the site occasionally occur. Numerous causative organisms have been isolated, with the most common being *Staphylococcus* spp., *Streptococcus* spp., and *Escherichia coli*. *Brucella canis* is less common but should be tested for because of human health implications. *Actinomyces* spp. are commonly implicated in L2-L4 diskospondylitis caused by migration of inhaled grass awns.

Diskospondylitis occurs most often in young and middle-aged medium- to large-breed dogs. German Shepherd dogs, Labrador Retrievers, Boxers, Rottweilers, and Great Danes may have an increased prevalence of this disorder. Diskospondylitis has also been recognized in juvenile dogs (<6 months), especially after spinal trauma or recovering from parvovirus infection. Diskospondylitis is very rarely diagnosed in cats. Males are affected more often than females in both species.

Clinical Features

Spinal pain is the most common initial clinical sign of diskospondylitis. Palpation of the affected region of the spine usually allows lesion localization. Systemic signs such as fever, anorexia, depression, and weight loss occur in 30% of affected dogs, but hematologic inflammatory changes are rarely observed unless there is concurrent endocarditis or some other systemic infection. Secondary (i.e., reactive) polyarthritis may occur (see Chapter 69), resulting in a generally stiff, stilted gait in some dogs.

Neurologic deficits occur in less than 50% of dogs and cats with diskospondylitis. In chronic or untreated cases, neurologic dysfunction can result from spinal cord compression by proliferating inflammatory tissue, pathologic fracture of lytic vertebrae, or extension of severe inflammation in the bone to the adjacent spinal cord, without any cord compression. Mild paraparesis and proprioceptive deficits are the most common neurologic abnormalities reported.

Diagnosis

The diagnosis of diskospondylitis is suspected after physical examination and confirmed by radiographic examination of the affected vertebrae. Radiographic changes characteristically include narrowing of the disk space, irregularity or lysis of one or both vertebral end plates (especially ventrally), sclerosis at the margins of bone loss, and osseous proliferation of adjacent vertebral bone (Fig. 65.13). The most commonly affected sites are the midthoracic, caudal cervical, thoracolumbar, and lumbosacral spine. It is common for diskospondylitis to affect more than one disk space (Fig. 65.14), so survey radiographs of the entire spine are recommended. Radiographic signs of diskospondylitis may not be apparent for several weeks after the onset of clinical signs. MRI or CT can be used to identify subtle end-plate erosion before radiographically apparent lesions are visible. Ultrasound can also be used to identify diskospondylitis lesions in the cervical or lumbar spine.

Blood culture is the most rewarding noninvasive method of isolating the organism responsible for the vertebral infection, yielding the organism in approximately 35% of cases. Echocardiography and urine culture are routinely recommended to evaluate the cardiac and urogenital systems as potential sources of infection. Percutaneous needle aspiration of the infected disk during general anesthesia using fluoroscopy or ultrasound has been effective in yielding positive

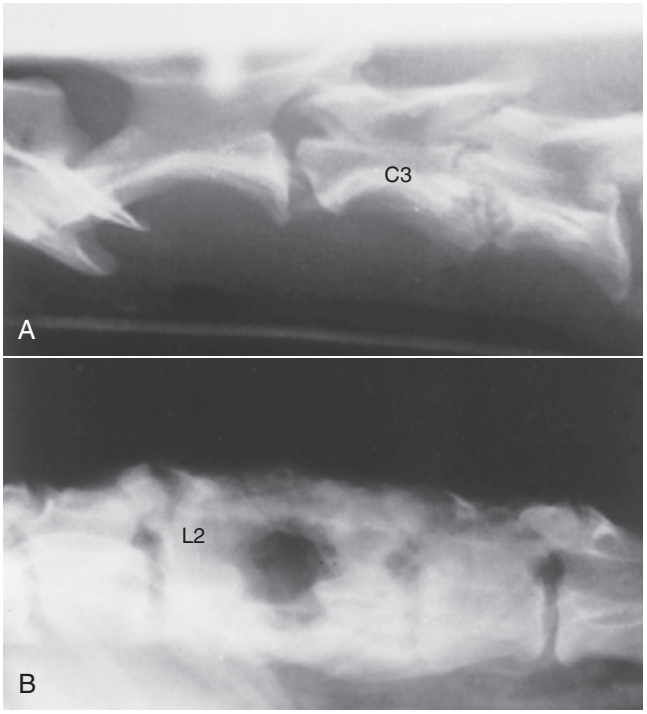


FIG 65.13
(A) Lateral radiograph of cervical vertebral column of an adult dog showing diskospondylitis between the third and fourth cervical vertebrae (C3/C4). **(B)** Lateral radiograph of lumbar vertebral column of an adult Pointer showing severe chronic diskospondylitis between the second and third lumbar vertebrae (L2/L3).

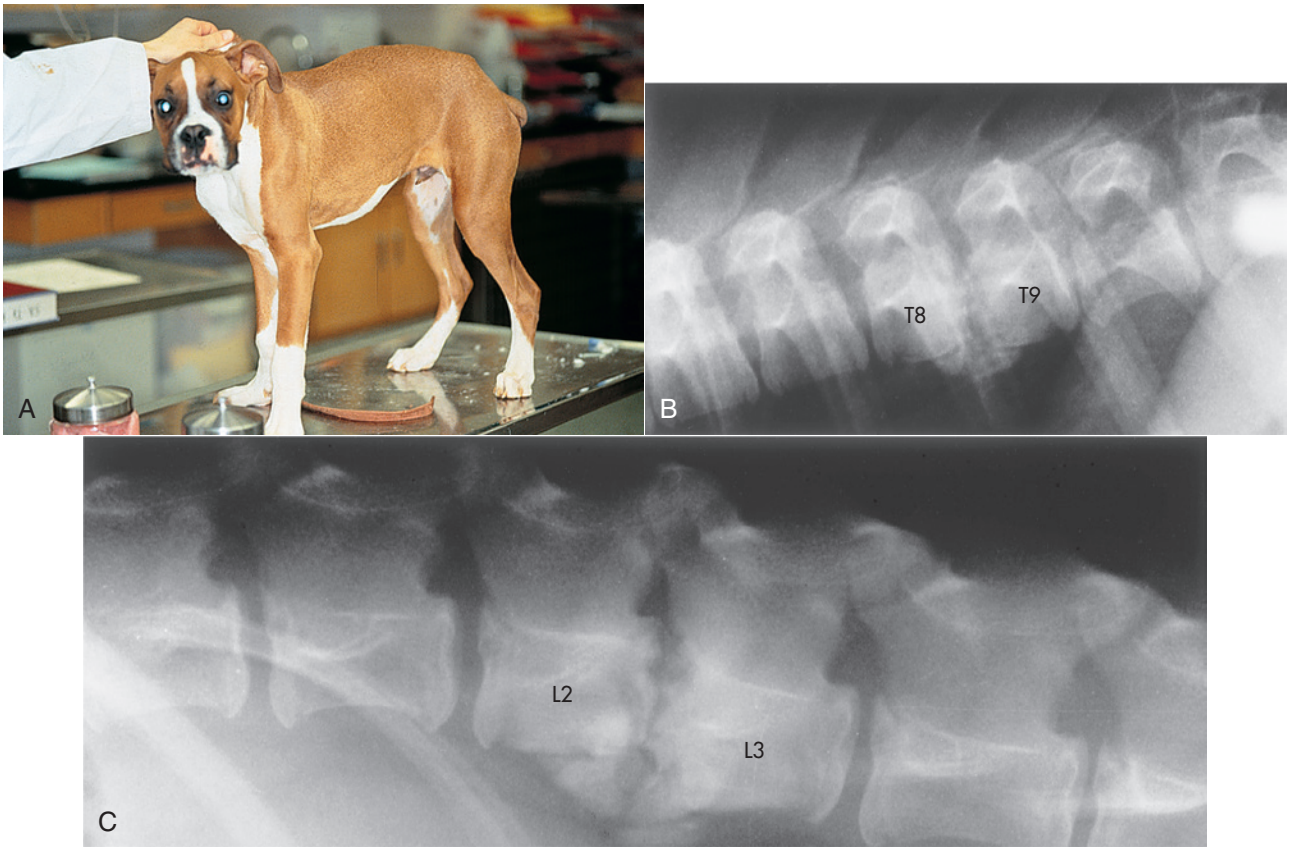


FIG 65.14
(A) A 5-month-old Boxer puppy with back pain resulting from diskospondylitis. **(B)** and **(C)** Lateral spinal radiographs reveal lesions at T8-T9 and L2-L3, with destruction of adjacent vertebral body end plates, collapse of the intervertebral disk spaces, shortening of the vertebral bodies, and new bone production around the ends of the affected vertebral bodies.

cultures in some cases with negative blood and urine cultures, but this is usually reserved for cases in which other culture techniques have yielded negative results and the response to an empirically selected antibiotic is inadequate. A spinal needle is guided into the disk space and a small amount of sterile saline (0.3-0.5 mL) is injected and then aspirated for culture. *Brucella* serology or polymerase chain reaction (PCR) should be considered in all affected dogs because of the public health significance of brucellosis (see Chapter 55), despite its very low prevalence (<10%) in the United States and Canada.

Treatment

Initial treatment of diskospondylitis consists of antibiotics, cage rest, and analgesics. If an organism is isolated, susceptibility testing should guide antibiotic therapy. If an organism is not found, initial treatment attempts should be directed against *Staphylococcus* spp. Bactericidal antibiotics with a spectrum against gram-positive organisms and the ability to concentrate in bone are recommended. First-generation cephalosporins (cefazolin, 25 mg/kg IV q8h; cephalexin, 22 mg/kg PO q8h) and amoxicillin with clavulanate (Clavamox, 12.5-25 mg/kg PO q8h) have been effective. Quinolones can be added if gram-negative organisms are suspected. Ampicillin is the antibiotic of choice for *Actinomyces* infections associated with grass awn migration. Antibiotics are administered parenterally for the first 3 to 5 days whenever neurologic deficits are present, then oral administration is continued for at least 8 weeks and up to 6 months if necessary.

In addition to antibiotic therapy, the patient's activity should be restricted to minimize discomfort and decrease the chance of pathologic fracture and luxation. Analgesics may be administered for 3 to 5 days, but their use will make it difficult to assess the efficacy of antibiotic therapy and may make it more difficult to enforce strict cage rest. Most dogs show very rapid clinical improvement within the first week of treatment. Dogs treated medically should be reevaluated clinically and radiographically every 3 weeks. With time, the lytic process should resolve and the affected vertebrae should fuse. Antibiotics should be administered for a minimum of 8 weeks and may then be discontinued if the spine is no longer painful over the affected sites and there is no radiographically visible lysis. Most treated animals do not relapse unless a foreign body causes the diskospondylitis.

CHRONIC PROGRESSIVE DISORDERS

Neoplasia

Tumors that grow and compress or infiltrate spinal cord parenchyma frequently cause chronic, progressively worsening signs of spinal cord dysfunction. Spinal tumors can be primary or metastatic. The most common tumors affecting the spinal cord in the dog are extradural tumors arising from the vertebral body (e.g., osteosarcoma, chondrosarcoma, fibrosarcoma, myeloma) and extradural soft tissue tumors, including metastatic hemangiosarcoma, carcinoma, liposarcoma, and lymphoma. Intradural extramedullary tumors such as meningiomas, neuroepithelioma, and peripheral nerve sheath tumors are also common, accounting for 35% of all spinal tumors. Intramedullary tumors are relatively rare in the dog, with the exception of metastatic hemangiosarcoma. Lymphoma can be extradural, intradural/extramedullary, or intramedullary in the dog and is usually a manifestation of multicentric disease. Lymphoma is the only common spinal tumor in the cat, and in 85% of cats with spinal lymphoma the tumor is also found in extraneural sites.

Most spinal cord tumors occur in middle-aged and older dogs, with the mean age at the time of diagnosis being 5 to 6 years. Two noteworthy exceptions are lymphoma (which can affect dogs of any age) and neuroepithelioma, a primary intradural extramedullary tumor that has a predilection for T10-L1 in young dogs, particularly German Shepherd dogs and Golden Retrievers. In addition, vertebral osteomas may occur in young dogs and result in spinal cord compression, as can cartilaginous exostoses, benign proliferative lesions of the bone indistinguishable from neoplasia except by biopsy (Fig. 65.15; see also Fig. 59.2). Spinal lymphoma is most common in young (mean age, 4 years) adult feline leukemia (FeLV)-positive cats. Certainly, spinal neoplasia cannot be eliminated as a differential diagnosis strictly on the basis of signalment.

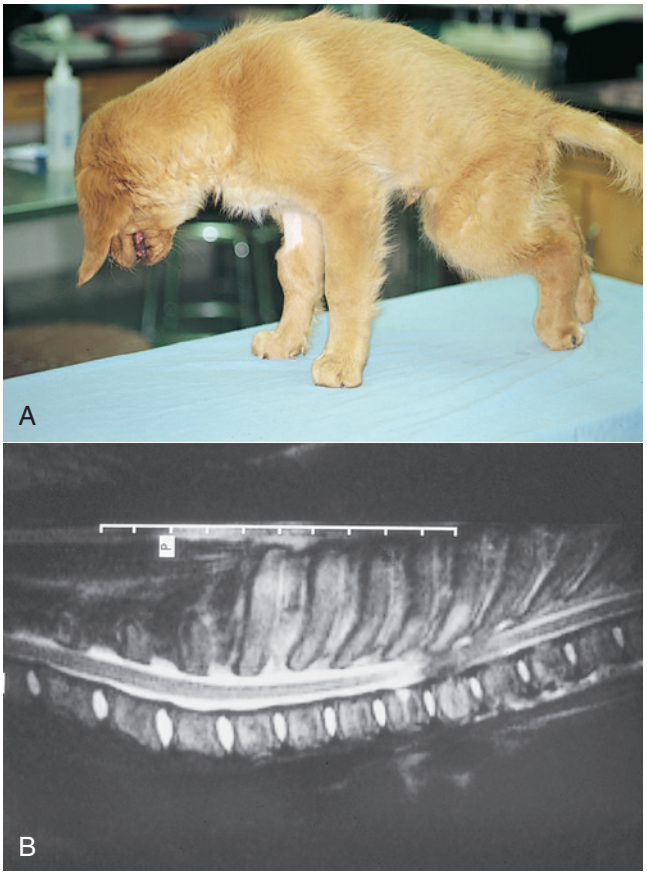


FIG 65.15
(A) A 3-month-old Golden Retriever puppy with spinal pain and progressive upper motor neuron (UMN) signs in both rear limbs resulting from a vertebral osteoma. **(B)** Magnetic resonance imaging showing severe compressive spinal cord damage from the caudal aspect of the T4 vertebral body extending caudally through the T6 vertebral body.

Clinical Features

Clinical signs are usually insidious and related to tumor location. Early diagnosis is difficult because neurologic abnormalities are not clinically apparent until there has been significant compression or destruction of the spinal cord. Many animals have months of slowly progressive clinical signs before a diagnosis is made. Pain may be a prominent feature in dogs and cats with nerve root tumors encroaching on the spinal cord, tumors involving the meninges, and aggressive tumors involving vertebral bone. Progressively worsening lameness and pain on limb manipulation (i.e., radicular pain, root signature) without initial neurologic deficits are common in dogs with peripheral nerve sheath tumors involving nerve roots in the cervical or lumbar intumescence. An ipsilateral Horner syndrome and/or loss of the panniculus reflex may be seen if the thoracic nerve roots are involved. Pain is not a common feature of intramedullary spinal cord primary tumors or metastases. Although animals with compressive lesions of the T3-L3 spinal cord typically maintain urinary and fecal continence until after the limbs are paralyzed, it is not uncommon for animals with intramedullary neoplasms affecting the central cord to become incontinent while still able to walk.

Differential diagnoses must include other disorders that cause slowly progressive neurologic dysfunction, including type II disk protrusion and degenerative myelopathy (DM). Rapidly growing extradural tumors such as lymphoma and primary or metastatic intramedullary tumors sometimes cause rapidly progressive neurologic signs more typical of inflammatory myelitis. Peracute paresis/paralysis is occasionally seen in dogs or cats with tumor-associated hemorrhage or vertebral pathologic fractures.

Diagnosis

Whenever a neoplasm is considered as a differential diagnosis for spinal cord dysfunction, a thorough physical examination, clinicopathologic evaluation, and systemic imaging are necessary to look for sites of primary tumor, metastases, and evidence of associated systemic disease. Fundic examination, palpation of lymph nodes, and rectal examination should be performed, as well as thoracic and abdominal radiographs

and abdominal ultrasound. In breeds at high risk for hemangiosarcoma, cardiac ultrasound may also be warranted. Aspiration of the lymph nodes, spleen, and/or liver and examination of peripheral blood or bone marrow smears may yield the diagnosis in dogs with lymphoma. Patients with multiple myeloma often secrete paraproteins, causing a hyperproteinemia and a monoclonal gammopathy. Most cats with spinal lymphoma are FeLV-positive (>80%), and many have obvious systemic disease and hematologic evidence of bone marrow involvement.

Survey radiographs of the affected region of the spine are recommended. Osteolysis or bone proliferation may be seen with vertebral tumors (Fig. 65.16). Fine-needle aspiration of a bone lesion sometimes yields a cytologic diagnosis. The entire axial and appendicular skeleton should be surveyed for lytic lesions if clinical findings make multiple myeloma likely. Soft tissue tumors of the spinal cord are almost never visible using survey radiographs. Although myelography is a fairly reliable method to localize and characterize spinal cord tumors, it is relatively invasive and provides less useful diagnostic information than MRI. CSF analysis should always precede myelography. With tumors compressing the spinal cord, CSF analysis typically reveals nonspecific changes, including slight increases in protein concentration and a mild mononuclear pleocytosis. Neoplastic cells are rarely identified except in cats and dogs with lymphoma (Fig. 65.17).

Myelography or MRI allows most spinal cord tumors to be characterized as intramedullary, extramedullary-intradural, or extradural. MRI adds valuable information regarding precise tumor location and degree of spinal cord involvement, which may be important when considering surgical treatment and/or radiation therapy.

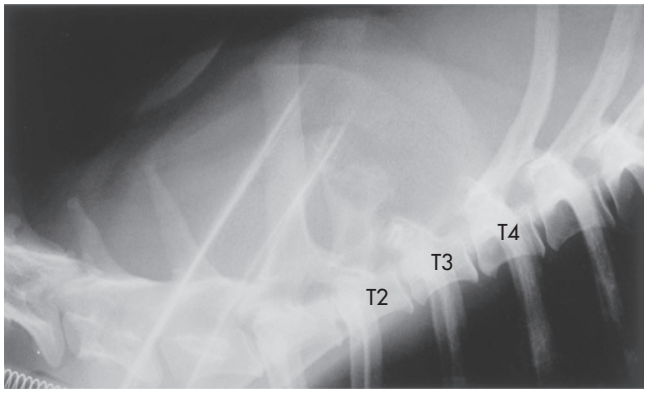


FIG 65.16
Lateral spinal radiograph from a 2-year-old Irish Setter with a 1-week history of progressive ataxia and a 12-hour history of upper motor neuron paralysis of the rear limbs and Schiff-Sherrington syndrome. The entire spinous process of T3, the roof of T3, and most of the spinous process of T2 are destroyed, most consistent with a neoplastic process. An undifferentiated sarcoma at this site was identified on postmortem examination.

Treatment

Surgical decompression and attempts at complete tumor excision are usually limited to well-encapsulated extradural tumors as a referral procedure. Feline meningiomas may have a good prognosis after surgical excision. Intramedullary tumors cannot usually be treated successfully with surgery because of their intimate involvement with neural tissue.

Radiation therapy may be of some benefit in dogs and cats with spinal lymphoma, plasma cell tumors, meningiomas, and some nerve sheath tumors. Chemotherapy is rarely effective because only a few of the commonly used drugs cross the blood-brain barrier. Corticosteroids may shrink lymphoreticular tumors such as lymphoma and myeloma and may decrease edema and inflammation associated with a variety of tumors, resulting in remarkable temporary improvement. Cytosine arabinoside has good CSF

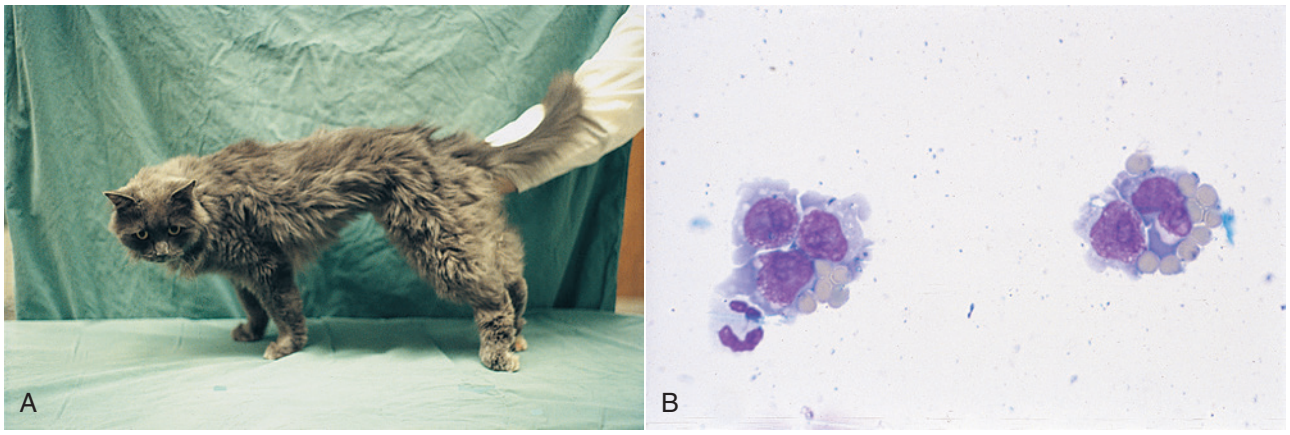


FIG 65.17
(A) A 2-year-old cat with a 5-day course of progressive rear limb ataxia and upper motor neuron paresis. **(B)** Cerebrospinal fluid analysis revealed an increased cell count consisting predominantly of neoplastic lymphoid cells.

penetration so may also be used to treat lymphoreticular tumors.

Spinal Articular Cysts

Cysts arising from the joint capsule of spinal facetal joints can, through enlargement, cause chronic progressive focal extradural compression of the spinal cord or nerve roots. These cysts can result from an outpouching of the synovium (i.e., synovial cysts), or they may arise from mucinous degeneration of periarticular connective tissue (i.e., ganglion cysts). Synovial cysts and ganglion cysts are clinically indistinguishable, and both arise secondary to degenerative changes in the facetal joints. Degenerative changes occur because of congenital malformations, vertebral instability, or trauma. Signs are referable to the site and degree of resulting spinal cord or nerve root compression. Young giant breeds of dogs such as Mastiffs, Great Danes, and Bernese Mountain Dogs most commonly develop single or multiple cysts in the cervical region, which cause a UMN myelopathy with proprioceptive ataxia, progressive tetraparesis, and occasionally cervical pain. Synovial cysts occur in 20% of dogs with CSM (wobbler syndrome). Older dogs, particularly German Shepherd dogs, have been identified with thoracolumbar or lumbosacral articular cysts that cause spinal cord or cauda equina compression.

Radiographs may reveal degenerative changes of the articular facets. Diagnosis of synovial cysts is best accomplished with MR imaging. The cysts are well-circumscribed extradural masses associated with the articular processes on one or both sides of the vertebral canal. CSF analysis reveals normal cytology and slightly increased protein, consistent with a noninflammatory chronic compressive myelopathy. Treatment usually consists of spinal cord decompression, cyst drainage, and arthrodesis of the facetal joint, and usually produces excellent results. A similar syndrome with degeneration and bony proliferation of multiple thoracolumbar articular facets causing spinal cord compression has been reported as a hereditary condition in 4- to 10-month-old Shiloh Shepherds.

Spinal Arachnoid Diverticula (Cysts)

Focal accumulations of CSF in cyst-like structures within the subarachnoid space can lead to slowly progressive, nonpainful spinal cord compression in young dogs (Fig. 65.18). The cyst-like structures containing CSF may represent a congenital intradural arachnoid diverticulum (most common) or a pocket caused by adhesions in the subarachnoid space secondary to trauma, disk extrusion or protrusion, or vertebral malformations. The cervical region and the caudal thoracic region are most often affected, with most diverticula in the dorsal aspect of the vertebral canal. A CSF flow disturbance may cause a functional one-way valve, so that as CSF fills the diverticulum it enlarges and causes compression of the spinal cord. Young large-breed male dogs are most likely to be affected by cervical diverticula, with Rottweilers overrepresented. Small-breed dogs, especially Pugs and French Bulldogs have a tendency to have thoracolumbar diverticula. Cats are rarely affected. Myelography or MRI reveals accumulation of CSF at the site (see Fig. 65.18). Exploration, fenestration of the diverticula with durotomy,

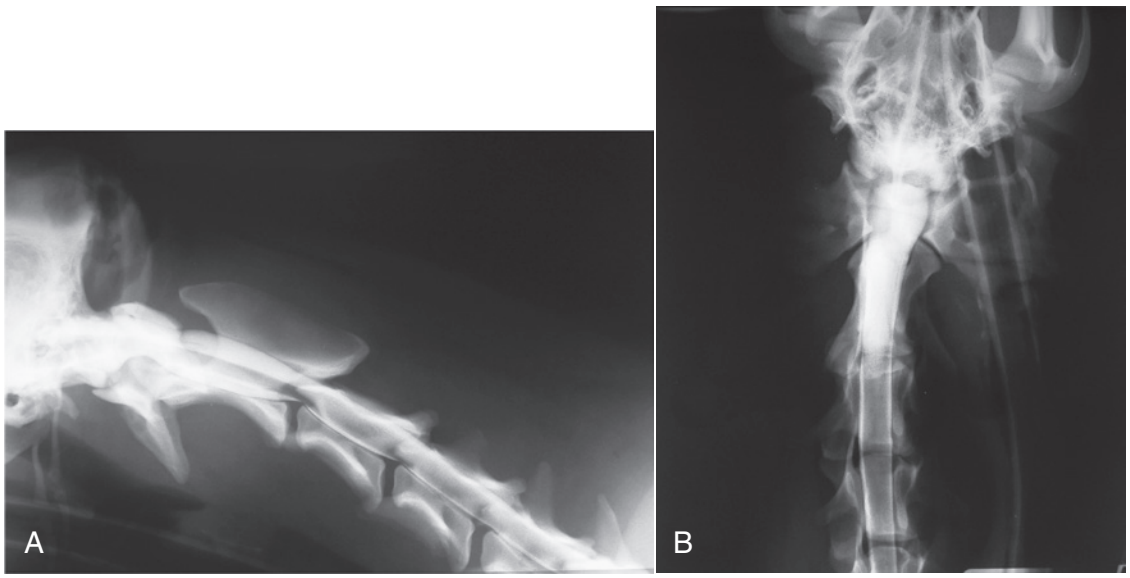


FIG 65.18
Lateral **(A)** and ventrodorsal **(B)** views of a myelogram from a 10-month-old Akita with progressive hypermetria of all four limbs and mild paraparesis. A well-defined bulbous dilation of the dorsal subarachnoid space communicating with the rest of the subarachnoid space was present at C2-C3, suggesting an arachnoid diverticulum. Surgical exploration and marsupialization resulted in rapid and persistent (>6 years) return to normal gait.

and marsupialization of the diverticulum are associated with a good prognosis for recovery if performed within 4 months of development of clinical signs and if neurologic deficits are not severe.

Type II Intervertebral Disk Protrusion

Fibroid degeneration of the IVD occurs in some dogs as part of the aging process, and this can lead to prolapse of a small amount of disk nucleus into the annulus fibrosus. A fibrotic reaction ensues, resulting in a round, dome-like dorsal bulging of the annulus so that it protrudes into the spinal canal and causes slowly progressive spinal cord compression (see Fig. 65.5). This type of disk protrusion (i.e., Hansen type II) is seen most commonly in aging large-breed nonchondrodystrophoid dogs, particularly German Shepherd dogs, Labrador Retrievers, and Doberman Pinschers, but it has also been recognized occasionally in small-breed dogs.

Clinical Features

Clinical signs result primarily from slowly progressive spinal cord compression, although spinal discomfort is apparent in a few dogs. Thoracolumbar type II disk protrusion results in UMN signs to the rear limbs, with normal forelimbs. Cervical type II disk disease may be seen in Doberman Pinschers, particularly in association with CSM (i.e., wobbler syndrome). In these dogs thoracic and pelvic limbs are affected, with UMN neurologic signs most prominent in the pelvic limbs.

Diagnosis

Slowly progressive signs of spinal cord dysfunction in an older dog should prompt consideration of type II disk protrusion, articular cysts, DM, or neoplasia. Neurologic examination localizes the lesion to a spinal cord region, but, because the site is not usually painful, spinal palpation rarely results in more precise localization. Survey radiographs of the spine are normal in most affected dogs, but disk space narrowing, osteophyte production, and end-plate sclerosis may be seen at the site of type II disk protrusion in some dogs. All of these are, however, common incidental findings, but these abnormalities are common at multiple sites in older large-breed dogs, so they may not help to further localize the lesion. Myelography or advanced imaging technique (i.e., CT, MRI) is necessary to determine the extent and location of the lesion and to distinguish type II disk protrusion from spinal neoplasia and DM.

Treatment

Restricted exercise, antiinflammatory drugs (NSAIDs or low-dose prednisone), and muscle relaxants will provide relief in dogs that are uncomfortable when the affected site is palpated or manipulated. The addition of methocarbamol or gabapentin may help to relieve cervical discomfort from muscle spasms or pinched nerve roots. Neurologic signs caused by spinal cord compression will continue to progress, however, and surgery is recommended as the definitive treatment. Ventral decompression is performed if the cervical vertebrae are affected, whereas hemilaminectomy for decompression at the site is usually attempted for type II disks in the thoracolumbar spine. Effective surgical decompression is often challenging to achieve because of the chronic nature of the lesion and the difficulty encountered in removal of the dorsal annulus. The goal of therapy is to stabilize the animal's neurologic status. The spinal cord has usually undergone considerable chronic compression before clinical signs appear, so full recovery is rare. A few dogs experience temporary or permanent worsening of clinical signs postoperatively.

Degenerative Myelopathy

A degenerative disorder of the spinal cord white matter characterized by widespread myelin and axon loss that is most severe in the mid to caudal thoracic spinal cord occurs most often in aging German Shepherd dogs. Affected dogs initially have a slowly progressive, often asymmetric, nonpainful, proprioceptive ataxia and UMN spastic paresis primarily affecting the pelvic limbs, suggesting a T3-L3 lesion. DM has been recognized in German Shepherd dogs from 5 to 14 years of age and is occasionally seen in older dogs of other large breeds including Boxers, Chesapeake Bay Retrievers, and Rhodesian Ridgebacks, and in Pembroke Welsh Corgis.

Etiology

The cause of the noninflammatory axonal degeneration that occurs in DM is uncertain. Some have speculated that deficiencies of nutrients or vitamins or vascular supply are responsible for the histologic changes. Recently homozygosity for a genetic mutation in the superoxide dismutase 1 (SOD1) gene has been identified as a necessary condition for the development of DM in breeds with a high familial predisposition for the condition. This mutation, together with the neuropathologic features of DM, suggests that it is a neurodegenerative spinal cord disorder similar to UMN-onset amyotrophic lateral sclerosis (ALS) in people.

Clinical Features

Clinically, DM results in a slowly progressive UMN paraparesis and ataxia of the rear limbs. A loss of proprioception results in knuckling, wearing of the dorsal nail surfaces of the digits of the rear limbs, and progressively worsening posterior ataxia. Most affected large-breed dogs progress from mild proprioceptive loss to nonambulatory UMN paraparesis within 6 to 9 months. A more slowly progressive form of DM has been identified in the Pembroke Welsh Corgi, with a median duration of progression of signs over 18 months. Although initially all dogs with DM show typical UMN paraparesis suggesting a T3-L3 lesion, if dogs are managed beyond the point of being unable to walk, their signs slowly progress to flaccid (LMN) paresis with muscle atrophy and loss of reflexes in all four limbs, suggesting widespread denervation.

Diagnosis

A diagnosis of DM should be suspected in any large-breed dog with slowly progressive UMN paresis in the rear limbs. Rear limb ataxia, a long-strided gait, toe scuffing, abnormal postural reactions (especially knuckling), and normal to increased rear limb reflexes are the most common findings. Affected dogs are systemically normal, with no site of localizable spinal pain. Neurologic findings distinguish DM from lumbosacral disease and from orthopedic disorders such as hip dysplasia and bilateral anterior cruciate ligament rupture. The primary differential diagnoses for chronic progressive UMN paresis in the rear limbs include DM, spinal cord neoplasia, spinal cord compression by articular cysts, and type II disk protrusion.

The antemortem diagnosis of DM is one of exclusion. Radiographs of the spine are normal, as is CSF analysis, although a slight increase in CSF protein concentration is occasionally found. Myelography or MRI must be performed to rule out spinal cord compression or focal spinal cord neoplasia. Normal spinal radiographs, a cytologically normal CSF, and normal spinal cord imaging in an older dog with slowly progressive UMN signs to the pelvic limbs warrant a diagnosis of DM. A DNA test based on the SOD1 mutation is commercially available but will only determine which dogs (homozygotes) are at risk of developing DM and which dogs are carriers for the trait. The test will not identify the cause of paraparesis in an individual dog. Recent reports suggest that measuring increased concentrations of a structural protein of myelinated motor axons (phosphorylated neurofilament heavy: pNF-H) in the CSF may be useful as a biomarker for the diagnosis of DM in dogs. Definitive diagnosis of DM can only be confirmed by postmortem identification of typical changes including axonal degeneration, demyelination, and astroglial proliferation in the lateral funiculus and dorsal columns of the thoracic spinal cord.

Treatment

No treatment has been proven effective in dogs with DM. Corticosteroids should not be administered, because they cause muscle wasting and exacerbate muscle weakness. Other immunosuppressive agents have not been shown to be beneficial. Some investigators have advocated vitamins (i.e., vitamin E, vitamin B complex, vitamin C), omega-3 fatty acids, and antioxidants, but conclusive evidence of benefit for any of these treatments is lacking. Exercise and intensive targeted physiotherapy may be helpful in slowing disease progression.

Cauda Equina Syndrome

In dogs, the last three lumbar spinal cord segments (L5, L6, L7) are within the fourth lumbar vertebra, the sacral segments (S1, S2, S3) are within the body of the fifth lumbar vertebra, and the coccygeal segments are within the sixth lumbar vertebra. Because nerve roots from these lumbar, sacral, and coccygeal segments of the spinal cord exit the spinal canal through the intervertebral foramina caudal to the vertebrae with the same number, they must course a considerable distance within the vertebral canal caudal to the point of termination of the spinal cord (Fig. 65.19; see also Table 65.2). This collection of nerve roots descending in the vertebral canal is termed the *cauda equina.* The spinal nerves from the sacral and caudal segments overlie the lumbosacral junction, so compressive disorders affecting this region are likely to involve the L7, sacral, and caudal nerves.

Compression of the nerves of the cauda equina (*cauda equina syndrome, degenerative lumbosacral stenosis*) is usually the result of acquired type II disk protrusion at the L7/S1 intervertebral space, together with progressive proliferation of joint capsules and ligaments in the region, perhaps caused by excessive motion or instability. This disorder is most common in large-breed dogs, including German Shepherd dogs, Labrador Retrievers, and Belgian Malinois, and particularly affects male working dogs older than 5 years of age. Rarely, compression of the cauda equina at this site could be

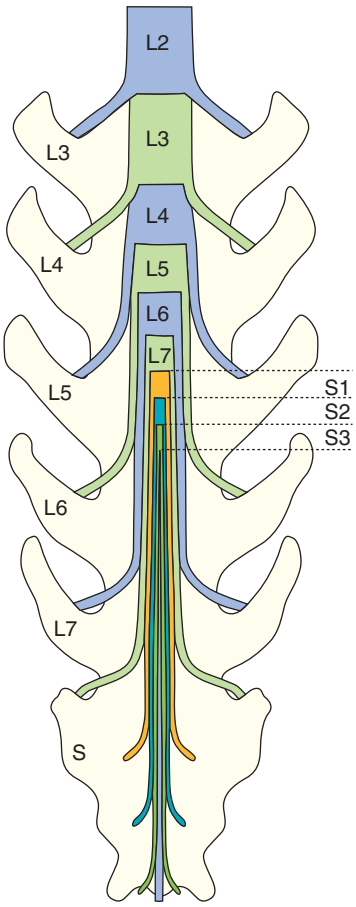


FIG 65.19
Anatomy of the cauda equina region in the dog. L5-L7 spinal cord segments sit within the L4 vertebra. S1-S3 spinal cord segments are within the L5 vertebra, and the coccygeal segments are within L6. Nerve roots from all of the lumbar, sacral, and coccygeal spinal cord segments leave the canal through the intervertebral foramen just caudal to the vertebra with the same number, so these nerve roots course a considerable distance within the vertebral canal.

caused by tumor, diskospondylitis, synovial cyst, vertebral or sacral osteochondrosis, or congenital bony malformations.

Genetic predisposition, conformation, and physical activity are all factors proposed to cause increased mechanical stress on the IVD at the lumbosacral junction, promoting type II disk prolapse at this site. Loss of the structural strength of the disk worsens instability at the site, resulting in proliferative changes in the articular facets, joint capsules, and ligamentum flavum. Proliferative changes result in further narrowing of the vertebral canal, compression of the cauda equina, and compression of the nerve roots as they exit the foramina (degenerative lumbosacral stenosis).

Clinical Features

Compression of the nerve roots of the cauda equina results in a very characteristic constellation of clinical signs. Affected dogs are slow to rise from a prone position and reluctant to run, sit up, jump, or climb stairs. Rear limb lameness worsens with exercise as the blood vessels accompanying the spinal nerve roots within the already crowded intervertebral foramen dilate and further compress the nerve roots. Affected dogs may be reluctant to raise or wag their tails.

The most consistent physical examination finding is pain elicited by deep palpation of the dorsal sacrum or by dorsiflexion of the tail or hyperextension of the lumbosacral region (Fig. 65.20). Most dogs have no neurologic deficits at the time of initial evaluation, making it difficult to distinguish affected dogs from those with pain and lameness caused by diskospondylitis, prostatic disease, or degenerative joint disease. When lumbosacral spinal canal and foraminal narrowing progress to cause compression of the L7, sacral, and caudal spinal nerves, subtle neurologic abnormalities including rear limb weakness, atrophy of the muscles of the caudal thigh and distal limb, and reduced or absent hock flexion during the withdrawal reflex will become apparent. The patellar reflex may appear increased in some dogs because there is a loss of tone in the opposing caudal thigh muscles (pseudohyperreflexia). In severely affected dogs, decreased anal tone and fecal and urinary incontinence will occur. Hyperesthesia or paresthesia of the perineum may develop, with self-inflicted moist dermatitis of the perineum and tail base.

Diagnosis

Historical, physical, and neurologic examination findings are the primary basis for reaching a tentative diagnosis of cauda equina syndrome in affected dogs. Spinal survey radiographs are useful to rule out unusual causes of lumbosacral pain (e.g., diskospondylitis, lytic vertebral neoplasia, fracture/luxation). Radiographs of this region in dogs with cauda equina syndrome may be normal or may reveal end-plate sclerosis and spondylosis of the L7 and S1 vertebral end plates and narrowing or collapse of the L7-S1 IVD space. These same abnormalities are common in clinically normal dogs.

Diagnosis is based on documentation of nerve compression using imaging. When available, MRI with the spine in extension provides the most sensitive, accurate, and noninvasive means of evaluating the lumbosacral region, allowing visualization of all components potentially involved in cauda equina compression (Fig. 65.21). There is some concern that routine use of MRI for diagnosis may lead to overinterpretation of incidental minor disk protrusions at this site, so clinical findings must support the MRI diagnosis. When available, electrophysiologic studies can be useful to confirm LMN disease and nerve root dysfunction of the rear limbs and tail.

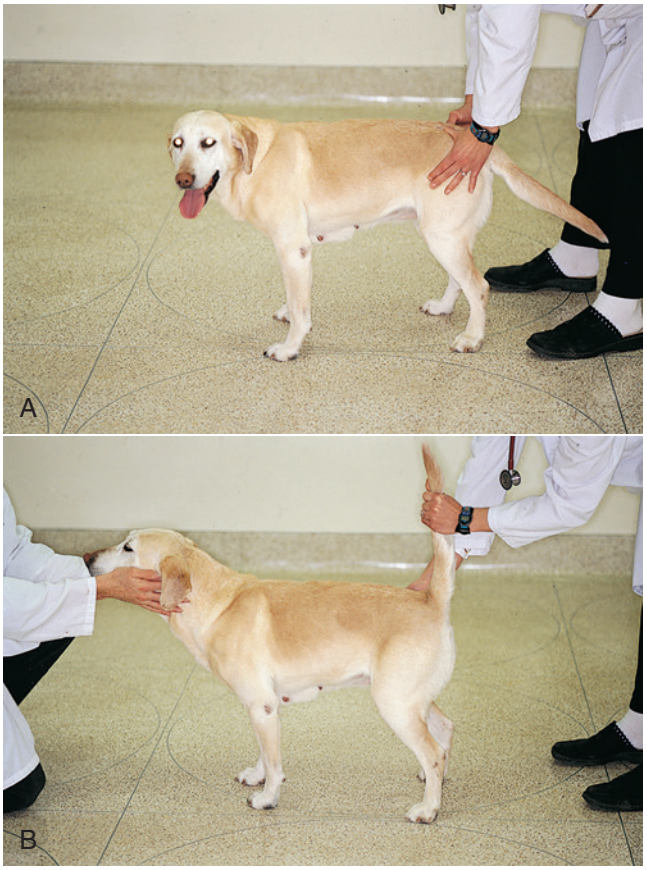


FIG 65.20
Dogs affected by cauda equina syndrome will often experience pain upon **(A)** deep palpation of the dorsal sacrum and **(B)** dorsiflexion of the tail.

Treatment

Restriction of exercise and the administration of analgesics or antiinflammatory drugs may result in temporary improvement in dogs with clinical signs limited to pain and lameness. Significant relief can often be achieved with gabapentin (8-10 mg/kg PO q8h) for neuropathic pain, together with NSAIDs and tramadol (3-5 mg/kg PO q8h). Signs usually recur when normal activity is resumed. More definitive treatment involves lumbosacral dorsal laminectomy, excision of compressing tissues, and foraminal decompression by foraminotomy when necessary. Decompressive surgery together with lumbosacral distraction and stabilization is recommended if instability is suspected. Descriptions of the surgical procedures are provided in the Suggested Readings.

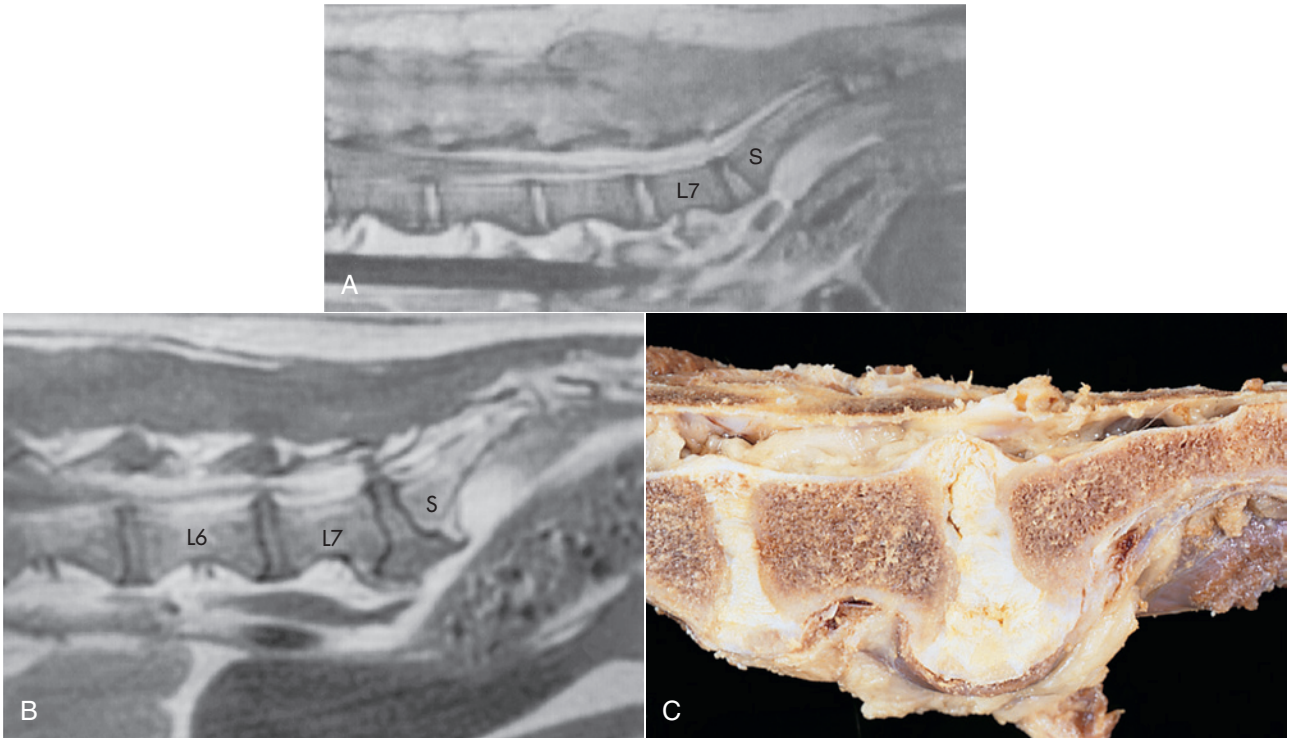


FIG 65.21
(A) Normal midline sagittal T1 on a magnetic resonance imaging (MRI) scan of the lumbar spine of a dog. (Image reveals high signal intensity *[white]* of the nucleus pulposus and epidural fat, in contrast to lesser signal density of the spinal cord and nerve roots of the cauda equina *[darker]*.) **(B)** MRI from a dog with lumbosacral pain showing T1-weighted midline sagittal, displacement of epidural fat, and ventral and dorsal compression of the nerve roots at the L7-S1 disk space. Spondylosis deformans ventral to the L7-S1 intervertebral disk space and disk protrusion at the L6-L7 space can also be seen. **(C)** Postmortem dissection of the lumbosacral region of a German Shepherd Dog with acquired degenerative lumbosacral stenosis and type II disk protrusion. The vertebral canal is compromised at the lumbosacral junction, resulting in compression of the nerves of the cauda equina. (**A** and **B** courtesy Dr. Greg Daniel, University of Tennessee.)

Rapid relief from pain occurs after surgery in most dogs. Strict postoperative confinement is important for 4 to 8 weeks, followed by a gradual return to exercise and work. The prognosis is good for resolution of lameness and mild neurologic deficits. Most dogs with mild to moderate deficits will return to working function, but occasionally there will be a recurrence of signs after 12 to 24 months. Dogs with severe LMN deficits or incontinence are likely to have permanent deficits.

Cervical Spondylomyelopathy (Wobbler Syndrome)

Cervical spondylomyelopathy (CSM), or *canine wobbler syndrome,* is a term used to describe caudal cervical spinal cord and nerve root compression in large- and giant-breed dogs that occurs secondary to developmental malformations, instability, or instability-associated changes in the spinal canal. Genetic predisposition, overnutrition, and conformation have all been implicated in the development of this disorder. Vertebral canal narrowing can be the result of malformed vertebral laminae, hypertrophy of the ligamentum flavum, articular facet enlargement, periarticular soft tissue hypertrophy, or (most often) a combination of these. In addition, changes in the vertebral body and end plates can lead to type II IVD protrusion, causing ventral spinal cord compression in affected dogs.

Great Danes with CSM typically have osseous narrowing of the spinal canal due to congenital malformations of their cervical vertebrae. Signs of spinal cord compression are usually evident before 2 years of age in this breed. Multiple vertebral sites (usually C4, C5, or C6) are often affected, and the degree of spinal cord compression and injury increases with cervical extension or dorsiflexion. In addition to the spinal cord compression caused by the bony malformations, most affected dogs have concurrent dorsal or lateral soft tissue compression of their spinal cord.

In dogs with CSM, hypertrophy of the ligamentum flavum leads to dorsal spinal cord compression. Dorsolateral and lateral compression occur secondary to articular process osteoarthritis and articular facetal joint hypertrophy. Young large-breed dogs such as Mastiffs, Rottweilers, and Bernese Mountain dogs with CSM most commonly experience dorsal

or dorsolateral spinal cord compression that becomes clinically evident when they are between 1 and 4 years of age. Degenerative changes of the articular facets, synovial cysts, and vertebral canal stenosis may all occur. Disk-associated wobbler syndrome (DAWS) causes ventral compression of the caudal cervical spinal cord in mature large-breed dogs, especially 6- to 8-year-old Doberman Pinschers. Affected Dobermans typically have a smaller than normal vertebral canal, hypertrophy of the ligamentum flavum, and protrusion of one or more intervertebral disks leading to their signs of spinal cord compression.

Clinical Features

A slowly progressive course of paresis and an uncoordinated or wobbling gait, particularly in the pelvic limbs, are characteristic of CSM. Affected dogs have a broad-based rear limb stance, ataxia, and abnormal postural reactions in the rear limbs (which are invariably more severely affected than the forelimbs). Neurologic findings in the forelimbs vary depending on whether spinal cord compression is centered in the cranial cervical region or in the caudal cervical region. Dogs with C1-C5 compression often have a floating or overreaching front limb gait. Dogs with caudal cervical lesions may have a short-strided, weak front limb gait with a weak withdrawal reflex and pronounced atrophy of the supraspinatus and infraspinatus muscles over the scapula. Lameness and muscle atrophy in one thoracic limb or pain when traction is applied to a limb (i.e., root signature; see Fig. 65.6) suggests that nerve root compression is present. Slowly progressive deterioration in neurologic status is common, but occasionally a traumatic episode or an acute disk extrusion results in sudden tetraplegia. Resistance to dorsal extension of the cervical spine is common, but overt cervical pain is the primary complaint in less than 10% of dogs with CSM.

Diagnosis

The diagnosis is suspected on the basis of signalment, history, and clinical findings. Survey radiographs are useful to rule out other disorders associated with cervical spinal cord compression but are not definitive for CSM. Severe articular facet changes or vertebral body malformations should raise the index of suspicion for CSM in a large-breed dog. Until recently, myelography or myelogram-CT has been the standard means of confirming a diagnosis of CSM, with the advantage that the degree of spinal cord compression could be observed with the spine in multiple positions, allowing differentiation between static and dynamic lesions. Compressive lesions that improve substantially with traction (dynamic lesions) include type II disks and ligamentous hypertrophy. Osseous lesions or type I disk extrusions are not expected to resolve with traction (static lesions; Figs. 65.22 and 65.23). This information can be used to determine whether the optimal surgery for a dog with CSM is direct decompression or indirect decompression through vertebral distraction.

MRI is now considered the gold standard test for evaluation of dogs suspected to have CSM. MRI is more accurate

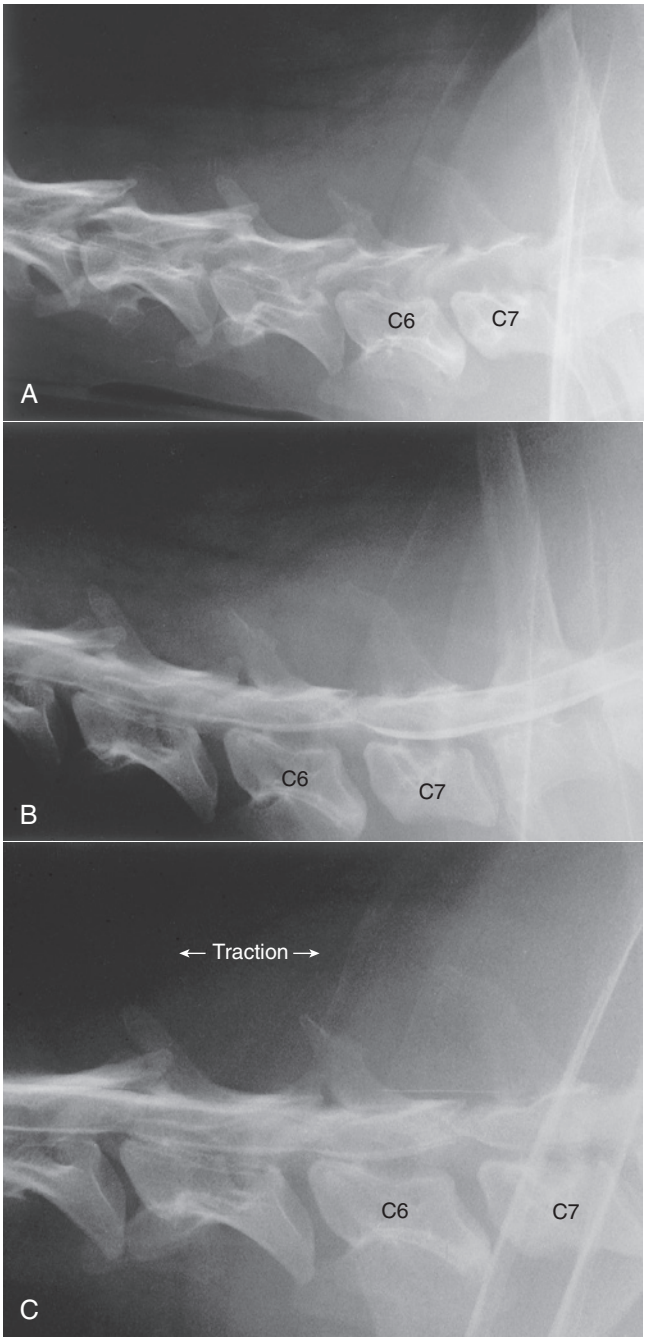


FIG 65.22
(A) Radiograph of the cervical region in a 6-year-old Doberman Pinscher "wobbler" with a sudden onset of ataxia, paraparesis, proprioceptive deficits and hyperreflexia in the rear limbs, and mild cervical pain. Slight narrowing of the C6-C7 disk space can be seen; vertebral canal is stenotic within the cranial aspect of C6 and C7. **(B)** Myelography shows spinal cord compression by a ventral extradural mass at C6-C7 that is not altered significantly with traction **(C).** Surgery revealed a large amount of disk material within the vertebral canal at this site.

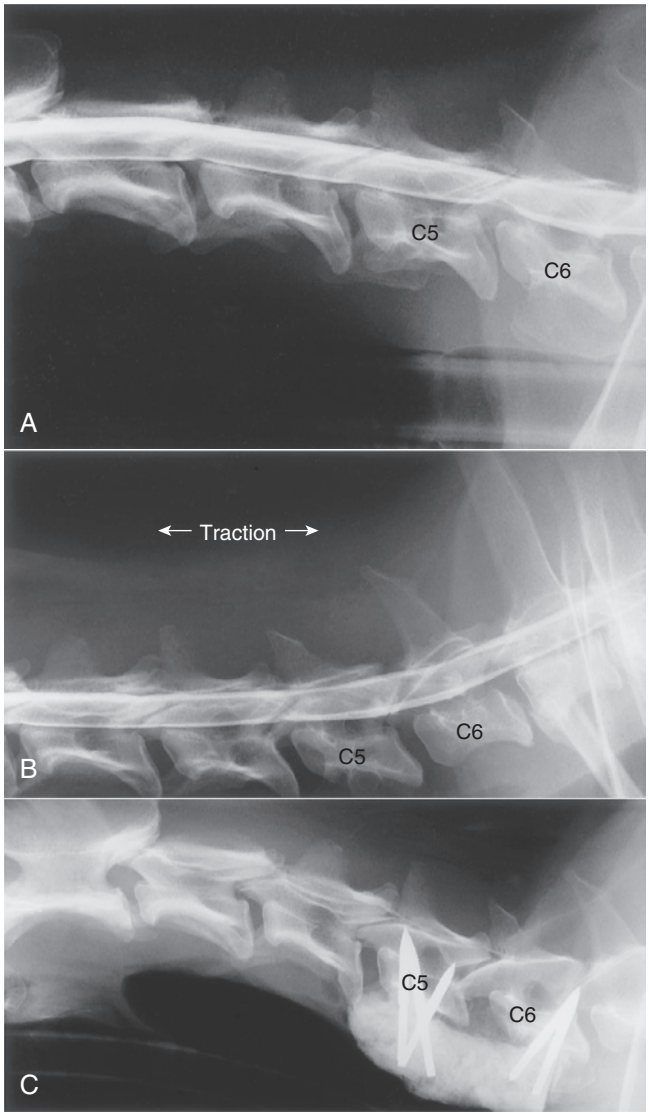


FIG 65.23
(A) Cervical myelogram of an 11-year-old Doberman/Weimaraner cross with a chronic history of nonpainful ataxia and hypermetria of all four limbs. Narrowing of the C5-C6 disk space and thinning of the dorsal contrast column over this site (in association with dorsal deviation and thinning of the ventral contrast column) can be seen. **(B)** Dramatic resolution of this spinal cord compression in the traction view suggests a dynamic compression by a bulging annulus fibrosus or ligamentum flavum. **(C)** Surgery was performed to maintain traction on the spine at this site.

in predicting the site, severity, and nature of spinal cord compression than other modalities. MRI also allows detection of signal changes within the spinal cord parenchyma that may be associated with prognosis for recovery.

Treatment

The clinical course of untreated wobbler syndrome is typically chronically progressive, but in up to 25% of mildly affected dogs signs will remain stable over time. Medical or surgical therapy can be used to attempt to relieve clinical signs of CSM. All affected animals should be evaluated for systemic disease before initiating medical or surgical therapy. In particular, Doberman Pinschers should be evaluated for concurrent hypothyroidism, von Willebrand disease, and cardiomyopathy.

Severe exercise restriction, use of a harness, and administration of antiinflammatory doses of prednisone may result in temporary improvement in neurologic function in dogs with CSM (prednisone, 0.5 mg/kg PO q12h for 2 days; then 0.5 mg/kg once daily for 2 days; then 0.5 mg/kg once every other day for 14 days; then 0.25 mg/kg once every other day for 2 months). NSAIDs can be used in place of corticosteroids if neck pain is severe or if the corticosteroids are not tolerated, but NSAIDs and corticosteroids should never be administered together. Medical management can be effective long term in 40% to 50% of dogs with minimal or mild signs of neurologic dysfunction.

Surgical treatment of CSM leads to a successful outcome in about 80% of cases, so it is recommended in most dogs with significant neurologic deficits. Surgery, however, does not alter long-term survival in dogs with CSM. Multiple lesions, chronic disease, and an inability to walk are all associated with a poor prognosis. Postoperative rehabilitation is critical to recovery. Primary factors determining the specific surgical procedure to be recommended are the degree and site of cord compression and the anatomic structures causing cord compression. Details of the surgical procedures and potential complications are discussed in the Suggested Readings.

PROGRESSIVE DISORDERS IN YOUNG ANIMALS

Breed-Associated Neuronal Abiotrophies and Degenerations

Neuronal abiotrophies and degenerative disorders have been recognized in many breeds of dogs. Progressive neurologic dysfunction usually begins early in life. In disorders affecting the entire spinal cord, clinical signs involving the rear limbs are often noted early in the course of disease, with progression to tetraparesis. Disorders that primarily affect white matter and result in UMN signs are most often seen in Rottweilers, Afghan Hounds, Dalmatians, and Jack Russell Terriers. Disorders primarily affecting gray matter and causing LMN signs are seen in Alaskan Malamutes, Boxers, Brittany Spaniels, German Shepherd dogs, English Pointers, and Maine Coon Cats. The disorders are diagnosed on the basis of the typical clinical course, signalment, and lack of any definable etiology on screening blood tests, spinal radiographs, CSF analysis, advanced imaging, and other diagnostic testing. Diagnosis is confirmed by necropsy examination in most cases. No treatment is available.

Metabolic Storage Diseases

A group of rare disorders characterized pathologically by accumulation of metabolic products in cells secondary to a genetically based enzyme deficiency may result in signs

of spinal cord dysfunction. The enzyme deficiency itself or accumulation of the metabolic intermediates within cells causes a gradual progression of neurologic signs. Spinal signs are usually UMN in nature, although peripheral nerve dysfunction may occur. Cortical signs (e.g., seizures) and cerebellar signs (e.g., hypermetria) are more common. Signs are gradually progressive and usually obvious within the first year or two of life. Metabolic storage diseases are diagnosed on the basis of the typical clinical course and signalment; the lack of any other identifiable etiology; and, in some cases, organomegaly, abnormal appearance, blindness, and other readily identifiable clinical abnormalities resulting from accumulation of metabolic products in extraneural sites.

Atlantoaxial Instability and Luxation

Normally, the atlas (C1) and axis (C2) are bound together by ligaments. The dens, a bony projection from the cranial aspect of the body of the axis, is held firmly against the floor of the atlas by the transverse ligament, maintaining alignment of these two vertebrae and integrity of the spinal canal. Malformation or absence of the dens leading to instability can be seen as a congenital defect in many small breeds of dogs, including the Yorkshire Terrier, Miniature or Toy Poodle, Chihuahua, Pomeranian, Maltese, and Pekingese. The malformation and resultant atlantoaxial instability can lead to dorsal displacement of the axis in relation to the atlas, with subsequent cervical spinal cord compression and repetitive spinal cord trauma. Trauma may cause C1/C2 luxation, precipitating a sudden onset of cervical pain, tetraparesis, paralysis, or death.

Clinical Features

Dogs with congenital atlantoaxial instability can present with acute or chronic signs of a C1-C5 myelopathy. Signs typically develop before 2 years of age. Clinical signs can include neck pain (50%-75%), low head carriage, ataxia, tetraparesis, and postural reaction, and proprioceptive deficits with normal to increased muscle tone and myotactic reflexes in all four limbs. Paralysis is rare, but if it does occur it may be accompanied by caudal brainstem signs such as hypoventilation and vestibular signs. Atlantoaxial luxation secondary to malformation should be suspected in any young (i.e., 6- to 18-month-old) toy-breed dog with a history of cervical pain, UMN tetraparesis, or tetraplegia, whether or not there is a history of trauma.

Diagnosis

Atlantoaxial subluxation can be diagnosed from survey radiographs of the cervical spine, but care must be taken to prevent inadvertent overflexion or twisting of the unstable cervical spine. Recumbent or standing lateral radiographs performed with minimal restraint are usually adequate to demonstrate dorsal displacement of the axis relative to the atlas. If sedation or anesthesia will be required, a Robert Jones–style bandage or splint can be applied to hold the neck in partial extension during induction, intubation, and imaging. Instability with significant luxation can be recognized on a lateral view as widening of the space between the dorsal lamina of the atlas and the dorsal spinous process of the axis and dorsal displacement of the body of the axis (Fig. 65.24). If preliminary radiographs are not diagnostic, the radiographs should be repeated with the head gently flexed to demonstrate instability.

Treatment

Emergency treatment for acute severe tetraparesis caused by atlantoaxial luxation should include medical treatment as for acute spinal cord trauma (see Fig. 65.4). Medical and surgical treatment options have been described. Nonsurgical treatment should include application of a ventrally reinforced neck brace to hold the head and neck in extension for 4 to 8 weeks, strict cage rest, and administration of analgesics. The aim is to stabilize the neck while the ligamentous structures heal. Medical treatment has been recommended for dogs younger than 6 months of age, those with mild neurologic deficits, those with an acute onset of clinical signs, small dogs that fracture a normal atlantoaxial articulation, and those owners with serious financial constraints. Surgical treatment is more effective but may be associated with high perioperative morbidity and mortality. Dorsal and ventral techniques are described in the Suggested Readings.

Prognosis

In dogs with congenital atlantoaxial instability that survive the perioperative period, the prognosis for recovery is good. Positive outcomes are more likely if onset of signs begins before the patient is 2 years old, signs have been present for less than 10 months, and surgical reduction is good.

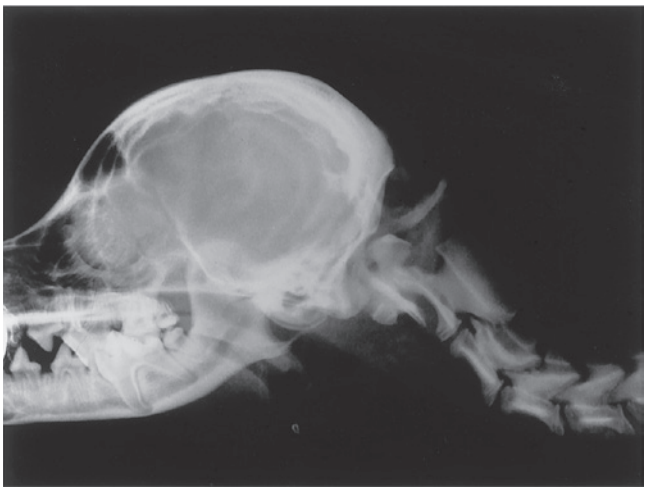


FIG 65.24
Atlantoaxial subluxation in a 7-month-old Bichon Frisé. The dens rises well above its normal position, consistent with rupture of its ligament and compression of the cervical spinal cord. The space between the arch of the atlas and the spinous process of the axis is increased. This dog had a chronic history of intermittent cervical pain and severe ambulatory upper motor neuron tetraparesis.

Syringomyelia/Hydromyelia

Cystic accumulations of fluid within the spinal cord causing compression of adjacent parenchyma are being recognized with increasing frequency as advanced diagnostic imaging techniques (i.e., CT, MRI) are used for neurologic diagnosis. *Syringomyelia* is development of a CSF-filled cavity (syrinx) within the parenchyma of the spinal cord, and *hydromyelia* is accumulation of excessive CSF within a dilated central canal. These disorders can develop as a result of altered CSF pressures within the spinal canal, a loss of spinal cord parenchyma, or secondary to obstructed CSF flow caused by congenital malformations, trauma, or inflammatory or neoplastic disorders. A relatively common cause of syringomyelia in dogs is a malformation of the skull (Chiari-like malformation [CM]) that reduces the volume of the caudal fossa and displaces the cerebellum and brainstem into the foramen magnum, obstructing CSF movement. The CSF, which normally flows through the foramen magnum during systole, becomes turbulent at the craniocervical junction, leading to syrinx formation. This disorder is inherited in the Cavalier King Charles Spaniel (CKCS). More than 95% of CKCS dogs have some degree of CM, 50% of those dogs have syringomyelia, and 35% of affected CKCS dogs show clinical signs.

Onset of clinical signs is usually in puppies and young-adult CKCS dogs, with most dogs showing signs before 4 years of age. The most consistent sign is neck pain that can be constant or intermittent. Some dogs randomly vocalize or resent touching of the ear, limb, face, or neck of the affected side. Others scratch repeatedly at their neck or shoulder, often without making skin contact (phantom scratching). Muscle atrophy and LMN weakness of the associated thoracic limb, and ataxia and UMN deficits of the rear limbs may also be seen. Scoliosis may develop as LMN damage within the cord causes asymmetric denervation of the paraspinal muscles, resulting in vertebral deviation.

CM and syringomyelia are hereditary conditions in the CKCS, suggested to be autosomal recessive with incomplete penetrance. Diagnosis is most reliably made with MRI, which shows a small caudal fossa secondary to a hypoplastic occipital bone, cerebellar crowding, and cerebellar compression or herniation through the foramen magnum (Fig. 65.25). Fluid-filled cavities (syrinxes) are sometimes identified within the spinal cord parenchyma, particularly in cervical regions. Maximum syrinx width is a strong predictor of the severity of signs in affected dogs.

Treatment is aimed at relieving pain and other neurologic signs. Analgesics such as NSAIDs, tramadol, gabapentin, or pregabalin may be recommended. Drugs to decrease CSF production (omeprazole, acetazolamide, prednisone) may also result in clinical improvement. If medical treatment does not alleviate the clinical signs, decompression of the caudal fossa with an occipital craniectomy to reestablish normal CSF flow can be effective, but recurrence is common in the long term and neuropathic pain may persist, requiring continued medical treatment.

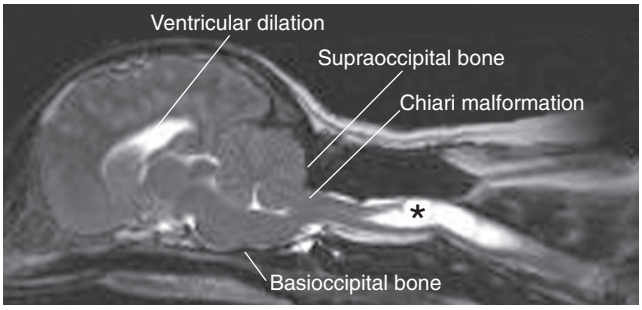


FIG 65.25
Midsagitally T2-weighted magnetic resonance imaging of the brain and upper cervical spinal cord from a 3-year-old Cavalier King Charles Spaniel with Chiari-like malformation and syringomyelia *(asterisk)*. (From Bonagura J, Twedt D: *Current veterinary therapy XIV,* St Louis, Elsevier, 2009, p 1102.)

CONGENITAL NONPROGRESSIVE DISORDERS IN YOUNG ANIMALS

Spina Bifida

Spina bifida results from embryonic failure of fusion of the two halves of the dorsal spinous processes of the vertebral arch. Although spina bifida may occur anywhere along the spinal canal, the caudal lumbar and lumbosacral region is most often affected. This malformation is most common in English Bulldogs and Manx cats. In the Manx cat, the condition is an autosomal recessive trait and may be associated with caudal agenesis. Clinical signs are nonprogressive and present from birth, including rear limb LMN paresis, fecal and urinary incontinence, loss of perineal sensation, and decreased tone of the anal sphincter. No therapy is available.

Caudal Agenesis of Manx Cats

Congenital malformations of the sacrococcygeal spinal cord and vertebrae are common in tailless Manx cats. Clinical signs result from agenesis or dysgenesis of the caudal vertebrae and sacral spinal cord. Signs are typically present from birth and include hopping or crouched pelvic limb gait, fecal and urinary incontinence, and chronic constipation.

Spinal Dysraphism

Spinal dysraphism is an inherited congenital malformation of the spinal cord. It results from abnormal development of the structures of the spinal cord along the central plane. The malformation includes a dilated or absent central canal, cavitation in the white matter, and the abnormal presence of ventral gray column cells across the median plane between the central canal and the ventral median fissure. Spinal dysraphism is recognized most commonly in Weimaraners, although other breeds are occasionally affected.

Clinical signs are present at birth. Affected dogs have a symmetric bunny-hopping pelvic limb gait, a wide-based stance, and depressed proprioception. The patellar reflex is normal. The pelvic limb flexor reflex stimulated in one limb usually elicits simultaneous flexion of both pelvic limbs.

Clinical signs caused by spinal dysraphism do not progress, and mildly affected dogs can live a normal life.

Suggested Readings

Bartholomew KA, et al. Clinical characteristics of canine fibrocartilaginous embolic myelopathy (FCE): a systematic review. *Vet Rec*. 2016;179:650.

Brisson BA. Intervertebral disc disease in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:829.

Burkert BA, et al. Signalment and clinical features of discospondylitis in dogs: 513 cases (1980-2001). *J Am Vet Med Assoc*. 2005;227:268.

Bush WW, et al. Functional outcome following hemilaminectomy without methylprednisolone sodium succinate for acute thoracolumbar disk disease in 51 non-ambulatory dogs. *J Vet Emerg Crit Care*. 2007;17:72.

Coates JR. Paraparesis. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Coates JR, Wininger FA. Canine degenerative myelopathy. *Vet Clin North Am Small Anim Pract*. 2010;40:929.

DaCosta RC, Cook LB. Cystic abnormalities of the spinal cord and vertebral column. *Vet Clin Small Anim*. 2016;46:277.

Da Costa RC. Cervical spondylomyelopathy (Wobbler syndrome) in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:881.

Jeffery ND. Vertebral fracture and luxation in small animals. *Vet Clin Small Anim*. 2010;40:809.

Meij BP, Bergknut N. Degenerative lumbosacral stenosis in dogs. *Vet Clin North Am Small Anim Pract*. 2010;40:983.

Olby NJ. Tetraparesis. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Platt S, Freeman AC. Neck and back pain. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2013.

Wolfe KC, Poma R. Syringomyelia in the Cavalier King Charles Spaniel (CKCS) dog. *Can Vet J*. 2010;51:95.

CHAPTER 66

Disorders of Peripheral Nerves and the Neuromuscular Junction



GENERAL CONSIDERATIONS

The clinically important peripheral nerves are the peripheral nerves arising from the spinal nerves in the cervical and lumbar intumescences to innervate the muscles of the limbs and the 12 pairs of cranial nerves originating in the brainstem. Spinal nerve or peripheral nerve lesions usually result in lower motor neuron (LMN) motor signs of weakness, decreased tone, and decreased reflexes in affected muscles and limbs. Sensory components of the peripheral nerves are rarely involved, but when they are, there may also be decreased, absent, or altered sensation in the skin supplied by that nerve and occasionally proprioceptive ataxia or postural reaction deficits.

At the neuromuscular junction (NMJ) a nerve impulse reaching the nerve terminal initiates the release of acetylcholine (ACh) into the synaptic cleft. ACh binds to ACh receptors (AChRs) on the postsynaptic (muscle) membrane, inducing a conformational change and ion flux that results in muscular contraction. Presynaptic NMJ disorders that interfere with the release of ACh from the nerve terminal result in generalized LMN signs of weakness and hyporeflexia similar to disorders affecting peripheral nerves. Myasthenia gravis (MG) is a unique postsynaptic disorder that causes partial failure of neuromuscular transmission, resulting in weakness with normal spinal reflexes, similar to the muscle disorders discussed in Chapter 67.

FOCAL NEUROPATHIES

TRAUMATIC NEUROPATHIES

Traumatic neuropathies are common. They result from mechanical blows, fractures, pressure, stretching, laceration, and the injection of agents into or adjacent to the nerve. Diagnosis is usually straightforward and is based on the history and clinical findings. Individual nerves or a group of adjacent nerves may be damaged. Traumatic radial nerve paralysis, complete avulsion of the entire brachial plexus, and sciatic nerve injury are most common in the dog and cat (Table 66.1; Fig. 66.1).

Electrodiagnostic testing, when available, can be used to evaluate the extent of nerve damage. In 5 to 7 days after denervation of a muscle, electromyography detects denervation action potentials (i.e., increased insertional activity and spontaneous action potentials) in the muscles normally supplied by the damaged nerve (see Table 66.1). Nerve conduction studies proximal and distal to the site of injury are also useful in assessing nerve integrity.

When an animal is presented with a peripheral nerve injury, careful mapping and assessment of cutaneous sensation and motor function help determine the precise location of the injury, and sequential mapping can be used to monitor progress (Fig. 66.2). The regenerative ability of a nerve is proportional to the continuity of connective tissue structures remaining around the damaged portion of the nerve. If adequate connective tissue scaffolding is left, axonal regeneration can occur at a rate of 1 to 4 mm/day. Severed nerve ends should be surgically brought into apposition and anastomosed to increase the likelihood of regeneration. The closer a nerve injury is to the innervated muscle, the better the chances of recovery.

Physical therapy such as swimming, limb manipulation, heat therapy, and massage help delay muscle atrophy and tendon contracture and speed return of function in animals with incomplete lesions. Self-mutilation may become a problem 2 to 3 weeks after injury because regeneration of sensory nerves can result in abnormal sensation lasting 7 to 10 days. Lack of improvement in motor function after 1 month warrants consideration of amputation of the affected limb or, when feasible, arthrodesis for limb salvage.

PERIPHERAL NERVE SHEATH TUMORS

Tumors of nerve sheath origin arise from cells surrounding the axons in peripheral nerves or nerve roots. Most of these tumors are anaplastic with a high mitotic index and aggressive biologic behavior and are therefore classified as malignant peripheral nerve sheath tumors (PNSTs) regardless of their cell of origin. These tumors are a relatively common cause of lameness and neuropathy when they involve the nerves of the brachial plexus. Lymphoma may also involve

TABLE 66.1

Traumatic Neuropathies

PERIPHERAL NERVES DAMAGED	MOTOR DYSFUNCTION	SKIN REGION OF SENSATION LOSS	MUSCLES AFFECTED
Lesions of Nerves of the Brachial Plexus			
Peripheral radial nerve damage (at level of elbow)	Loss of carpus and digit extension; may walk on dorsal paw or carry limb	Cranial and lateral forearm and dorsal forepaw	Extensor carpi radialis, ulnaris lateralis, extensors
Brachial plexus avulsion (proximal damage)			
Suprascapular nerve ([C5],C6,C7)	Loss of shoulder extension; muscle atrophy over scapular spine	None	Supraspinatus, infraspinatus
Axillary nerve ([C6],C7,C8)	Reduced shoulder flexion Deltoid muscle atrophy	Lateral brachium over humerus and scapula	Deltoideus, teres major, teres minor, subscapularis
Musculocutaneous nerve (C6,C7,C8)	Reduced elbow flexion	Medial forearm	Biceps brachii, brachialis, nerve coracobrachialis
Radial nerve (C7,C8,T1,[T2])	Reduced extension of elbow, carpus, and digits; cannot support weight	Cranial and lateral forearm and foot (except digit 5)	Triceps brachii, extensor carpi radialis, ulnaris lateralis, digital extensors
Median nerve (C8,T1[T2])	Reduced flexion of carpus and digits	None	Flexor carpi radialis, digital flexors
Ulnar nerve (C8,T1[T2])	Reduced flexion of carpus and digits	Caudal forearm distal to elbow, 5th digit	Flexor carpi ulnaris, deep and digital flexors
Lesions of Nerves of the Lumbosacral Plexus			
Femoral nerve damage L4,L5,L6	Inability to extend stifle Cannot support weight Atrophy of quadriceps Loss of patellar reflex	Medial limb (toes to thigh)	Iliopsoas, quadriceps, sartorius
Obturator nerve ([L4],L5,L6)	Abduction of limb at hip	None	External obturator, pectineus gracilis, adductor
Sciatic nerve paralysis (L6,L7,S1,[S2])	Reduced flexion and extension of hip; loss of stifle flexion; loss of hock flexion and extension; hock dropped; paw is knuckled, but weight bearing does occur; absent withdrawal reflex; atrophy of cranial, tibial, semimembranosus, and semitendinosus muscles	All regions below stifle except medial surface	Biceps femoris, semimembranosus, semitendinosus
Tibial branch (L7, S1,[S2])	Dropped hock	Plantar paw and limb distal to stifle	Gastrocnemius, popliteus, digital flexors
Peroneal branch (L6,L7,S1,S2)	Stands knuckled; no cranial tibial reflex; weak hock flexion	Cranial and lateral limb (distal to stifle)	Peroneus longus, digital extensors, cranial tibial
Cranial and caudal gluteal (L7,S1,S2)	Reduced hip flexion; stifle rotates laterally during weight bearing	None	Superficial, middle, and deep gluteals, tensor fascia lata

the nerve roots or peripheral nerves of dogs and cats (Fig. 66.3).

Clinical Features

Clinical signs depend on tumor location and the nerves involved. Trigeminal nerve sheath tumors cause ipsilateral atrophy of the temporalis and masseter muscles. Malignant PNSTs in dogs most commonly affect the caudal cervical (C6-C8) or cranial thoracic (T1-T2) nerve roots of the brachial plexus, resulting in lameness, muscle atrophy, and pain. There may be pain on shoulder manipulation, and at rest the dog may lift the affected leg to relieve muscle spasm



FIG 66.1
(A) Traumatic brachial plexus avulsion in a Chesapeake Bay Retriever. **(B)** Horner syndrome in the same dog.



FIG 66.2
Mapping the region of sensory loss is important in localizing lesions and monitoring improvement. This dog has a caudal brachial plexus avulsion, so he has lost superficial limb sensation distal to the elbow.



FIG 66.3
Dramatic muscle atrophy and sensory loss in a cat with lymphoma involving the L6-S1 nerve roots.

(root signature). The insidious onset of these tumors may make it difficult to differentiate them from lameness caused by a vague musculoskeletal injury or nerve root compression caused by intervertebral disk disease. With progression of the tumor, atrophy, weakness, and loss of reflexes may occur as the affected peripheral nerve is destroyed. Tumors involving the T1-T3 nerve roots commonly interrupt the sympathetic pathway and result in ipsilateral Horner syndrome. Similarly, the ipsilateral cutaneous trunci reflex will be absent if the C8-T1 ventral nerve roots are damaged. Tumors originating in the spinal canal and extending peripherally and tumors originating in the brachial plexus and extending proximally into the vertebral canal will often cause upper motor neuron (UMN) deficits in the ipsilateral hindlimb as the tumor expands, but this may not be clinically apparent until significant spinal invasion has taken place.

Diagnosis

Radiographs of the spine are indicated if a neoplasm involving a spinal nerve root is suspected. Nerve sheath tumors rarely cause bony changes, although expanding tumors that pass through an intervertebral foramen may cause widening of the foramen as a result of pressure necrosis. Myelography can be useful to identify spinal cord compression. Electromyography and nerve conduction velocity determinations may confirm the presence of a peripheral nerve lesion and aid in localization. Deep palpation and ultrasound examination of the axilla under general anesthesia may reveal a mass. MR imaging is the best way to

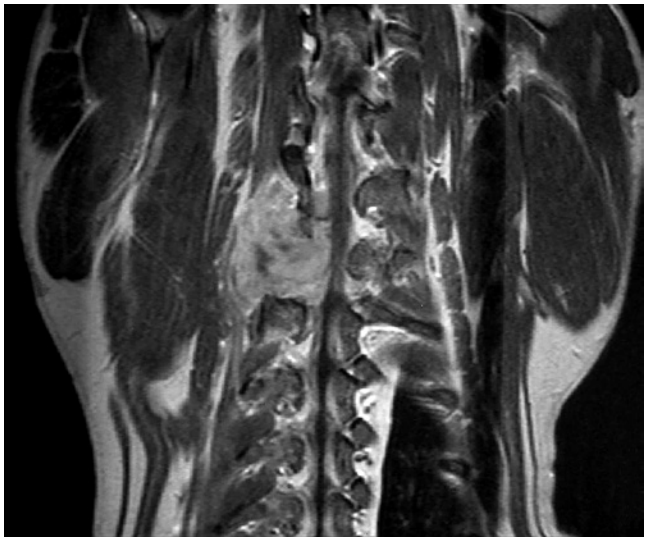


FIG 66.4
Magnetic resonance imaging of the spine of a dog with a nerve root tumor causing lameness and lower motor neuron paresis of the right forelimb reveals tumor invasion into the vertebral canal.

delineate tumor masses and detect vertebral canal invasion (Fig. 66.4).

Treatment

The treatment of choice for a PNST is early surgical removal. Aggressive removal of distally located tumors can result in a cure. Extensive neurologic damage by the tumor, damage affecting several spinal nerves or nerve roots, or severely atrophied muscles usually necessitate amputation of the limb. Nerve root tumors that have progressed to cause spinal cord compression usually involve multiple nerve roots, are rarely completely resectable, and are associated with a poor prognosis. Postoperative irradiation may be indicated in an attempt to slow tumor recurrence.

Facial Nerve Paralysis

Facial nerve (CN7) paralysis is recognized frequently in dogs and cats. In 75% of dogs and 25% of cats with acute facial nerve paralysis, there are no associated neurologic or physical abnormalities and no underlying cause can be found, prompting a diagnosis of idiopathic facial nerve paralysis. The most important differential diagnoses to consider include damage to branches of the facial nerve within the middle/inner ear secondary to inflammation, infection, neoplasia, or benign nasopharyngeal polyps. Traumatic injury to the facial nerve is unlikely without major trauma. Canine hypothyroidism is occasionally associated with a mononeuropathy involving the facial nerve, but the causality is uncertain.

Clinical Features

Clinical manifestations of facial nerve paralysis include an inability to close the eyelid, move the lip, or move the ear.

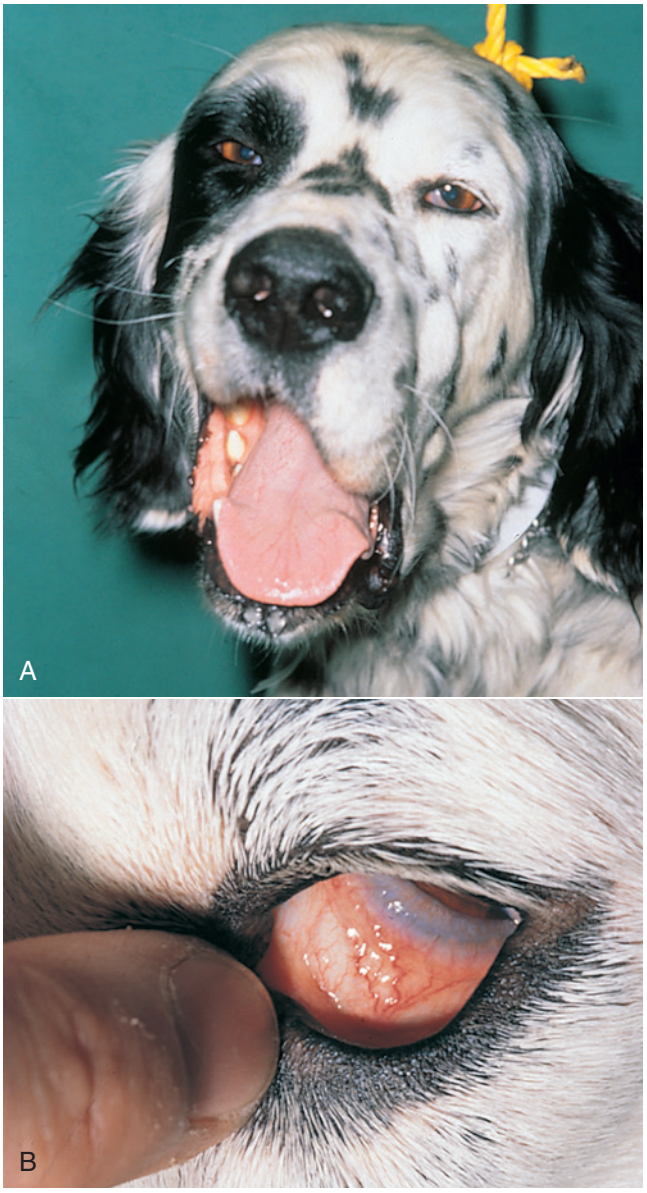


FIG 66.5
Idiopathic facial nerve paralysis in a 4-year-old English Setter. Note the drooping lip and ear **(A)** and the inability to blink **(B).** The paralysis resolved in 14 days without therapy.

Affected animals are unable to blink spontaneously or in response to visual or palpebral sensory stimulation. Corneal ulceration may occur because of an inability to distribute the tear film by blinking (neuroparalytic keratitis) and loss of facial nerve (parasympathetic)–stimulated lacrimal gland secretion (neurogenic keratitis). Drooping of the ear and lip as a result of loss of muscle tone on the affected side is common (Fig. 66.5). Rarely, a painful syndrome of hemifacial spasm with facial muscle contracture and lip retraction may occur as a result of facial nerve irritation. This should be differentiated from nonpainful muscle atrophy and contracture, which occur relatively commonly in animals with long-standing facial nerve paralysis (Fig. 66.6). Many dogs



FIG 66.6
Contraction of the muscles on the left side of the face developed in an adult dog with a 2-month history of idiopathic left-sided facial nerve paralysis. Note the erect left ear and nasal deviation to the left.

and cats with facial nerve paralysis caused by middle/inner ear disease also develop peripheral vestibular signs and/or Horner syndrome because of the close proximity of the nerves in the area of the middle and inner ear.

Diagnosis

Idiopathic facial nerve paralysis can be diagnosed only after excluding all other causes. A complete neurologic examination should be performed to ensure there are no other cranial nerve deficits, ataxia, or proprioceptive deficits suggesting a brainstem lesion. Clinicopathologic testing (i.e., complete blood count [CBC], serum biochemistry profile, urinalysis) is required to evaluate for systemic or metabolic disease. A suspicion of hypothyroidism warrants evaluation of thyroid function (see Chapter 48).

All dogs and cats with facial nerve paralysis should be evaluated carefully for disease of the middle and inner ear. Careful otoscopic examination is important even if general anesthesia is required. Most animals with otitis media or otitis interna have obvious otitis externa and a tympanic membrane that appears abnormal or ruptured, but occasionally the otoscopic examination is normal. If the suspicion for middle and inner ear disease is high, general anesthesia for radiographs or CT and myringotomy to collect a sample from the middle ear are warranted (Fig. 66.7).

Treatment

Medical treatment for bacterial otitis media/interna is discussed in Chapter 63. No treatment exists for idiopathic facial nerve paralysis. If keratoconjunctivitis sicca is present, the eye should be medicated as needed. The paralysis may be permanent, or spontaneous recovery may occur in 2 to 6 weeks.

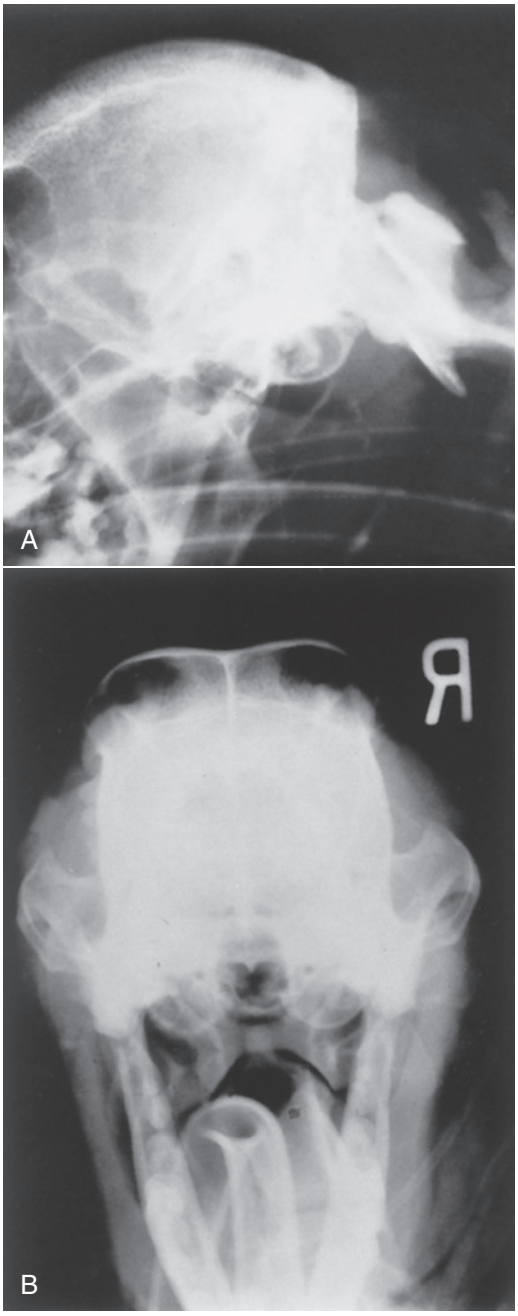


FIG 66.7
(A and B) Skull radiographs of a 4-year-old Cocker Spaniel with bilateral otitis media resulting in bilateral facial nerve paralysis. Both bullae chambers are opacified, and the left bulla is thickened by irregular and slightly indistinct new bone.

TRIGEMINAL NERVE PARALYSIS

Bilateral motor paralysis of the trigeminal nerves results in sudden onset of an inability to close the jaw or prehend food.

The mouth hangs open, but it can be physically closed and manipulated without resistance (Fig. 66.8). Swallowing is normal. Severe rapid atrophy of the muscles of mastication may occur, and about 8% of dogs display concurrent Horner syndrome or facial paresis. Sensory loss (trigeminal distribution) is variable, occurring in approximately 30% of dogs, if hyposensitization of the corneal surface occurs, there will be decreased reflex tear formation and loss of trophic factors, leading to corneal ulceration without significant discomfort (neurotrophic keratitis).

Idiopathic trigeminal paralysis is most commonly seen in middle-aged and older dogs, and Golden Retrievers are overrepresented. This disorder is rare in cats. The diagnosis relies on clinical signs and on ruling out other possible causes. Rabies and other inflammatory central nervous system (CNS) diseases are unlikely in the absence of other clinical signs, but *Neospora caninum* infection and severe idiopathic polyneuritis have occasionally been diagnosed in dogs with similar signs. Neoplastic and traumatic disorders are not usually bilateral, although bilateral motor trigeminal nerve infiltration has been reported in a dog and numerous cats with focal or multicentric lymphoma and dogs with myelomonocytic leukemia.



FIG 66.8
Idiopathic trigeminal nerve motor paralysis resulting in a dropped jaw and excessive drooling in a 9-year-old Labrador Retriever. Paralysis resolved in 14 days without therapy.

The etiology of this idiopathic disorder is unknown. If biopsy of the nerve is performed, it reveals bilateral nonsuppurative neuritis of all motor branches of cranial nerve 5 associated with demyelination. Treatment consists of supportive care. Most dogs can drink and maintain adequate hydration if they are given water in a deep container (e.g., bucket). Hand-feeding may be necessary. Holding the mouth partially closed in a sling may facilitate eating and drinking during recovery (Fig. 66.9). Lubricating eye ointments may help prevent corneal ulceration. The prognosis is excellent, with most animals recovering completely within 2 to 4 weeks. Repeat episodes are rare.

Hyperchylomicronemia

Peripheral neuropathies have been observed in cats of all ages with a mutation in the gene encoding lipoprotein lipase. Affected cats have delayed clearance of chylomicrons from the circulation, resulting in formation of lipid granulomas (xanthomas) in the skin and other tissues. These xanthomas may compress a nerve against bone, resulting in neuropathology. Horner syndrome and tibial and radial nerve paralysis are most often seen, but facial, trigeminal, and recurrent laryngeal nerve paralysis are also reported. Clinicopathologic testing reveals fasting hyperchylomicronemia and blood that looks like cream-of-tomato soup. Diagnosis is by biopsy of the xanthomas or measurement of lipoprotein lipase concentration. The neurologic signs are reversible if hyperchylomicronemia can be controlled by feeding affected cats a low-fat, high-fiber diet.

ISCHEMIC NEUROMYOPATHY

Caudal aortic thromboembolism causes paralysis from ischemic damage to affected muscles and peripheral nerves. Ischemia is caused by vasoconstriction of the collateral circulation to the limbs as a result of release of thromboxane A_2 and serotonin from activated platelets in a clot lodged in the aortic trifurcation. Caudal aortic thromboembolism is common in cats and rare in dogs. An acute onset of LMN pelvic limb paralysis or paresis is seen. Femoral pulses are weak or absent. The legs and feet are cool, and the pads and

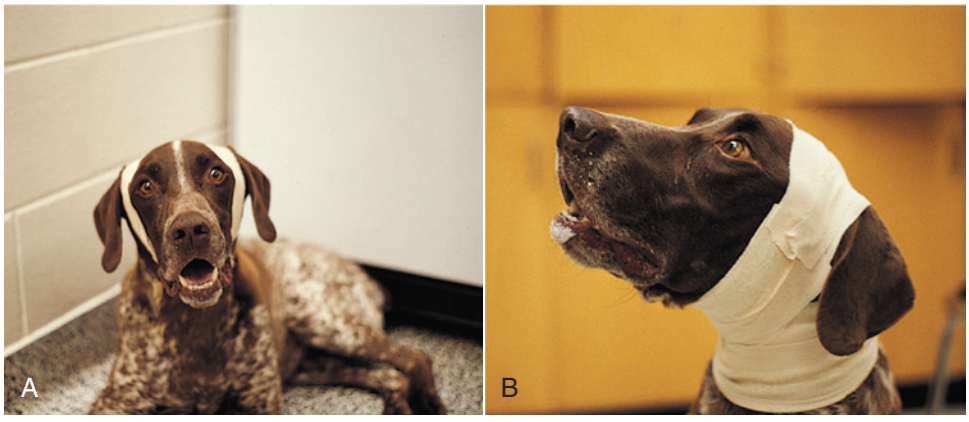


FIG 66.9
(A and B) Use of a sling to support the jaw and hold the mouth partially closed can help dogs with idiopathic trigeminal motor paralysis to eat.



FIG 66.10
(A) Acute severe lower motor neuron (LMN) paralysis of the rear limbs occurred in this 6-week-old Dalmatian puppy. The limbs were cool, and no femoral pulses were palpable. **(B)** The footpads on the front feet were warm and pink, whereas those on the rear feet were cool and pale. Ultrasound examination revealed a caudal aortic thrombus. **(C)** Acute LMN paralysis in the left hindlimb of a 9-year-old cat caused by an iliac artery thrombus. **(D)** The left hindlimb was cool, had no palpable femoral arterial pulse, and had pale footpads.

nailbeds are pale or cyanotic (Fig. 66.10). Hemorrhage does not occur when a toenail is cut short on an affected foot. The affected muscles are swollen and painful. LMN paralysis with complete areflexia of the rear limbs is common, although occasionally the patellar reflex is maintained. Within hours, rigid extension of the legs may occur as a result of contracture of ischemic muscle. In cats, cardiomyopathy is the most common cause, whereas in dogs some other disorder associated with hypercoagulability can usually be identified (see Chapter 12). Dogs should be evaluated for nephrotic syndrome, hyperadrenocorticism, heartworm disease, neoplasia, and endocarditis. Diagnosis and treatment of feline aortic thromboembolism is discussed in Chapter 12.

POLYNEUROPATHIES

Polyneuropathies affect more than one group of peripheral nerves, resulting in generalized LMN signs that include flaccid muscle weakness or paralysis, marked muscle atrophy, decreased muscle tone, and reduced or absent reflexes. Proprioception is normal unless the sensory portions of the nerves are severely affected. Electromyography, when available, reveals evidence of denervation, and nerve conduction velocity is decreased. Muscle biopsies reveal denervation and atrophy, and nerve biopsies typically reveal axonal degeneration and demyelination regardless of the underlying cause, so a thorough systemic investigation of possible etiologies is required to reach a diagnosis and recommend appropriate treatment (Box 66.1). A few of the inherited and acquired polyneuropathies have characteristic changes apparent on nerve biopsy.

CONGENITAL/INHERITED POLYNEUROPATHIES

A number of breed-associated degenerative peripheral neuropathies occur. They usually affect young animals (6 weeks to 6 months) and are presumed to have a hereditary basis. In some breeds, signs are not apparent until 1 to 4 years of age or older. Most of these disorders primarily affect the motor components of the nerves and cause progressive generalized LMN dysfunction. Pathologic lesions vary with each

BOX 66.1

Generalized Disorders of Peripheral Nerves and the Neuromuscular Junction

Chronic Lower Motor Neuron Paresis

Breed-associated degenerative neuropathies
Metabolic disorders
- Diabetes mellitus
- Hypothyroidism

Paraneoplastic disorders
- Insulinoma
- Other tumors

Immune-mediated polyneuritis
- Primary immune
- Systemic lupus erythematosus

Chronic inflammatory demyelinating polyneuropathy
Chronic idiopathic polyneuropathy

Acute Lower Motor Neuron Paresis/Paralysis

Acute canine polyradiculoneuritis (Coonhound paralysis)
Tick paralysis*
Botulism*

Episodic Weakness, Normal Neurologic Exam

Myasthenia gravis*

*Disorder of the neuromuscular junction.

disorder but may involve degeneration of the motor neurons in the ventral horn of the spinal cord (motor neuron diseases), degeneration of the peripheral nerves (axonopathies), degeneration of only the terminal and intramuscular branches of motor nerves (distal denervating disease), or demyelination of peripheral nerves. Many of the breed-specific disorders predominantly affect the rear limbs initially and then progress to affect the forelimbs. Most of these predominantly motor neuropathies cause severe tetraparesis, plantigrade stance, muscle wasting, and hyporeflexia, and some cause concurrent cranial nerve deficits.

Concurrent development of tetraparesis with laryngeal paralysis and megaesophagus due to widespread motor axonal degeneration has been recognized as an inherited syndrome called laryngeal paralysis polyneuropathy complex. Affected breeds include Rottweilers, Dalmatians, Alaskan Malamutes, Pyrenean Mountain dogs, Leonbergers, Russian Black Terriers, and others. Siberian and Alaskan Huskies, white German Shepherd dogs, Rottweilers, and Bouvier des Flandres have inherited polyneuropathies that cause laryngeal paralysis without clinically evident limb weakness due to neuronal degeneration that primarily involves the brainstem and peripheral cranial nerves. When a young dog of any of these breeds is evaluated for laryngeal paralysis, it is important to determine whether there are concurrent LMN deficits that would impact prognosis.

Many breeds of dogs have been identified with spinal muscular atrophy (degeneration of motor neurons in the brainstem and/or spinal cord), or inherited polyneuropathies with widespread axonal degeneration or demyelination. Signs are of progressive LMN paresis with muscle atrophy and loss of reflexes. Several breeds of cats also have hereditary neuropathies. Inherited peripheral neuropathies and neuronal degeneration disorders are caused by a variety of different mutations in genes that produce proteins involved in the structure and function of motor neurons, peripheral nerve axons, or the myelin sheath.

The typical neurologic findings in animals with a peripheral neuropathy include weakness, muscle atrophy, and loss of reflexes with no loss of proprioception and normal postural reactions. An exception occurs when sensory portions of the nerves are severely affected. Familial sensory or mixed sensory/motor neuropathies occur uncommonly, causing diminished or altered sensation/nociception and self-mutilation (English Pointers) or proprioceptive ataxia and dysmetria (Longhaired Dachshunds, Golden Retrievers, Boxers). All of these conditions are extremely rare and are reviewed in detail in the Suggested Readings and online sites. Presumptive diagnosis is by recognition of typical breed, age of onset, and presentation, and by ruling out other disorders. Genetic testing is available for a few disorders. Definitive diagnosis requires electrophysiologic evaluation of nerve function and nerve biopsy.

ACQUIRED CHRONIC POLYNEUROPATHIES

Diabetic Polyneuropathy

Poorly controlled diabetes mellitus causes distal axonal degeneration. Clinical signs of diabetic polyneuropathy are usually subtle or inapparent in the dog but may be dramatic in the cat. Weakness of the rear limbs, reluctance to jump, a plantigrade pelvic limb stance, and weakness of the tail are characteristic (Fig. 66.11). Physical examination findings may include marked muscle atrophy and rear limb hyporeflexia, particularly loss of hock flexion when the withdrawal reflex is tested. Over time the forelimbs can be affected as well. Severely affected dogs may also have proprioceptive deficits suggesting a mixed motor and sensory neuropathy, and concurrent laryngeal paralysis has been reported. Diagnosis is suspected in animals with poorly controlled diabetes mellitus and classic neurologic findings. Definitive diagnosis would require electrodiagnostic testing and peripheral nerve biopsy, but this is rarely performed (see Chapter 49 for more information). If diabetic polyneuropathy is recognized early, establishing improved glucose regulation can result in stabilization or improvement of neurologic signs in some cats and most dogs.

Hypothyroid Polyneuropathy

Hypothyroidism has been associated with a variety of peripheral nerve abnormalities, including diffuse LMN paresis, unilateral peripheral vestibular disease, facial nerve paralysis, laryngeal paralysis, and megaesophagus in dogs. The exact relationship between neuropathies and hypothyroidism is unclear. Nerve and muscle biopsies in affected dogs

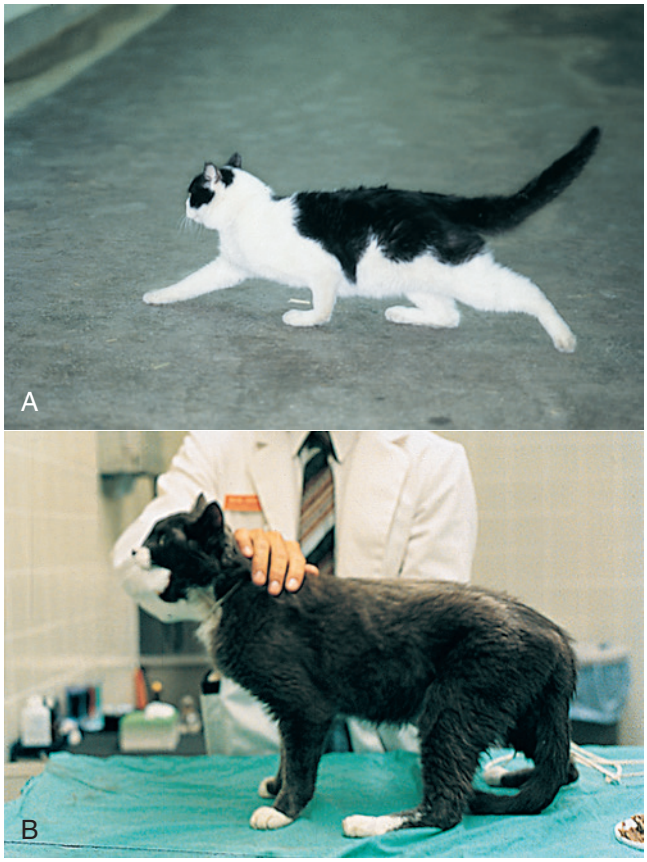


FIG 66.11
Plantigrade stance in **(A)** an 11-year-old cat and **(B)** a 6-year-old cat with polyneuropathy caused by diabetes mellitus.

may show neuronal degeneration and regeneration, as well as muscle fiber type grouping that is most indicative of denervation. In some hypothyroid dogs, neurologic signs resolve within 2 to 3 months once supplementation with thyroid hormone is initiated (Fig. 66.12) (see Chapter 48 for more information).

Insulinoma Polyneuropathy

Insulin-secreting tumors have been associated with a paraneoplastic polyneuropathy in dogs. Affected dogs may initially have a stiff rear limb gait, but this progresses to generalized weakness, muscle atrophy, and sciatic hyporeflexia. Treatment of the insulinoma may result in resolution of the polyneuropathy (see Chapter 49 for more information).

Paraneoplastic Polyneuropathy

Although clinically significant paraneoplastic neuropathies are infrequently recognized in dogs and cats, histologic lesions of polyneuropathy are evident in many dogs with cancer. LMN paresis caused by paraneoplastic polyneuropathy has been reported in dogs with bronchogenic carcinoma, hemangiosarcoma, mammary carcinoma, pancreatic carcinoma, prostatic carcinoma, lymphoma, and multiple myeloma. Complete systemic evaluation and cancer search



FIG 66.12
Plantigrade stance and weak gait in a 6-year-old Newfoundland with severe hypothyroid neuropathy. All neurologic signs and weakness resolved, and the dog lost 60 pounds within 12 months of thyroid hormone supplementation.

(thorough physical examination, thoracic and abdominal radiographs, abdominal ultrasound, lymph node aspirates) are warranted in all animals presented for chronic progressive LMN dysfunction. In some cases, treatment or removal of the offending neoplasm resolves clinical signs of polyneuropathy.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) causes slowly progressive LMN tetraparesis in adult dogs and cats. Subtle weakness and exercise intolerance are the initial manifestations, followed by progressive muscle atrophy, hyporeflexia, and severe tetraparesis. Some animals develop concurrent laryngeal or facial paresis or paralysis. When clinical findings suggest a polyneuropathy, tests should be performed to eliminate endocrine and paraneoplastic causes and to look for other systemic manifestations of a polysystemic immune-mediated disease like systemic lupus (Fig. 66.13). CIDP is largely an elimination diagnosis, but, when performed, electrophysiologic studies and nerve biopsies reveal multifocal demyelination and a mononuclear infiltrate. Immunosuppressive therapy should be initiated using prednisone and azathioprine. The short-term prognosis for clinical response and recovery may be good, but there is a tendency for this idiopathic inflammatory disorder to relapse and progress over time.

Chronic Idiopathic Polyneuropathy

Chronic idiopathic demyelinating polyneuropathies occur in dogs and cats where systemic evaluation does not reveal an underlying cause and there is no response to treatment as an



FIG 66.13
A 4-year-old Great Dane with severe weakness, hyporeflexia, and muscle atrophy caused by polyneuritis resulting from systemic lupus erythematosus. The dog also had dermatitis, polyarthritis, glomerulonephritis, and a positive antinuclear antibody test. Polyneuritis was confirmed on postmortem examination.

immune-mediated disorder. The presumptive diagnosis is made of an idiopathic degenerative disorder with no available treatment. This is thought to be the cause of the subclinical idiopathic polyneuropathy present in many geriatric large-breed dogs presented for laryngeal paralysis and stridor. The tendency for laryngeal weakness to be the earliest manifestation of this very slowly progressive polyneuropathy has been attributed to the length of the recurrent laryngeal nerve. Over time, some affected dogs will exhibit other manifestations of a progressive polyneuropathy, including paraparesis or tetraparesis, sciatic hyporeflexia, proprioceptive deficits, dysphagia, and megaesophagus.

Acute Lower Motor Neuron Tetraparesis

Weakness that begins in the pelvic limbs and rapidly progresses over 4 to 72 hours to flaccid tetraparesis or tetraplegia is an uncommon presenting complaint in dogs and cats. The major disorders causing acute flaccid tetraparesis in dogs and cats are acute idiopathic polyradiculoneuritis, botulism, tick paralysis, and acute fulminating acquired myasthenia gravis. A complete neurologic examination with attention to detail can help to differentiate these disorders (Table 66.2). Acute polyradiculoneuritis is a disease of the peripheral nerves and nerve roots, so weakness, hyporeflexia, and rapid severe muscle atrophy are the characteristic features. Botulism and tick paralysis are presynaptic NMJ disorders, so profound weakness, loss of reflexes, and cranial nerve deficits but no muscle atrophy is expected. Animals with acute fulminating MG (discussed later in this chapter) are weak but typically have normal spinal reflexes and no muscle atrophy.

Acute Polyradiculoneuritis

Acute canine polyradiculoneuritis (ACP) is the only acute-onset polyneuropathy commonly diagnosed in dogs. The disorder is clinically and histologically very similar to human Guillain Barré syndrome (GBS), an autoimmune allergic neuritis thought to be caused by exposure to a triggering antigen. The similarities between GBS and ACP have prompted investigators to look for antigens, infectious processes, or events that are triggering the immune system in dogs with ACP to cause extensive demyelination, inflammatory cell infiltration, and disruption of the ventral (motor) nerve root and spinal nerve components of peripheral nerves.

The popular name for ACP, *Coonhound paralysis*, originates in the fact that many of the early cases developed signs 7 to 14 days after hunting dogs were bitten by a raccoon. Raccoon saliva injection does not reliably produce the disorder in every dog, but in roughly 50% of North American dogs with ACP there is documented recent raccoon exposure, and serum antibodies against raccoon saliva are demonstrable (Fig. 66.14).

Acute polyradiculoneuritis also occurs in many dogs with no possible exposure to raccoons. Previous systemic illness or vaccination, *Campylobacter jejuni* infection, and *Toxoplasma gondii* infection have all been implicated as potential initiating antigens, but in most cases no cause-and-effect relationship can be proven. Rarely, an acute onset of areflexic flaccid tetraparesis or tetraplegia similar to ACP has been diagnosed in the cat. An inciting event cannot usually be determined, but rabies virus vaccination has been implicated.

Clinical Features

Inflammation of the axons and myelin sheaths at the level of the ventral nerve roots causes an acute, rapidly progressive LMN paresis or paralysis. A stilted, short-strided, weak rear limb gait progresses rapidly over a few days to tetraparesis, with most affected dogs tetraplegic within 5 to 10 days of onset. The progression of signs is variable, with some dogs remaining ambulatory but weak and others developing a flaccid nonambulatory tetraplegia. In recumbent dogs, neurologic examination reveals remarkably decreased muscle tone, rapidly progressive muscle atrophy, and severely diminished or absent reflexes. Because the disease primarily affects the ventral nerve roots, proprioception and postural reaction testing remains normal if the animal can still move its limbs and its weight is supported during testing. Some dogs seem to be hyperesthetic, reacting vigorously to mild stimulation such as muscle palpation or pinching of the toes. This hyperesthesia is a feature of polyradiculoneuritis that does not occur in association with the NMJ disorders tick paralysis or botulism, the two major differential diagnoses for rapidly progressive LMN tetraplegia in dogs. Despite the severe paresis or paralysis, dogs with ACP remain bright and alert, continue to eat and drink when supported, and can vigorously wag the tail. Bladder and rectum functions remain normal. As a rule, cranial nerves are not involved; no problems with chewing or swallowing exist, nor do any pupillary abnormalities. Most dogs do, however, have a hoarse bark and a small percentage of very severely affected dogs have

TABLE 66.2

Clinical and Diagnostic Differences Among Disorders Causing Rapidly Progressive Lower Motor Neuron Tetraparesis in the Dog

DISEASE	WEAKNESS	MUSCLE TONE	SPINAL REFLEXES	MUSCLE ATROPHY	CRANIAL NERVES	SENSATION	CSF	EMG
Acute canine polyradiculoneuritis (Coonhound paralysis)	Generalized weakness, often progressing to paralysis within 5-10 days	Decreased	Decreased or absent	Rapid and severe	Hoarse bark Able to eat and drink normally Rarely facial paresis	Hyperesthetic	Normal or increased protein	Denervation after 4-5 days
Tick paralysis Geographic potential for exposure Rapid recovery after tick removal	Generalized weakness, rapid progression	Decreased	Decreased or absent	None	Hoarse bark Dysphagia Facial paresis Decreased jaw tone	Normal	Normal	Normal
Botulism Often a group outbreak	Generalized weakness, often progressing to paralysis within 24 hours	Decreased	Decreased or absent	None	Hoarse bark Dysphagia, megaesophagus Facial paresis Decreased jaw tone Dilated pupils, absent PLR	Normal	Normal	Normal
Acute fulminating myasthenia gravis Some (50%) respond to anticholinesterase administration (see Box 66.2)	Generalized weakness but maintains ability to move	Decreased	Normal	None	Hoarse bark Dysphagia, mega-esophagus, aspiration pneumonia Facial nerve paresis (±), fatigable palpebral reflex	Normal	Normal	Normal

PLR, Pupillary light reflex.

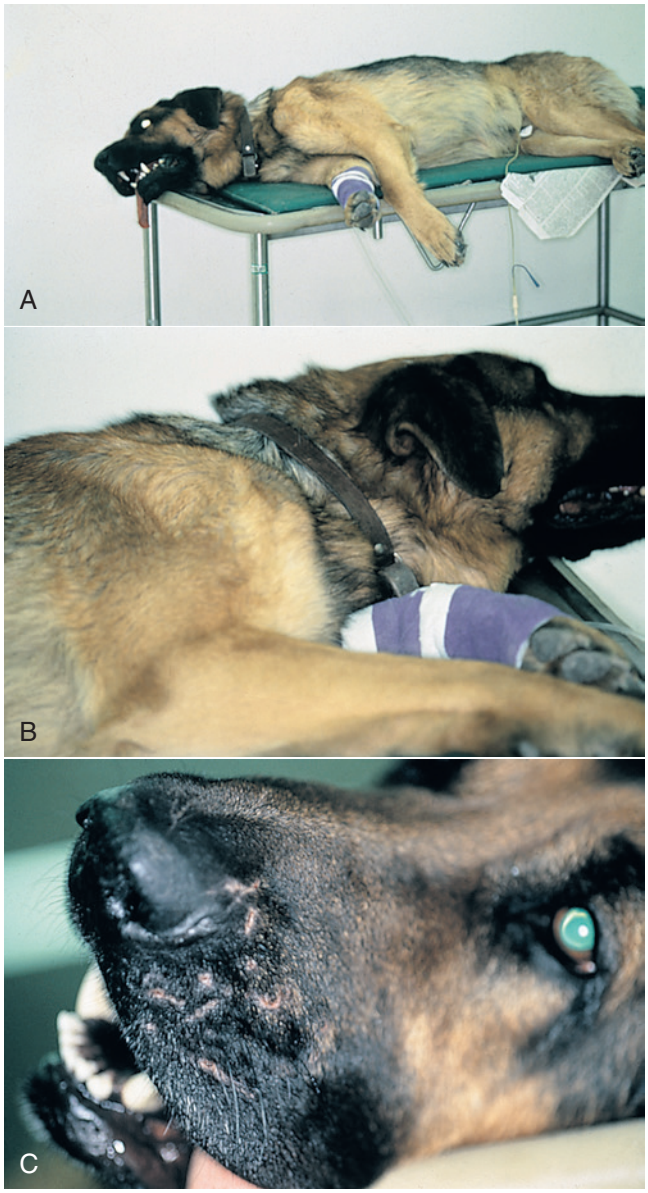


FIG 66.14
A 4-year-old German Shepherd dog with **(A)** rapidly progressive ascending lower motor neuron paralysis, **(B)** severe appendicular muscle atrophy, and **(C)** healing facial wounds presumed to be from an encounter with a raccoon. The tentative diagnosis in this dog was acute polyradiculoneuritis. Supportive care was initiated, and the dog returned to normal after a prolonged recovery lasting 3 months.

concurrent bilateral facial nerve paresis. In a few dogs, respiratory paralysis can lead to death or require mechanical ventilation.

Diagnosis

The diagnosis of ACP is suspected on the basis of historical, clinical, and neurologic findings. The most important and challenging aspect of diagnosis is differentiating this disorder from NMJ disorders causing acute LMN tetraparesis (e.g., tick paralysis, botulism, acute fulminating myasthenia gravis) using clinical features and (when available) electrodiagnostic testing (see Table 66.2). Owners should be questioned about any possible inciting event or exposure 7 to 14 days earlier. Systemic evaluation including routine bloodwork, urinalysis, thoracic radiographs, and abdominal ultrasound are usually recommended. Normal cranial nerve and esophageal function and the presence of hyperesthesia and rapidly progressive muscle atrophy make ACP most likely. When performed 6 or more days after the onset of paresis, electromyography reliably reveals diffuse denervation (fibrillation potentials and positive sharp waves), a finding not expected with NMJ disorders. Additional EMG features described in the Suggested Readings indicate a motor axonopathy and demyelination that is most pronounced in the ventral nerve roots and proximal nerves. Lumbar CSF analysis typically reveals a normal cell count and distribution as well as an increase in CSF protein, particularly 7 days or more into clinical signs. In cases where there is no history of potential raccoon exposure or recent vaccination, diagnostic testing for an inciting cause (*Toxoplasma, Neospora*) should be considered. Definitive diagnosis can also be established by nerve biopsy, but this is rarely necessary.

Treatment

No specific treatment exists for ACP. During the initial progressive phase, dogs must be monitored for respiratory compromise, especially if they have had a rapid progression to recumbency. Signs typically stabilize after 5 to 10 days, after which patients can usually be managed with supportive care at home. They may require assistance in sitting up to eat and drink. If possible, they should be kept on an air mattress, waterbed, lounge chair, or bed of straw and turned periodically to prevent lung atelectasis and pressure sores. Glucocorticoid treatment is not beneficial, and may actually slow recovery, but treatment with human intravenous immunoglobulin (IVIG, 0.5 g/kg slow intravenous [IV] infusion q24h for 4 doses) (Sandoglobulin [Behring]) may help speed recovery.

Prognosis

The prognosis for recovery in the dog is good. Most dogs begin to improve after the first week and are fully recovered within 3 to 4 weeks. Recovery may take 4 to 6 months in severely affected dogs, and some dogs never recover completely. The prognosis for complete recovery in the cat is poor. Affected animals that have recovered may be prone to recurrences, particularly if exposed again to the initiating antigen.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Presynaptic disorders that prevent ACh release into the NMJ cause rapidly progressive generalized LMN paresis or paralysis and loss of reflexes. Careful attention to clinical clues or diagnostic evaluation is required to differentiate these

disorders of neurotransmission (tick paralysis, botulism) from the more common acute peripheral nerve disorder ACP.

TICK PARALYSIS

A rapidly ascending flaccid motor paralysis has been recognized in dogs infested with certain species of ticks. Most of the reported cases in North America are associated with selected strains of ticks including *Dermacentor andersoni* in the Pacific Northwest and *Dermacentor variabilis* in the East. When a female tick feeds, she elaborates a circulating salivary neurotoxin that interferes with ACh release at the NMJ, causing presynaptic neuromuscular blockade.

Clinical Features

Dogs with tick paralysis exhibit a rapidly progressive ascending flaccid paralysis 4 to 9 days after tick attachment, when the tick is fully engorged. Signs begin in the pelvic limbs and progress rapidly to LMN tetraplegia within 12 to 72 hours. Muscles are flaccid, and spinal reflexes are decreased or absent, but muscle atrophy is not pronounced. Pain is perceived normally, with no evidence of hyperesthesia. In most cases the cranial nerves are not significantly affected, but facial weakness, an altered voice, dysphagia, or decreased jaw tone may be recognized. Without treatment, death due to respiratory paralysis may occur in 1 to 5 days.

Diagnosis

Tick paralysis is often confused with other causes of acute tetraparesis such as acute polyradiculoneuritis, botulism, and acute fulminating MG (see Table 66.2). Tick paralysis is suspected on the basis of the history, clinical signs, and knowledge of the geographic region. Sometimes a tick can be found on the animal, and diagnosis is confirmed by documenting rapid (hours to days) improvement after tick removal. Electromyography, if performed, does not reveal spontaneous muscle activity, because the muscles are not denervated as they would be in ACP. There is diminished amplitude of the muscle action potential in response to a single supramaximal stimulus, as expected with a defect in neuromuscular transmission.

Treatment

Removal of a tick or dipping the animal in an insecticidal solution results in dramatic recovery within 24 to 72 hours. The prognosis for complete recovery is good when the proper diagnosis is made.

BOTULISM

Botulism is rarely recognized in dogs and has been reported only once in cats. It results from ingestion of spoiled food or carrion (usually raw meat) containing a preformed type C neurotoxin produced by the bacterium *Clostridium botulinum*. This toxin blocks the release of ACh at the NMJ, resulting in complete presynaptic neuromuscular blockade and LMN paralysis. Clinical signs occur hours to days after ingestion of the toxin.

Clinical Features

Affected dogs develop a short-strided, weak, shuffling gait that rapidly progresses from pelvic limb weakness to recumbency over 12 hours to 4 days. Muscle tone is poor and spinal reflexes are absent, but there is no significant muscle atrophy. The tail wag is preserved. Proprioception and pain perception are normal, without hyperesthesia. By the time they are unable to rise, most affected dogs have multiple cranial nerve deficits causing dilated pupils with a sluggish pupillary light reflex, weak palpebral response, drooling, dysphagia, decreased jaw tone, and a hoarse voice/weak bark. Megaesophagus and regurgitation are common. The amount of ingested toxin determines severity of signs. Clinical signs can last for weeks, and death can occur if respiratory muscles are impaired.

Diagnosis

The diagnosis is based on clinical findings and/or a history of ingestion of spoiled food. Botulism is especially likely if an outbreak of areflexic LMN paralysis is seen in a group of dogs with access to rotting garbage or carrion. Rabies must be considered as a differential diagnosis in severely affected individual dogs, but it is usually associated with abnormal mentation. Weakness of the muscles of the face, jaw, and pharynx is much more pronounced with botulism than would be expected with acute polyradiculoneuritis or tick paralysis. When electromyography is available, it reveals no evidence of denervation, but there is diminished amplitude of the muscle action potential in response to a supramaximal stimulus, similar to the findings in tick paralysis. A definitive diagnosis is based on demonstration of botulinum neurotoxins (BoNT) in blood, vomitus, feces, or stomach contents from affected dogs, or in remnants of the spoiled food that they ingested, but often the toxin is no longer detectable by the time neurologic signs are evident, making this a presumptive diagnosis.

Treatment

No specific treatment for botulism exists. Laxatives and enemas may help remove unabsorbed toxin from the gastrointestinal tract if ingestion was recent. Antitoxin, if it was available, would simply bind and inactivate circulating toxin that had not yet penetrated nerve endings, potentially limiting the severity of clinical signs but not reversing them. Commercially available human trivalent antitoxin are directed against toxin types A, B, and E, so it will not be effective for canine or feline cases, which are all type C. Supportive care should include fluid and nutritional support and esophageal and gastric suctioning to prevent aspiration. Ventilatory support may be required in severely affected dogs. Most dogs recover in 1 to 3 weeks with supportive care, although aspiration pneumonia is a common complication during recovery.

MYASTHENIA GRAVIS

MG is the most common disorder of the NMJ diagnosed in dogs and cats, but because it is an incomplete postsynaptic

disorder, many of the clinical findings are much more suggestive of a muscle disorder than a complete NMJ blockade, such as occurs in botulism or tick paralysis. MG is characterized by a normal neurologic examination at rest, normal muscle mass and reflexes, and weakness exacerbated by exercise and alleviated by rest. Congenital and acquired forms of MG have been recognized. The congenital myasthenic syndromes (CMSs) are a rare group of hereditary disorders of neuromuscular transmission caused by structural or functional defects of the neuromuscular junction. Most CMSs result from an inherited deficiency of AChRs at the postsynaptic membranes in skeletal muscle, causing initial signs of impaired neuromuscular transmission in puppies or kittens 6 to 9 weeks old. The disorder has been recognized in English Springer Spaniels, Smooth Fox Terriers, and Jack Russell Terriers, with rare reports in other breeds and a few cats. The genetic mutation causing this CMS has been identified in Jack Russell Terriers. More recently, genetic mutations have been identified causing CMSs in Golden Retriever and Labrador Retriever puppies. An unusual, poorly classified transient CMS has also been identified in Miniature Dachshunds; the signs in these dogs resolve with maturation.

The acquired form of MG is a common immune-mediated disorder in which antibodies are directed against a portion of the nicotinic AChRs of skeletal muscle. Antibodies bind to the receptors, reducing sensitivity of the postsynaptic membrane to ACh. When nerve stimulation occurs and ACh is released into the synapse, there are less successful interactions between ACh and AChRs, causing smaller muscle endplate potentials and failure to reliably generate a muscle action potential, resulting in weakness. Weakness is compounded during exercise when some of the functional AChRs are already bound by ACh.

Acquired MG affects dogs of all breeds and both genders. German Shepherd dogs, Golden Retrievers, Labrador Retrievers, and Dachshunds are most commonly affected, but this may merely reflect the popularity of these breeds. Breeds that seem to be at increased risk for acquired MG relative to their popularity include the Akita, some terrier breeds, German Shorthaired Pointers, and Chihuahuas. A familial form of acquired MG occurs in young (2-year-old) Newfoundlands and Great Danes. Young-adult dogs (mean age, 2-3 years) and older dogs (mean age, 9-10 years) make up most of the affected population. Cats are rarely affected, but breed predispositions include the Abyssinian and Somali.

Clinical Features

Most dogs (50%-60%) with acquired MG have generalized MG with appendicular muscle weakness that worsens with exercise and improves with rest. Mentation, postural reactions, and limb reflexes are normal. Excessive salivation and regurgitation are common, caused by megaesophagus (seen in 80% of dogs with acquired generalized MG). Megaesophagus is less common in cats with MG (40%) and in dogs with congenital MG. Cats with acquired MG usually present for persistent generalized weakness (floppy cats) and cervical ventroflexion. Dysphagia, hoarse character of the bark or meow, persistently dilated pupils, and facial muscle weakness are sometimes seen.

A focal form of MG causing megaesophagus or dysphagia with no detectable appendicular weakness occurs in approximately 25% to 40% of dogs and 14% of cats with acquired MG. In addition to regurgitation, affected dogs may exhibit weakness of the pharyngeal, laryngeal, and/or facial muscles, and dogs and cats may have a fatigable palpebral reflex. About 25% to 40% of all dogs with adult-onset megaesophagus actually suffer from acquired focal MG, so this disorder should always be considered as a differential diagnosis early in the course of evaluation of dogs with megaesophagus.

An acute fulminating form of acquired MG occurs in 5% to 15% of dogs and cats with acquired MG, causing a sudden onset and rapid progression of severe appendicular muscle weakness that does not improve with rest. They are often nonambulatory and in lateral recumbency with profound weakness but preserved reflexes. Weakness may affect the intercostal muscles and/or the diaphragm resulting in respiratory distress. This form of MG is commonly associated with severe megaesophagus, pharyngeal and laryngeal muscle weakness, aspiration pneumonia, respiratory failure, and death.

Diagnosis

MG should be considered as a differential diagnosis in any dog with a normal neurologic examination and generalized muscular weakness and in all dogs with megaesophagus. Definitive diagnosis of acquired MG is made by demonstrating circulating antibodies against AChRs by immunoprecipitation radioimmunoassay. This test is readily available (Comparative Neuromuscular Laboratory, University of California, San Diego) and is positive in 85% of all dogs and cats with acquired disease and in 98% of those with generalized acquired disease. False-positive results have not been documented. Rarely, dogs with acquired MG are negative for circulating AChR antibodies, perhaps because of very high affinity antibodies that remain bound to AChRs or antibodies directed against junctional antigens other than AChRs.

When results of the serum test for antibodies are not yet available, or in animals with suspected congenital disease, support for the diagnosis of MG can be gained by demonstrating a positive response to administration of a short-acting anticholinesterase. Edrophonium chloride (Tensilon; 0.1 mg/kg), the ultra–short-acting anticholinesterase that was traditionally used for this purpose, is no longer available, so Neostigmine methylsulfate is used instead (Box 66.2). Anticholinesterase drugs inhibit enzymatic hydrolysis of ACh at the NMJ, increasing the effective concentration of ACh and the duration of its effect in the synaptic cleft, optimizing the opportunities for successful interactions between ACh and the AChRs. Atropine (0.02 mg/kg) is administered with the Neostigmine to minimize muscarinic effects. Equipment should be available for intubation and ventilation in the event that anticholinesterase administration results in neuromuscular blockade. Most animals with generalized

BOX 66.2

Anticholinesterase Test Protocol

1. Place an intravenous catheter.
2. Mix together in one syringe:
   Neostigmine methylsulfate 0.01 mg/kg
   Atropine 0.02 mg/kg
3. Have equipment available for intubation and ventilation.
4. Exercise to the point of detectable weakness.
5. Administer the Neostigmine/Atropine combination
6. Monitor weakness.

Route	Onset of Effect	Maximum Effect	Duration
IV	4-8 min	20-30 min	45-60 min
IM	20-30 min	30 min	60-90 min

MG exhibit obvious improvement in clinical signs (e.g., resolution of weakness) within 5 to 10 minutes after administration of intravenous Neostigmine, with the effect lasting approximately 60 minutes (see Box 66.2). A dramatic unequivocal response is very suggestive of MG. Failure to respond does not rule out MG. The response can be difficult to assess in dogs and cats with focal MG, and approximately 50% of dogs with acute fulminating MG will have no response because there has been marked antibody-mediated destruction of AChRs. A negative test also does not completely exclude the diagnosis of congenital MG because several of the CMSs have a poor response.

Electrodiagnostic testing (showing a decremental response of the compound muscle action potentials during repetitive nerve stimulation) can be performed as an aid to reaching a definitive diagnosis of MG, but this test requires general anesthesia—something that should be avoided whenever possible in animals with megaesophagus because of the risk of aspiration during recovery.

Whenever MG is considered as a diagnosis, thoracic radiographs should be assessed for megaesophagus, aspiration pneumonia, or thymoma, and the animal should be evaluated systemically for underlying or associated immune-mediated and neoplastic disorders. If a cranial mediastinal mass is identified, fine-needle aspiration cytologic evaluation should be used to confirm the suspicion that it is a thymoma—a tumor that has been identified in fewer than 5% of dogs with acquired MG but in more than 25% of cats. Concurrent immune-mediated disorders are common in dogs with MG, including hypothyroidism, immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, hypoadrenocorticism, polymyositis, and SLE. Rarely, MG and polyradiculoneuritis occur simultaneously in dogs. MG may also develop as a paraneoplastic disorder in association with a wide variety of tumors, including hepatic carcinoma, anal sac adenocarcinoma, osteosarcoma, cutaneous lymphoma, and primary lung tumors. Acquired drug-induced MG has also been documented in hyperthyroid cats treated with methimazole.



FIG 66.15
Upright feeding in animals with megaesophagus facilitates emptying of esophageal contents into the stomach. Animals should be maintained in this position for 10 to 15 minutes after eating.

Treatment

Treatment of acquired MG includes supportive care and the administration of anticholinesterase drugs and occasionally immunosuppressive agents. Animals with megaesophagus and regurgitation should be maintained in an upright position during feeding, while drinking, and for 10 to 15 minutes afterward to facilitate the movement of esophageal contents into the stomach, decreasing the chance of aspiration (Fig. 66.15). Dogs can be trained to eat and drink while standing with their front feet on a raised platform, or a vertical feeding system (Bailey chair) can be used. If severe regurgitation remains a problem, a gastrostomy tube can be placed to assist in the delivery of nutrients, fluids, and medications, but this will require a short general anesthesia (see Chapter 28). Whenever aspiration pneumonia is present, a transtracheal wash (see Chapter 20) should be performed for culture, and then aggressive treatment for the pneumonia should be initiated using antibiotics, fluids, nebulization, and coupage. Administration of antibiotics that impair neuromuscular transmission (e.g., ampicillin, aminoglycosides) should be avoided.

Anticholinesterase drugs are commonly administered in an attempt to improve muscular strength in dogs and cats with MG. Pyridostigmine bromide (oral [PO] Mestinon, 1-3 mg/kg q8h) has been used in dogs. In cats pyridostigmine bromide syrup (0.25-1 mg/kg PO q12h, diluted 1:1 with water to decrease gastric irritation) has been recommended. For both dogs and cats the dose must be individualized on the basis of clinical response. Ideally, feeding should be timed to coincide with peak drug effect (2 hours). In dogs initially unable to tolerate oral medication because of severe

megaesophagus, neostigmine methylsulfate (0.04 mg/kg IM q6-8h) can be used.

If an animal appears to be responding to anticholinesterase treatment but then suddenly gets worse, it is important to determine whether the deterioration is due to underdosage of the anticholinesterase drug (myasthenic crisis) or overdosage (cholinergic crisis). These are clinically indistinguishable, but administering one dose of a short-acting anticholinesterase (Neostigmine methylsulfate) allows the clinician to distinguish between them. The animal in a myasthenic crisis improves after anticholinesterase administration, whereas the condition of an animal in a cholinergic crisis becomes transiently worse or does not change.

Acquired MG is an immune-mediated disease, and administration of glucocorticoids and other immunosuppressive drugs may be associated with a more rapid clinical response, a decrease in AChR antibody, and an improved outcome in some dogs. Ideally, immunosuppressive drugs should be administered only to stable patients without aspiration pneumonia. Glucocorticoids at standard immunosuppressive doses commonly cause transient worsening of muscular weakness in dogs with MG, so treatment should be initiated with a low dose (oral prednisone, 0.5 mg/kg/day) and the dosage gradually increased over 2 to 4 weeks. Oral administration of azathioprine (Imuran, 2 mg/kg/day) or mycophenolate mofetil (CellCept, 10-20 mg/kg q12h) or Cyclosporine (5-6 mg/kg q12h) alone or in combination with prednisone has been associated with a positive clinical response in some dogs.

If a thymoma is identified during initial evaluation of a dog or cat with acquired MG, prompt surgical removal should be considered if the animal can be stabilized for surgery. Megaesophagus, dysphagia, and aspiration pneumonia are all risk factors decreasing the odds of short-term survival. Many animals with MG will have a decrease in AChR antibody titer and dramatic resolution of their signs after thymectomy. Adjunctive treatment may be required to prevent thymoma regrowth and recurrence of the signs of MG.

Prognosis

Response to medical management of MG can be good if aspiration pneumonia is not severe. Severe aspiration pneumonia, persistent megaesophagus, acute fulminating MG, and the presence of a thymoma or another underlying neoplasm are all associated with a poor prognosis for recovery. Many affected dogs die of either acute fatal aspiration or euthanasia within 12 months of diagnosis. Anticholinesterase drugs effectively control appendicular muscle weakness in most animals, but their effect on esophageal and pharyngeal function is variable. Response to various immunosuppressive protocols is difficult to determine because most dogs with acquired MG (>85%) will go into a spontaneous permanent clinical and immunologic remission within 18 months after diagnosis (average, 6.4 months) regardless of the treatment used. Spontaneous remission is unlikely in animals with thymoma or other neoplastic disease and in cats with MG. Because sequential antibody determinations in an individual animal are correlated with disease progression or remission, it is recommended that AChR antibody concentrations be measured and monitored every 4 to 8 weeks in animals treated for MG.

DYSAUTONOMIA

Dysautonomia is a polyneuropathy affecting sympathetic and parasympathetic nerves of the autonomic nervous system. Historically, it was recognized as a problem of cats in the United Kingdom, but since the late 1980s it more commonly affects dogs in the Midwestern United States, particularly in rural Kansas, Missouri, Oklahoma, and Wyoming. The etiology is unknown, although toxic and autoimmune mechanisms have been proposed. Clinical signs reflect failure of autonomic function in multiple organ systems.

Clinical Features

The disease affects primarily young adult dogs from rural environments, with a median age of 18 months. Cats are occasionally affected. Affected animals have a rapid onset of clinical signs that progress over days to weeks. Common presenting complaints are vomiting or regurgitation, straining to urinate, dribbling urine, photophobia, purulent nasal discharge, depression, and anorexia. Physical examination findings include decreased or absent anal tone, dilated pupils that do not respond to light; dry nose, eyes, and mucous membranes; and prolapse of the nictitating membranes. The bladder may be distended and easy to express.

Diagnosis

Diagnosis is suspected on the basis of the observed clinical signs. Thoracic and abdominal radiographs may reveal megaesophagus, aspiration pneumonia, generalized ileus, constipation/obstipation, and a large distended urinary bladder. The bladder is easily expressed, suggesting diminished urethral sphincter tone. Anal tone is usually decreased. Pharmacologic testing can be used to support the diagnosis. When very dilute (0.05%-0.1%) pilocarpine (Isopto Carpine 1% [Alcon Laboratories] diluted with saline) is applied to the eye of a dog with dysautonomia, pupillary constriction and nictitating membrane retraction will occur within 60 minutes or less, documenting denervation hypersensitivity. There should be no response when this solution is applied to the eye of a normal dog or cat. Subcutaneous (SC) administration of bethanechol (0.04 mg/kg) may also enable an affected dog with a distended bladder and urine dribbling to void normally. SC administration of atropine (0.04 mg/kg) does not produce a change in heart rate in affected dogs. These findings suggest the diagnosis of dysautonomia, but definitive diagnosis requires the demonstration of lesions within the autonomic nervous system at postmortem examination. Loss of nerve cell bodies results in decreased neuron density in all autonomic ganglia, especially the pelvic, mesenteric, and ciliary ganglia.

Treatment

Treatment is largely supportive and includes administering fluids, total parenteral nutrition or percutaneous gastrostomy tube feeding, bladder and colon emptying, lubricating eye ointments, and physical therapy. Pilocarpine (1%, one drop q6-12h) may improve lacrimation and decrease photophobia. SC bethanechol (0.05 mg/kg q8-12h) may improve urinary function, and prokinetic drugs (metoclopramide, cisapride) may improve gastrointestinal tract motility. The prognosis is generally poor, with a mortality rate of about 70% to 90%.

Suggested Readings

Anor S. Acute lower motor neuron tetraparesis. *Vet Clin North Am Small Anim Pract*. 2014;44:1201.

Braund KG. Degenerative disorders of the central nervous system. In: Braund KG, ed. *Clinical neurology in small animals: localization, diagnosis and treatment*. Ithaca, NY: International Veterinary Information Service; 2003. www.ivis.org.

Bruchim Y, et al. Toxicological, bacteriological and serological diagnosis of botulism in a dog. *Vet Rec*. 2006;158:768.

Coates JR, et al. Congenital and inherited neurologic disorders of dogs and cats. In: Bonagura JD, ed. *Current veterinary therapy XIII*. Philadelphia: WB Saunders; 2001.

Cuddon PA. Acquired canine peripheral neuropathies. *Vet Clin North Am*. 2002;32:207.

Harkin KR, Andrews GA, Nietfeld JC. Dysautonomia in dogs: 65 cases (1993-2000). *J Am Vet Med Assoc*. 2002;220:633.

Khorzad R, et al. Myasthenia gravis in dogs with an emphasis on treatment and critical care management. *J Vet Emerg Crit Care (San Antonio)*. 2011;213:13.

Mayhew PD, Bush WW, Glass EN. Trigeminal neuropathy in dogs: a retrospective study of 29 cases (1991-2000). *J Am Anim Hosp Assoc*. 2002;38:262.

Shelton GD. Myasthenia gravis and other disorders of neuromuscular transmission. *Vet Clin North Am Small Anim Pract*. 2002;32:188.

Shelton GD. Routine and specialized laboratory testing for the diagnosis of neuromuscular diseases in dogs and cats. *Vet Clin Pathol*. 2010;39:278.

Thieman KM, et al. Histopathological confirmation of polyneuropathy in 11 dogs with laryngeal paralysis. *J Am Anim Hosp Assoc*. 2010;46:161.

CHAPTER 67

Disorders of Muscle



GENERAL CONSIDERATIONS

Skeletal muscle functions to maintain posture and produce movement. Patients with generalized muscle disease generally present with weakness. This may manifest as a stiff and stilted gait, trembling while standing, a low head carriage (ventral neck flexion), and exercise intolerance. When a complete nervous system examination is performed, animals with muscle disease are not ataxic and most have normal postural reactions and spinal reflexes. Most muscle disorders cause muscle atrophy and/or fibrosis, whereas others cause muscle pain and muscle swelling.

Myopathies in dogs and cats can be either inherited or acquired. Genetic testing or phenotype recognition can be useful in diagnosing some of the inherited disorders. Acquired muscle disorders include infectious and immune-mediated inflammatory disorders as well as metabolic and endocrine disorders. Characteristic clinical findings may suggest a specific diagnosis, but systemic evaluation and muscle biopsies submitted to a laboratory specializing in canine and feline muscle disorders may be required for definitive diagnosis. Results of histologic examination may identify a specific disease or guide additional diagnostic testing required to demonstrate and characterize functional abnormalities.

INFLAMMATORY MYOPATHIES

MASTICATORY MYOSITIS

Masticatory muscle myositis (MMM) is a common immune-mediated disorder involving only the muscles of mastication in dogs. The masticatory muscles are composed primarily of a unique myofiber (type 2M) not present in limb muscles, and in dogs with MMM, immunoglobulin (Ig)G is directed against the unique myosin component of these fibers. Masticatory myositis can occur in any breed of dog, but the German Shepherd dog, retrieving breeds, Doberman Pinscher, and other large breeds are most commonly affected. Primarily young or middle-aged dogs are affected, but the diagnosis has been made in puppies as young as 3 months of age. No apparent gender predilection exists. The disorder has not been documented in cats.

Clinical Features

The acute form of the disease involves recurrent painful swelling of the temporalis and masseter muscles. Pyrexia, submandibular and periscapular lymphadenopathy, and tonsillitis are variably present. Dogs are reluctant to eat and are usually presented for anorexia and depression. Palpation of the muscles of the head and attempts to open the mouth are met with resistance because of pain.

As this disorder progresses, there is progressive severe atrophy of the temporalis and masseter muscles, resulting in a skull-like appearance of the head. Although this is a bilateral disease, the atrophy can be asymmetric. Opening the mouth is not painful in chronic MMM but is restricted by atrophy and fibrosis of the masticatory muscles (Fig. 67.1). The globes may sink deep into the orbits because of the dramatic loss of muscle mass (see Fig. 61.9). Many dogs are presented for evaluation as they progress from the acute to the chronic form of the disease wherein they have pain on opening the mouth, together with muscle atrophy. Some dogs with MMM will present with nonpainful severe atrophy of the muscles of mastication without any history of signs related to previous acute episodes of pain.

Diagnosis

Diagnosis is suspected on the basis of the clinical findings. In dogs presented for pain on opening the mouth, differentials must include retrobulbar abscess or mass, dental disease, and abnormalities of the temporomandibular joint or the bullae. The severe atrophy observed in chronically affected dogs must be differentiated from atrophy caused by disorders of the trigeminal nerves, widespread polymyositis (PM; any etiology), polyneuropathy, or systemic disorders such as hypothyroidism, hyperadrenocorticism, or cancer cachexia.

A hemogram may be normal or reveal mild anemia and neutrophilic leukocytosis; occasionally a peripheral eosinophilia is found. Serum creatine kinase (CK), aspartate



FIG 67.1
Chronic masticatory muscle myositis (MMM) causing **(A)** severe temporalis and masseter muscle atrophy and **(B)** inability to open the mouth more than a few centimeters in an adult Vizsla.

aminotransferase (AST), and globulin concentrations are occasionally increased. Proteinuria sometimes occurs. Circulating antibodies against masticatory myosin binding protein-C can be detected in the serum of many (80%-90%) dogs with acute MMM, but they may not be present in dogs with chronic disease. Electromyography (EMG), when available, can demonstrate acute myositis in the masticatory muscles and confirm that other muscle groups are unaffected, making PM less likely. Histopathologic evaluation of a biopsy from the affected muscles establishes the diagnosis. Fresh and formalin-fixed muscle should be submitted to permit the use of histochemical and immunohistochemical stains to identify antibody bound to type 2M muscle fibers.

Treatment

Oral (PO) administration of glucocorticoids (prednisone, 1-2 mg/kg q12h) usually results in rapid elimination of pain



FIG 67.2
Bilateral exophthalmos and upper eyelid retraction caused by extraocular myositis in a Border Collie.

in acutely affected dogs and a more gradual improved ability to open the mouth in chronically affected dogs. After about 3 weeks, the dose of corticosteroids can be decreased (to 1 mg/kg q24h) and then gradually tapered over 4 to 6 months to the lowest possible alternate-day dose. Inadequate dosing or treatment for an insufficient period of time is associated with a high rate of relapse. Dogs that do not respond adequately to corticosteroid therapy and dogs that relapse each time attempts are made to decrease the dose may benefit from use of other immunosuppressive drugs, such as azathioprine (Imuran [Burroughs Wellcome] given 2 mg/kg PO once daily until the patient shows signs of improvement, then every 48 hours) or cyclosporine (Atopica, 6 mg/kg PO q12h). Dogs treated aggressively have a good prognosis for recovery. They should be carefully monitored for relapse (using jaw mobility and discomfort, and serum CK), particularly as the glucocorticoid dose is tapered. Lifelong treatment may be required.

Historically it was recommended that dogs with chronic MMM have their jaws opened by force under anesthesia to stretch the fibrous tissue and muscle. This practice is not recommended because it does not improve clinical outcome, it increases the inflammation in torn muscle fibers, and it carries an inherent risk of iatrogenic mandibular luxation or fracture.

EXTRAOCULAR MYOSITIS

A unique form of myositis confined to the extraocular muscles, resulting in acute exophthalmos, has been described in dogs (Fig. 67.2). Affected dogs are usually young, with a

median age at presentation of 8 months. Golden Retrievers, Labrador Retrievers, and other large-breed dogs are especially susceptible, with females most predisposed. Bilateral exophthalmos and eyelid retraction are common, often with concurrent chemosis but without third eyelid prolapse. Vision may be impaired. Serum CK concentrations are usually normal. Orbital sonography or magnetic resonance imaging (MRI) confirms swollen extraocular muscles and eliminates retrobulbar abscess or mass as differentials. Definitive diagnosis requires biopsy of affected muscles (but this is rarely performed), revealing a lymphocytic inflammatory infiltrate. Response to treatment with oral prednisone (1-2 mg/kg q24h) is generally rapid and complete. Treatment should continue for at least 4 to 6 weeks. If relapse occurs during prednisone dose tapering, additional immunosuppression should be considered with Imuran or cyclosporine as for MMM. There is a good prognosis for complete and permanent recovery with proper therapy. Unilateral or bilateral restrictive ventromedial strabismus due to scarring has developed in a few young dogs with atypical extraocular muscle myositis, requiring surgical correction to restore eye position and vision.

CANINE IDIOPATHIC POLYMYOSITIS

Idiopathic PM is a diffuse inflammation of skeletal muscle presumed to be an autoimmune process. Large-breed adult dogs are most commonly affected, with many reported cases in German Shepherd dogs, Boxers, Newfoundlands, Pembroke Welsh Corgis, and Labrador and Golden Retrievers. A breed-specific PM primarily involving the masticatory, pharyngeal, and esophageal muscles has been described as a cause of dysphagia and regurgitation in Viszlas.

Clinical Features

Mild to severe weakness and a stiff, stilted gait that may be exacerbated by exercise are the most common features in dogs with PM. Muscles are painful in some dogs, whereas nonpainful severe atrophy occurs in others. Regurgitation caused by megaesophagus, dysphagia, excessive salivation, and a weak bark may occur, particularly in Newfoundlands with PM. Signs may be intermittent in mild cases or early in the course of the disease. Some dogs with acute severe disease are pyrexic and experience generalized pain. Muscle atrophy is usually prominent, especially involving the temporalis and masseter muscles and often the proximal limb muscles. Neurologic examination typically reveals normal mental status, cranial nerve examination, proprioception, and spinal reflexes, but spinal reflexes may be diminished in dogs with concurrent polyneuritis.

Diagnosis

The diagnosis of PM is based on clinical signs, CK determination, EMG, and muscle biopsy. High serum CK (2- to 100-fold increase) and AST activities are seen in most affected dogs at rest, and even more dramatic increases occur after exercise. Gamma globulins may also be increased. When available, EMG can be performed to document that multiple muscle groups are involved and to select a severely affected muscle for biopsy. A definitive diagnosis of idiopathic PM requires muscle biopsy and elimination of infectious causes of PM. Typical histopathologic findings include multifocal necrosis and phagocytosis of myofibers, and lymphocytic and plasmacytic infiltration into muscle. Muscle biopsy results may be normal in some dogs because of the multifocal patchy nature of the disease, so this should not preclude a diagnosis of myositis if the clinical findings, EMG, and serum CK concentration suggest the diagnosis. MR imaging using rapidly acquired short tau inversion recovery (STIR) sequences or postcontrast T1-weighted images has recently been shown to be a useful test to document the location of inflamed muscle prior to biopsy.

PM can occur as an idiopathic primary immune-mediated disorder, or it can be secondary to systemic immune-mediated disease (e.g., systemic lupus erythematosus), or systemic neoplasia. All dogs with PM should have a complete blood count (CBC), biochemistry profile, synovial fluid analysis, urinalysis, serum antinuclear antibody (ANA) titer, and protozoal serology, and/or immunohistochemical staining of muscle biopsies for protozoal antigens (to eliminate protozoal PM). Assessment of thoracic radiographs and abdominal ultrasound should focus on a search for systemic infection or neoplasia and identification of megaesophagus and aspiration pneumonia. Lymph node, spleen, and liver aspirates and bone marrow biopsy may be indicated because many dogs with a diagnosis of PM (including 20% of Boxers) develop lymphoma within a few months, suggesting that PM may be a preneoplastic syndrome in these dogs. If all these tests are normal, a diagnosis of idiopathic PM is made.

Treatment

Prednisone administration (1-2 mg/kg q12h for 14 days, then q24h for 14 days, then q48h) results in dramatic clinical improvement and recovery for most dogs. In dogs with megaesophagus, upright feeding of small meals (see Fig. 66.15) may be beneficial to prevent aspiration. Aspiration pneumonia, if it occurs, should be treated with antibiotics. Prednisone treatment should continue for at least 4 to 6 weeks at decreasing doses, with long-term treatment for 12 months or longer occasionally required. Azathioprine should be administered if the response to prednisone is inadequate or if relapse occurs during dose tapering.

Prognosis

The prognosis is good for recovery in dogs without severe dysphagia, megaesophagus, or aspiration pneumonia if no underlying neoplastic cause for the PM can be identified. Spontaneous recovery before treatment is initiated occurs in a few dogs.

FELINE IDIOPATHIC POLYMYOSITIS

An acquired inflammatory disorder of skeletal muscle similar to canine PM has been described in a few cats. Affected cats experience a sudden onset of weakness with pronounced

ventral neck flexion, an inability to jump, and a tendency to sit or lie down after walking short distances. Muscle pain may be evident. Neurologic examination reveals normal mentation, cranial nerves, proprioception, and reflexes.

Diagnosis is made on the basis of clinical features, increases of serum CK and AST activities, and multifocal EMG abnormalities. Many affected cats (70%) are slightly hypokalemic, suggesting a possible relationship between this disorder and hypokalemic polymyopathy. Because some clinical features of PM also mimic mild thiamine deficiency, evaluating the cat's response to thiamine injections (intramuscular [IM], 10-20 mg/day) and correcting hypokalemia are recommended before proceeding with extensive diagnostic testing for PM.

Serum titers against *Toxoplasma gondii* should be evaluated, as should tests for feline leukemia virus (FLV) antigen and feline immunodeficiency virus (FIV) antibody. A complete drug history should be obtained to eliminate the possibility of drug-induced PM. Thoracic and abdominal radiographs and abdominal ultrasound should be considered to look for an underlying neoplastic cause. PM has been diagnosed in many cats with thymoma, sometimes concurrent with acquired myasthenia gravis. Muscle biopsy reveals my fiber necrosis and phagocytosis, muscle regeneration, variation in muscle fiber size, lymphocytic inflammation, and fibrosis. Empirical treatment for *Toxoplasma* myositis is sometimes recommended (clindamycin, 12.5-25 mg/kg PO q12h); if the animal has a dramatic response to clindamycin, the treatment should be continued for at least 6 weeks. It is important to realize, however, that spontaneous recovery or remission is observed in at least one third of all cats with PM. Glucocorticoid therapy (prednisone, 4-6 mg/kg/day initially, tapered over 2 months) may aid recovery in some cats. Recurrences are common.

DERMATOMYOSITIS

Dermatomyositis is an uncommon disease characterized by dermatitis and PM. Familial canine dermatomyositis is an autosomal dominant condition with incomplete penetrance recognized in juvenile Rough-Coated and Smooth-Coated Collies, Shetland Sheepdogs (i.e., Shelties), Kelpies, Beauceron Shepherds, and Pembroke Welsh Corgis. Sporadic cases have been observed in a few other breeds, including Australian Cattle Dogs and Border Collies. The disease has not been recognized in cats. Dermatomyositis is a complement-mediated microangiopathy in which complement deposition in small vessels leads to vascular damage and skin and muscle ischemia. Skin lesions include erythema, crusts, scales, and scarring alopecia on the inner surfaces of the pinnae and on the face, distal extremities, tail tip, and other boney prominences subjected to mechanical trauma (Fig. 67.3). With progression, erosions and ulcerations are common and secondary pyoderma may be superimposed, resulting in pruritus. Histopathologic findings include hydropic degeneration of basal cells and separation of the dermoepidermal junction. A perivascular mononuclear infiltrate may be seen. Dermatologic lesions appear during the first 3 months of life and may improve or resolve with time. The course often fluctuates.



FIG 67.3
Shetland Sheepdog with typical skin lesions of dermatomyositis. This dog also had megaesophagus and generalized muscular weakness.

Dogs severely affected by dermatomyositis may develop signs of concurrent muscle disease, especially in the muscles of mastication making it difficult to prehend and chew food and lap water. Generalized muscle weakness and atrophy and a stiff gait may also occur. Megaesophagus occurs occasionally. Mentation, proprioception, and reflexes are normal. Dysphagia is common, as is regurgitation due to megaesophagus. EMG reveals spontaneous my fiber discharges, including fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges in affected muscles by 13 to 19 weeks of age, even in dogs without clinical signs of muscle weakness. Nerve conduction velocities are normal. Muscle biopsies reveal my fiber necrosis with mononuclear cell infiltrates, atrophy, regeneration, and fibrosis.

Diagnosis of dermatomyositis relies on recognition of typical clinical dermatologic changes and confirmation with histology of skin and muscle. Breeding should be discouraged. Dogs with muscular manifestations of this disorder are usually treated with immunosuppressive doses of glucocorticoids, with a variable response. Additional immunosuppressive treatments are administered as needed. Dermatologic lesions may respond to oral administration of tetracycline and niacinamide (250 mg of each q8h if <10 kg, 500 mg of each q8h if >10 kg) or pentoxifylline (Trental, 10-25 mg/kg q8-12h) and vitamin E (200-600 IU orally every 12 hours).

INFECTIOUS INFLAMMATORY MYOSITIS

Infectious myositis can be caused by protozoal, viral, rickettsial, and bacterial infections, many of which are multisystemic. Myositis caused by *T. gondii* or *N. caninum* can occur alone or in conjunction with lumbar polyradiculoneuritis in dogs, causing severe muscle atrophy and weakness of the pelvic limbs followed by rigid pelvic limb hyperextension (see Chapter 64). In cats, *T. gondii* more often causes fever and diffuse PM with muscle pain and weakness. Leishmaniasis may cause bilateral masticatory muscle pain and atrophy

with or without involvement of the limb muscles in dogs. Muscle inflammation is common in dogs with acute Leptospirosis and dogs with tick-borne infections, but signs referable to muscular involvement are often overlooked due to the severity of systemic disease. Clinical signs of muscle inflammation typically include focal or diffuse muscle pain, muscle atrophy, and weakness. Increases in CK concentration are common, and serum titers or cultures of infected tissues may be positive for the offending organism. EMG reveals spontaneous activity in affected muscles. Definitive diagnosis of infectious myositis requires muscle biopsy and identification of organisms within tissues using molecular or immunohistochemical methods. More discussion of *Neospora caninum* PM and polyradiculoneuritis can be found in Chapter 64.

ACQUIRED METABOLIC MYOPATHIES

In addition to the myopathies associated with infectious and inflammatory disease, myopathies may accompany hyperadrenocorticism (i.e., Cushing's disease), administration of exogenous corticosteroids, and perhaps hypothyroidism. In cats, a myopathy associated with hypokalemia has been recognized, and a poorly defined diffuse myopathy causing weakness is common in hyperthyroidism.

GLUCOCORTICOID EXCESS

Glucocorticoid excess due to spontaneous hyperadrenocorticism or exogenous administration of high doses of glucocorticoids can cause a degenerative myopathy. Muscle weakness and atrophy are common. Atrophy may be most pronounced in the muscles of mastication. Diagnosis is suspected on the basis of a history of exogenous steroid administration or clinical findings consistent with steroid excess (e.g., polyuria, polydipsia, hair loss, pendulous abdomen, thin skin). Muscle biopsy reveals nonspecific changes, including type 2 my fiber atrophy, focal necrosis, and fiber size variation. Diagnostic tests for hyperadrenocorticism may confirm the diagnosis (see Chapter 50). Supplementation with L-carnitine, coenzyme Q10, and riboflavin may improve muscular strength. Control of excess glucocorticoids may result in some clinical improvement.

Rarely, dogs with hyperadrenocorticism or chronic exogenous glucocorticoid administration develop a myotonia-like disorder manifested by limb rigidity, stiff gait, and hypertrophy of proximal limb muscles. CK may be mildly increased. EMG confirms repetitive high-frequency myotonic discharges, resulting in this disorder being called pseudomyotonia. Treatment consists of resolving the glucocorticoid excess whenever possible, and attempting to stabilize muscle fiber membranes (see congenital myotonia, page 1186), but the prognosis is guarded for resolution of the muscular signs.

HYPOTHYROIDISM

Hypothyroidism may be associated with a mild myopathy in dogs, causing weakness, muscle cramping, atrophy, and reduced exercise tolerance. Spinal reflexes are normal unless concurrent polyneuropathy is present. Serum CK may be normal or elevated. Biopsy typically reveals mild type 2 my fiber atrophy, an increase in type 1 myofibers, and multifocal nemaline rod inclusions. Documentation of hypothyroidism and response to thyroid hormone supplementation are required for diagnosis. Physical therapy and oral carnitine supplementation have been recommended to speed recovery.

FELINE HYPOKALEMIC POLYMYOPATHY

A polymyopathy linked to decreased dietary intake or increased urinary excretion of potassium leading to total body potassium depletion has been recognized in cats of all breeds, ages, and genders. Cats with chronic renal failure and those consuming acidifying diets are most commonly affected, but cats with polyuria or polydipsia secondary to hyperthyroidism, cats with anorexia from any etiology, and Burmese kittens with an inability to maintain a balance between their intracellular and extracellular potassium are at risk. Cats with primary hyperaldosteronism because of functional adrenal neoplasia also commonly present with weakness secondary to hypokalemic polymyopathy.

The predominant clinical feature in all of these cats is weakness characterized by persistent ventroflexion of the neck (Fig. 67.4), a stiff stilted gait, and reluctance to move.

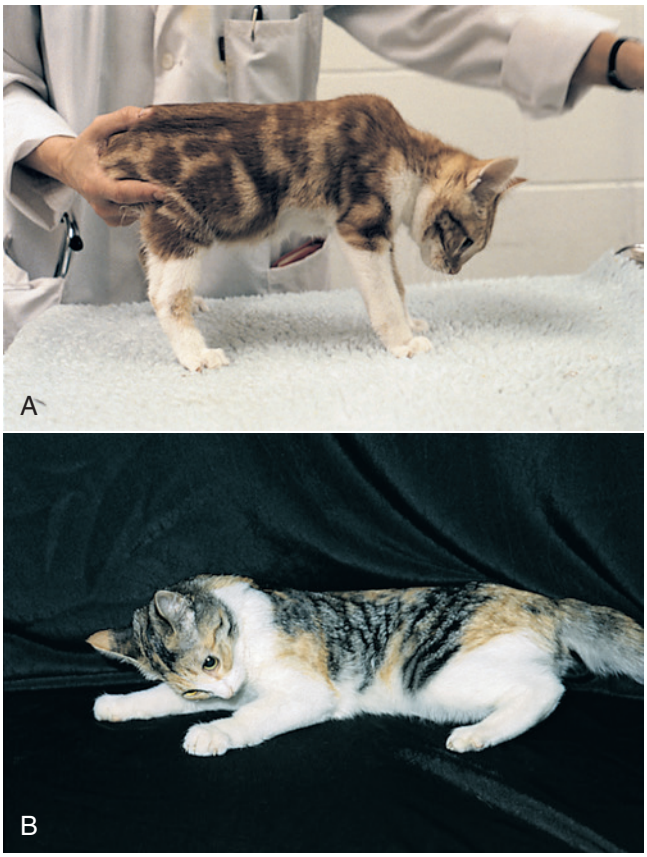


FIG 67.4
Feline hypokalemic myopathy resulting in weakness and cervical ventroflexion in **(A)** a kitten with congenital renal disease and **(B)** a hyperthyroid cat. The weakness resolved in both cats after potassium supplementation.

Some cats exhibit excessive dorsal scapular movement during walking, exertional tremor, and even collapse. Muscle pain may be apparent, but the neurologic examination is otherwise unremarkable, with normal postural reactions and spinal reflexes. Clinical signs may have an acute onset and be episodic. Serum CK activity is usually increased (10-30 times normal), and serum potassium concentration is decreased (usually <3.0 mmol/L). Adequate dietary intake of potassium should be verified, and renal function should be evaluated by measuring serum urea and creatinine concentrations, and performing a urinalysis and urine specific gravity. Interpretation of these parameters can be difficult because hypokalemia can itself decrease renal blood flow and glomerular filtration rate (GFR), interfering with urine-concentrating mechanisms. All cats with persistent hypokalemia and weakness should be tested for hyperthyroidism, and imaging should be performed to evaluate the kidneys and adrenal glands.

In cats with hypokalemic polymyopathy, EMG abnormalities are found in multiple muscle groups and include frequent positive sharp waves, fibrillation potentials, and occasional bizarre high-frequency discharges with normal nerve conduction velocities. Muscle histopathology is normal.

Signs of hypokalemic polymyopathy usually resolve after parenteral or oral supplementation of potassium and resolution of the underlying reason for hypokalemia if it can be identified. Oral treatment with potassium gluconate is recommended for mildly affected cats (Kaon Elixir, Adria Laboratories, Columbus, Ohio) at a dose of 2.5 to 5 mEq/cat twice a day for 2 days, then once a day. The dose administered is adjusted on the basis of serum potassium levels. Cats with more dramatic hypokalemia (<2.5 mEq/L) or those with severe muscular weakness with the potential to cause respiratory compromise require parenteral administration of lactated Ringer's solution, intravenously or subcutaneously, supplemented with at least 80 mEq/L of potassium chloride per liter of fluid. Intravenous (IV) supplementation of potassium should not exceed 0.5 mEq/kg/h. Long-term oral supplementation with potassium gluconate may be required. Periodic monitoring of serum potassium concentration is recommended.

NONINFLAMMATORY INHERITED MYOPATHIES

MUSCULAR DYSTROPHY

The muscular dystrophies (MDs) are a heterogeneous group of inherited degenerative noninflammatory muscle disorders. Most of the MDs recognized in dogs and cats are associated with absence or abnormalities of the cytoskeletal protein dystrophin, caused by genetic mutation of the dystrophin gene. This very large dystrophin gene is located on the X-chromosome, so MD is generally inherited as an X-linked recessive trait, clinically apparent in male dogs and transmitted by female carriers that are asymptomatic. Canine X-linked muscular dystrophy (CXMD) has been most completely described in Golden Retrievers but has also been reported in many other breeds of dogs.

Dogs with CXMD typically show clinical signs at birth or very early in life. Golden Retriever muscular dystrophy (GRMD) has been well described, and, despite the fact that all affected male dogs have the same genetic lesion, the severity of clinical expression within a litter is variable. Puppies with GRMD are often stunted even before weaning. Abduction of the elbows, a bunny-hopping gait, and difficulty opening the mouth may be noted. With time, affected puppies develop a progressively stilted gait, exercise intolerance, a plantigrade stance, muscle contractures, and atrophy of the truncal, limb, and temporalis muscles. Muscle strength deteriorates until approximately 6 months of age, when the signs tend to stabilize. Most dogs retain the ability to walk. Proprioceptive positioning and spinal reflexes are normal, but spinal reflexes may be difficult to elicit once muscle fibrosis and joint contractures occur. Severely affected dogs may develop hypertrophy of the tongue and pharyngeal or esophageal dysfunction, making it difficult to eat. Respiratory or cardiac failure may occur at 1 to 2 years of age, resulting in death.

MD should be suspected when typical clinical signs are seen in a young male puppy of a predisposed breed. Serum CK levels are markedly increased as early as 1 week of age and peak at 6 to 8 weeks of age. Very dramatic increases in CK occur after exercise. Genetic testing is available to confirm dystrophin-deficient MD in Golden Retrievers but not in other breeds. EMG reveals pseudomyotonic discharges in most muscles by 10 weeks of age. Muscle biopsies reveal marked my fiber size variation, necrosis, and regeneration, with multifocal my fiber mineralization. Immunocytochemical studies document the absence of the sarcolemmal protein dystrophin. Rarely, genetic mutations occur in dogs and cats that affect other proteins in the dystrophin-glycoprotein complex, resulting in signs identical to dystrophin-deficient MD but muscle biopsies that are not dystrophin-deficient. Importantly, many of these disorders are inherited as an autosomal recessive trait, so males and females may be affected equally.

An X-linked dystrophin-deficient MD has also been reported in the cat. Clinical signs first appear at 5 to 6 months of age. Affected cats exhibit marked generalized muscular hypertrophy, protrusion of the tongue, excessive salivation, stiff gait, and bunny hopping. Megaesophagus is common. Serum CK is greatly elevated (often >30,000 U/L). Diagnosis requires muscle biopsy and dystrophin immunostaining. No effective treatment exists for MD in dogs or cats. Low-dose prednisone (0.5 mg/kg orally q24h) and physical therapy have been recommended to help slow the progression of muscular weakness.

CENTRONUCLEAR MYOPATHY OF LABRADOR RETRIEVERS

An inherited myopathy of Labrador Retrievers known as *centronuclear myopathy* (CNM) may occur in as many as 1% of dogs of this breed tested either because of clinical signs

or for prebreeding purposes. This disorder has been previously reported as hereditary Labrador Retriever myopathy (HLRM), autosomal recessive muscular dystrophy, and type 2 my fiber deficiency. Affected puppies appear normal at birth. Muscular weakness, an awkward gait, exercise intolerance, and muscle atrophy without myalgia typically become apparent by 3 to 5 months of age, with a few puppies showing signs at 6 to 8 weeks. The age of onset and severity of clinical signs vary dramatically among affected litter mates. Severely affected dogs exhibit a low head carriage and a short-strided, stilted gait (Fig. 67.5). Their back may be arched, and a bunny-hopping gait may develop with exercise. Muscle atrophy may be marked, especially in the proximal limbs and the muscles of mastication. Neurologic examination is normal except for consistent patellar hyporeflexia or areflexia. Megaesophagus causing regurgitation has been seen in a few affected dogs. Clinical signs are worse with stress, exercise, excitement, or cold temperatures. Muscular weakness and atrophy are typically slowly progressive, but a few affected puppies will be recumbent within 1 to 2 months. Clinical signs stabilize after 12 months of age in mildly affected dogs. Serum CK is normal or moderately elevated, and on EMG examination spontaneous electrical activity and bizarre high-frequency discharges are seen. CNM is histologically characterized by mild to marked variation in fiber size, atrophic type 1 and type 2 myofibers, replacement of type 2 myofibers by type 1 myofibers resulting in a type 2 predominance, and a marked increase in centralization of nuclei within muscle cells. CNM has an autosomal recessive inheritance pattern. The causative protein tyrosine phosphatase-like A (PTPLA) genetic mutation has been identified, and a DNA test is commercially available. Dogs homozygous for the mutation are symptomatic whereas carriers are normal. No treatment is available, but mildly affected dogs can function as pets.



FIG 67.5
A 1-year-old Labrador Retriever with centronuclear myopathy (CNM) exhibiting proximal muscle atrophy, a stiff stilted gait, and ventroflexion of the neck that worsens with exercise.

X-LINKED MYOTUBULAR MYOPATHIES

X-linked myotubular myopathies are a subgroup of centronuclear myopathies characterized by a very early onset of signs and the presence of very small muscle fibers with centrally located nuclei resembling fetal myotubes. Affected puppies, all male, are presented at less than 3 months of age for rapidly progressive severe weakness, muscle atrophy, and failure to thrive. CK is normal or slightly increased. This disorder, associated with absence of the protein myotubularin, is a very rare inherited condition identified in Labrador Retrievers, Manchester Terriers, and Rottweilers. A genetic mutation causing myotubularin-deficient X-linked myotubular myopathy has been identified in Labrador Retrievers and Rottweilers, and testing is possible.

INHERITED MYOPATHY OF GREAT DANES

Inherited myopathy of Great Danes (IMGD) is a hereditary noninflammatory myopathy similar to other centronuclear and myotubular myopathies. Weakness, muscle atrophy and exercise intolerance are evident before 6 months of age and progress rapidly. Most dogs lose the ability to walk and die or are euthanized, but approximately 20% are less severely affected and survive to adulthood. This disorder is inherited as an autosomal recessive trail and is seen in male and female, fawn- or brindle-colored Great Danes. CK is normal or mildly increased. A genetic test is available.

MYOTONIA

Myotonia is a rare disorder of muscle recognized in Chow Chows, Cocker Spaniels, Staffordshire Bull Terriers, Miniature Schnauzers, Labrador Retrievers, Rhodesian Ridgebacks, Samoyeds, West Highland White Terriers, Great Danes, and individual dogs of a number of breeds. Affected kittens have also been identified. Myotonia causes a failure of muscle relaxation so that muscle contraction persists after voluntary movement or muscle percussion. Congenital myotonia usually results from altered chloride conductance, which causes postexcitement depolarization of the muscle membrane and continued contraction, but sodium, potassium, and chloride channel defects may also

occur. In Miniature Schnauzers, Australian Cattle dogs, and Jack Russell Terriers, mutant skeletal muscle chloride channel alleles have been identified, and genetic testing is available.

Clinical signs include generalized muscle stiffness and hypertrophy that begin at a young age (i.e., 1-4 months) and difficulty rising after a period of inactivity. Dogs with myotonia are neurologically normal. No abnormalities of proprioception or mentation exist. Cold weather, excitement, sudden changes in position or posture, and exercise exacerbate the clinical signs. Affected dogs may remain in rigid recumbency for up to 30 seconds if they are suddenly placed in lateral recumbency. Hypertrophy of the proximal appendicular and axial skeletal muscles is common. Serum CK and AST activities may be mildly increased, indicating muscle fiber necrosis. Bizarre high-frequency discharges that wax and wane ("dive-bomber sound") are revealed by EMG and, when present, confirm the diagnosis. Muscle biopsy alone is rarely diagnostic. Membrane-stabilizing agents such as procainamide (10-30 mg/kg PO q6h) and the sodium channel blocker mexiletine (Mexitil [Boehringer Ingelheim], 8 mg/kg PO q8h) have been beneficial in the treatment of some cases. Avoidance of cold temperatures is also advised. Most dogs are euthanized because of the severity of their signs.

INHERITED METABOLIC MYOPATHIES

Genetically based metabolic myopathies caused by a biochemical defect of the skeletal muscle energy system are infrequently described in dogs and cats. All such disorders cause signs of muscle dysfunction, including exercise intolerance, muscular weakness, a stiff stilted gait, muscle pain, muscle tremors, and muscle atrophy. Mitochondrial myopathies, glycogen storage diseases, lipid storage myopathies, and disorders causing nemaline rod accumulation within myofibers have all been reported. Genetic tests are available for a few disorders. Establishing the precise cause of a metabolic myopathy can be difficult because of the wide range of biochemical abnormalities that can arise and the codependence of all the structural proteins making up a muscle fiber. Sometimes metabolic testing can be beneficial; for example, inappropriate lactic acid accumulation with exercise suggests mitochondrial dysfunction. Evaluation of plasma lactate and pyruvate before and after exercise and quantitative analysis of urinary organic acids and plasma, urine, and muscle carnitine will help document that a metabolic myopathy is present and may help determine the affected biochemical pathway. After metabolic testing, histologic and ultrastructural examination of skeletal muscle should be performed. This metabolic testing and biopsy evaluation should be performed by a laboratory specializing in metabolic disorders of dog and cat muscle. When testing suggests a mitochondrial myopathy or a lipid myopathy, nonspecific treatment with an oral combination of L-carnitine (50 mg/kg q12h), coenzyme Q10 (100 mg/dog q24h), and riboflavin (100 mg/dog q24h) may result in improved muscle strength.

INVOLUNTARY ALTERATIONS IN MUSCLE TONE AND MOVEMENT

Tetanus, opisthotonos, myoclonus, and dyskinesias are all involuntary alterations of muscle tone or movement that are not the result of muscle disease. Tetanus is a sustained tonic contraction of the muscles. Opisthotonos is a very severe form of tetanus in which spasm of the limb and neck muscles results in lateral recumbency with dorsiflexion of the neck and extensor rigidity of the limbs. Myoclonus is the rhythmic repetitive contraction of a particular group of muscles. Dyskinesias, a group of poorly defined movement disorders that can be hard to differentiate from partial seizures, were previously discussed in Chapter 62.

OPISTHOTONOS

Opisthotonos is a very severe form of sustained muscular contraction resulting in dorsiflexion of the neck and extensor rigidity of the limbs. Opisthotonos can be seen during seizure activity, as a component of generalized extensor rigidity in patients with tetanus, or in animals with decerebrate or decerebellate rigidity (see Fig. 58.9).

TETANUS

Tetanus, defined as sustained contraction of extensor muscles without relaxation, is most often seen in dogs and cats and is due to infection with the bacterium *Clostridium tetani* and its production of tetanospasmin toxin. *C. tetani* is a gram-positive anaerobic bacillus that produces spores that persist for long periods in the environment. If a deep wound or an area of tissue damage becomes contaminated with these spores, the spores may be anaerobically converted to a vegetative form, and a toxin (tetanospasmin) is produced. The toxin ascends peripheral nerves to the spinal cord, where it blocks release of neurotransmitter from the inhibitory interneurons (Renshaw cells), releasing extensor muscles from inhibition and resulting in tetany. Cats are more resistant to the toxin than dogs.

Clinical signs of tetanus appear 5 to 18 days after wound infection. Animals with mild or early tetanus show a stiff gait, erect ears, an elevated tail, and contraction of the facial muscles (risus sardonicus; Fig. 67.6). The signs may be most severe in the area of the body adjacent to where the toxin is being produced. In severe disease the animal is recumbent and shows extensor rigidity of all four limbs and opisthotonos. The animal may die as a result of an inability to ventilate adequately. A presumptive diagnosis of tetanus is usually made on the basis of clinical signs and history of a recent wound.

Treatment should consist of rest in a warm, dark, quiet environment, immediate wound debridement, antibiotics, and intensive supportive care. Initially, aqueous penicillin (potassium or sodium salt, 40,000 units/kg IV q8h) can be given. Alternatively, metronidazole (10-15 mg/kg IV q8h) may be administered; it is bactericidal against most anaerobes and achieves a therapeutic concentration even in



FIG 67.6
Tetanus in two dogs, with the erect ears and risus sardonicus resulting from contraction of the head and facial muscles. Both dogs had wounds on a forelimb, which were presumed to be the site of entry of the toxin.

necrotic tissues. Antibiotics are administered for 2 weeks or until clinical recovery occurs.

When available, tetanus antitoxin is given to neutralize any toxin that remains unbound to the central nervous system (CNS) to prevent progression of signs. Anaphylactic reactions occasionally occur, so a test dose (0.1 mL) of tetanus antitoxin (equine origin) is injected intradermally 15 to 30 minutes before administering a treatment dose. If no wheal develops after the test dose, the antitoxin is given intravenously (200-1000 units/kg; maximum, 20,000 units). This dose is *not* repeated; a therapeutic blood concentration persists for 7 to 10 days after a single injection, and repeated administration of antitoxin increases the chance of an anaphylactic reaction. Injecting a small dose of antitoxin (1000 units) just proximal to the wound site may be beneficial in dogs and cats with localized tetanus.

The animal is maintained in a quiet, dark environment to minimize sensory stimulation. Muscle spasms are controlled with intermittent IV boluses (1 mg/kg) or an IV constant rate infusion (CRI; 1 mg/kg/h) of diazepam or subcutaneous acepromazine (0.05-0.1 mg/kg q8-12h as needed), methocarbamol (50-100 mg/kg IV q8h), and phenobarbital (2-6 mg/kg IV or IM q6h). Magnesium sulfate ($MgSO_4$) 70 mg/kg over 30 minutes followed by a low-dose CRI (100 mg/kg/day) may improve relaxation and decrease the need for additional sedative medications. If needed, treatment can be intensified as for status epilepticus (see Chapter 62). Nutritional support may have to be provided through an esophageal or gastrostomy tube until the animal can eat and drink. The animal is hand-fed as soon as it is able to prehend food and swallow. In some animals, urinary and fecal retention must be managed by repeated catheterization and enemas. Physiotherapy and massage can improve blood and lymph flow to and from the muscles, promote relaxation, decrease discomfort, and aid return of muscle function. Improvement is usually noticeable within 1 week, but signs may persist for 3 to 4 weeks. The prognosis is poor if the signs progress rapidly, but about 50% of affected dogs survive if managed intensively.

MYOCLONUS

Myoclonus movements are sudden, brief, shock-like involuntary movements resulting in contraction of a portion of a muscle, an individual muscle, or a group of muscles. A constant repetitive myoclonus, occurring as often as 60 times per minute, is commonly observed in dogs currently or previously affected by canine distemper encephalomyelitis (see Chapter 64). Limb and facial muscles are most often involved, and these rhythmic contractions do not abate during sleep or general anesthesia. Meningoencephalomyelitis causes focal lesions of the lower motor neurons of the spinal cord or cranial nerve nuclei resulting in creation of an autonomous pacemaker, generating these rhythmic muscle contractions. Although myoclonus is most commonly associated with canine distemper meningoencephalomyelitis, other focal inflammatory or neoplastic lesions of the spinal cord can also produce myoclonus in rare cases. The prognosis for resolution of the myoclonus is grave.

Familial reflex myoclonus causing intermittent spasms of the axial and appendicular muscles with occasional episodes of opisthotonos has been recognized in 4- to 6-week-old Labrador Retriever litter mates. These signs worsen when the animal is stressed or excited. Treatment with diazepam and clonazepam has not been successful. The prognosis for recovery is grave.

Animals with progressive myoclonic epilepsy experience seizures characterized by sudden muscular twitching, jerky involuntary movements, or muscle fasciculations that may or may not progress to generalized tonic-clonic seizures. Myoclonic seizures often occur in response to specific tactile, visual, or auditory stimuli (see reflex seizures, Chapter 62). Myoclonic epilepsy has been recognized as a

slowly progressive disorder in adult (mean 7 years) Miniature Wirehaired Dachshunds, Bassett Hounds, Beagles, and others with Lafora disease, a degenerative brain disorder. Audiogenic reflex seizures have also been described in cats. Levetiracetam appears to be the most effective AED for treatment of myoclonic seizures in dogs and cats.

TREMORS

A tremor is a rhythmic, oscillatory movement of a body part. Intention tremors of the head, usually associated with cerebellar disease, substantially worsen as the animal intends to initiate movement, as when the head nears a target during goal-oriented movement such as attempts to eat, drink, or sniff an object.

When animals are presented with a single occurrence of an acute onset of generalized tremors and increased extensor muscle tone, a toxic cause should be suspected (see Box 62.3). Strychnine, metaldehyde, chlorinated hydrocarbons, tremorgenic mycotoxins, and organophosphates are the most common toxic causes of tremors. Drug-induced tremor can be associated with metoclopramide, fentanyl/droperidol, or diphenhydramine administration. Metabolic disturbances such as hypoglycemia, hepatic encephalopathy, and hypocalcemia can also cause tremors, muscle fasciculations, and tetany.

Young-adult (5 months to 3 years of age) small-breed dogs presenting with an acute onset of generalized head and body tremors may have steroid-responsive encephalitis. Historically this disorder was first identified only in white dogs (Maltese, West Highland White Terrier), and the syndrome was called "little white shaker syndrome." Diagnosis requires testing to eliminate toxic and metabolic disorders as well as infectious causes of encephalitis (described in further detail in Chapter 64—meningoencephalitis).

A congenital diffuse tremor syndrome associated with abnormal development of myelin in the CNS has been observed in puppies. Affected puppies stand with a wide-based stance and show whole-body tremors that worsen with exercise or excitement. This syndrome is progressive and severe in male Welsh Springer Spaniels, usually resulting in death within 2 to 4 months. Less progressive tremor syndromes have been recognized in the Weimaraner, Bernese Mountain dog, Samoyed, Dalmatian, and Chow, as well as sporadically in other breeds, with signs apparent by 4 weeks of age. Diagnosis is based on the signalment and clinical findings in the absence of other neurologic deficits or clinicopathologic abnormalities. In the Chow and Weimaraner, gradual clinical recovery may occur within 1 to 3 months without treatment. Genetic testing is available for these hypomyelination disorders in Springer Spaniels, Chow Chows, and Weimaraners.

Trembling of the pelvic limbs (senile tremors) may develop in older dogs that are weak but otherwise neurologically normal. The trembling disappears at rest but is apparent when the animal stands, and it worsens with exercise. Results of all tests are normal, and there is no effective treatment. Diagnostically, it is important to rule out electrolyte disturbances, hypothyroidism, hypoadrenocorticism, hip dysplasia, and lumbosacral disease.

DYSKINESIAS

Dyskinesias are CNS disorders that result in involuntary movements in fully conscious individuals. These movement disorders have only occasionally been described in dogs and cats and may be difficult to distinguish from focal seizures or stereotypical behavior disorders (see Chapter 62). Signs consist primarily of episodic, unpredictable, rhythmic, involuntary limb hyperextension or hyperflexion; head bobbing; or the adoption of abnormal postures.

DISORDERS CAUSING EXERCISE INTOLERANCE OR COLLAPSE

Reluctance to exercise or inability to exercise for a prolonged period is a common complaint among dog owners. Exercise intolerance can result from orthopedic, cardiovascular, respiratory, hematologic, metabolic/endocrine, neurologic, neuromuscular, and muscular disorders (Box 67.1). When evaluating a dog for a primary complaint of exercise intolerance, the veterinarian must perform a careful physical and neurologic examination. Muscle atrophy or pain and weakness at rest but normal postural reactions and reflexes may suggest a muscle disorder. Joint pain may indicate that the dog has polyarthritis, orthopedic disease, or degenerative joint disease. Abnormalities of cardiac auscultation or arterial pulse character should prompt thorough cardiac evaluation. Routine systemic evaluation with clinicopathologic tests and survey radiographs should be completed. When all examinations and tests are normal at rest, affected dogs should be evaluated while performing the exercise historically associated with their exercise intolerance. Characteristic clinical features during the exercise intolerance (e.g., weakness, cyanosis, stridor, lameness, arrhythmia) sometimes provide a clue about etiology. Depending on clinical findings, additional testing may be recommended, including measuring antibodies against acetylcholine receptors (AChRs), continuous electrocardiographic monitoring, thyroid and adrenal function evaluation, arterial blood gas, and measuring preexercise and postexercise parameters (i.e., electrolytes, glucose, creatinine kinase). Canine dynamin-associated exercise-induced collapse (dEIC) in Labrador Retrievers and other breeds and Border Collie collapse (BCC) have been well characterized and should be recognizable based on classical signalment and signs; a genetic test is available for dEIC. These two conditions are described in Chapter 62 because they are paroxysmal disorders often confused with partial seizures. When neurologic examination and ancillary testing suggests an unknown muscular cause for exercise intolerance, special metabolic testing should be considered (urinary organic acid and plasma amino acid analysis, carnitine measurement and pre- and postexercise

BOX 67.1

Important Causes of Acquired Exercise Intolerance in Dogs

Orthopedic

Developmental disorders
Bone pain
Degenerative joint disease
Polyarthritis
Ligamentous injuries

Cardiovascular

Congestive heart failure
Cardiac tamponade
Cardiac arrhythmias

Respiratory

Laryngeal paralysis
Airway obstruction
Lung parenchymal disease
Pulmonary vascular disease
Pleural space disease

Hematologic

Anemia
Polycythemia

Metabolic/Endocrine

Hypoglycemia (often intermittent)
Hypoadrenocorticism
Hypothyroidism
Hyperadrenocorticism

Neurologic/Neuromuscular

Myasthenia gravis
Generalized or partial seizures (induced by exercise/hyperventilation)
Idiopathic polymyositis
Infectious myositis
Inherited myopathies
Diskospondylitis
Cauda equina syndrome
Dynamin-associated exercise-induced collapse (EIC)
Border Collie collapse (BCC)

acid-base parameters, blood lactate, and pyruvate). These samples and fresh and fixed muscle biopsies should be sent to a laboratory specializing in the investigation of veterinary muscle disorders.

Suggested Readings

Allgoewer I, et al. Extraocular muscle myositis and restrictive strabismus in 10 dogs. *Vet Ophthalmol*. 2000;3:21.

Bandt C, et al. Retrospective study of tetanus in 20 dogs: 1988-2004. *J Am Anim Hosp Assoc*. 2007;43:143.

Cosford KM, Taylor SM. Exercise intolerance in retrievers. *Vet Med*. 2010;105:64.

Evans J, Levesque D, Shelton GD. Canine inflammatory myopathies: a clinicopathologic review of 200 cases. *J Vet Intern Med*. 2004;18:679.

Gaschen F, Jaggy A, Jones B. Congenital diseases of feline muscle and neuromuscular junction. *J Feline Med Surg*. 2004;6:355.

Klopp LS, et al. Autosomal recessive muscular dystrophy in Labrador Retrievers. *Compend Contin Educ Pract Vet*. 2000;22:121.

Lowrie M, Garosi L. Classification of involuntary movements in dogs: myoclonus and myotonia. *J Vet Intern Med*. 2017;31:979–987.

Platt SR, Shelton GD. Exercise intolerance, collapse and paroxysmal disorders. In: Platt SR, Olby NJ, eds. *BSAVA manual of canine and feline neurology*. Gloucester: BSAVA; 2004.

Shelton GD, Engvall E. Muscular dystrophies and other inherited myopathies. *Vet Clin North Am Small Anim Pract*. 2002;32:103.

Taylor SM. Selected disorders of muscle and the neuromuscular junction. *Vet Clin North Am Small Anim Pract*. 2000;30:59.

Taylor SM. Exercise-induced weakness/collapse in Labrador Retrievers. In: Tilley LP, Smith FW, eds. *Blackwell's five minute veterinary consult: canine and feline*. 6th ed. Ames, Iowa: Blackwell; 2016.

Vite CH. Myotonia and disorders of altered muscle cell membrane excitability. *Vet Clin North Am Small Anim Pract*. 2002;32:169.



Drugs Used in Neurologic Disorders

DRUG NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Acepromazine	Relaxation (tetanus), sedation, decrease urethral smooth muscle tone	0.1-0.2 mg/kg IV, SC, IM q6h 1-2 mg/kg PO q6-8h	Same 0.5-2 mg/kg PO q6-8h
Activated charcoal (1 g/5 mL water)	Gastrointestinal adsorbent	10 mL/kg PO	Same
Ampicillin	Antibiotic	22 mg/kg PO q8h or 22 mg/kg IV, SC, IM q6h	Same
Amoxicillin with clavulanic acid (Clavamox)	Antibiotic	12.5-25 mg/kg PO q8h	Same
Apomorphine	Emetic	0.08 mg/kg SC or 6 mg (1 crushed tablet) in conjunctival sac	Use alternative (xylazine)
Atropine	Premedication for anticholinesterase testing for myasthenia gravis Antidote for cholinergic toxins	0.02 mg/kg IV or 0.04 mg/kg IM 0.5 mg/kg IV, then 1.5 mg/kg SC q6-8h	Same Same
Azathioprine (Imuran)	Immune-mediated diseases	2 mg/kg PO q24h	Do not use
Bethanechol (Urecholine)	Treat bladder atony	0.04 mg/kg PO, SC q8h	Same
Calcium gluconate (10%)	Treat hypocalcemia	0.5-1 mL/kg IV	Same
Cefotaxime	Antibiotic	20-40 mg/kg IV q6h	Same
Ceftriaxone	Antibiotic	25 mg/kg, IV or SC, q12-24h	Same
Cephalexin (Keflex)	Antibiotic	20-40 mg/kg PO q8h	Same
Chlorpromazine (Thorazine)	Antiemetic (vestibular)	0.5 mg/kg IV, SC, IM q8h	Same
Clindamycin	Antibiotic	10-15 mg/kg PO q8h	Same
Cyclosporine (Atopica)	Treat GME	6 mg/kg PO q12h	None
Cytosine arabinoside (Cytosar)	Treat GME	50 mg/m^2 SC q12h on 2 consecutive days q21d	None
Dextrose (50%)	Treat hypoglycemia	2 mL/kg IV	Same
Diazepam (Valium)	Anticonvulsant, chronic seizure management Status epilepticus	0.3-0.8 mg/kg PO q8h 5-20 mg, IV or rectal	Same 5 mg, IV or rectal
Diphenhydramine	Antiemetic (vestibular)	2-4 mg/kg, IM or SC	1-2 mg/kg, IM or SC
Doxycycline	Antibiotic	5-10 mg/kg PO, IV q12h	Same
Edrophonium chloride (Tensilon)	Tensilon test for myasthenia gravis	0.1-0.2 mg/kg IV	0.2-1 mg/cat IV
Enrofloxacin (Baytril)	Antibiotic	5-20 mg/kg PO, IV, IM q24h	5 mg/kg, PO or IM, q24h
Felbamate (Felbatol)	Anticonvulsant	15 mg/kg PO q8h	Same
Furosemide (Lasix) Decrease intracranial pressure	Diuretic	2-4 mg/kg IV, IM 1 mg/kg IV	Same Same
Gabapentin (Neurontin)	Anticonvulsant	10-20 mg/kg PO q8h	Same
Ipecac syrup	Emetic	6.6 mL/kg PO	Same
Leflunomide	Treat GME	2-4 mg/kg PO q24h	10 mg/cat PO



Drugs Used in Neurologic Disorders—cont'd

DRUG NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Levetiracetam (Keppra)	Anticonvulsant (chronic) Anticonvulsant (status epilepticus)	20 mg/kg PO q8h 60 mg/kg IV	Same Unknown
Mannitol 20%	Cerebral edema treatment	1-3 g/kg IV over 15 min	Same
Meclizine	Vestibulosedative antiemetic	1-2 mg/kg PO q24h	Same
Methocarbamol (Robaxacin)	Muscle relaxant	20 mg/kg PO q8-12h	None
Methylprednisolone sodium succinate (SoluMedrol)	Spinal trauma (acute)	20-40 mg/kg IV	Same
Metronidazole (Flagyl)	Antibiotic	10-15 mg/kg PO q8h 7.5 mg/kg IV q8h	Same Same
Mycophenolate mofetil (CellCept)	Treat GME/Myasthenia gravis	20 mg/kg PO q12h × 30 days, then 10 mg/kg q12h	None
Neostigmine methylsulfate	Myasthenia gravis treatment Testing for myasthenia gravis	0.04 mg/kg IM q6-8h 0.01 mg/kg IV after premedicating with atropine	Same Same
Pentobarbital	Anticonvulsant/anesthetic	5-15 mg/kg IV to effect	Same
Phenobarbital	Anticonvulsant	2.5-3 mg/kg PO q12h; adjust based on blood level	Same
Phenoxybenzamine	Decrease urethral smooth muscle tone	0.25-0.5 mg/kg PO q8h	2.5-5 mg/cat PO q12h
Potassium bromide	Anticonvulsant	15-20 mg/kg PO q12h; adjust based on blood level	None
Potassium gluconate (Kaon Elixir)	Treat hypokalemia	None	2.5-5 mEq PO q12h
Pralidoxime chloride (2-PAM)	Treat organophosphate intoxication	20 mg/kg IM q12h	Same
Prednisone	Immunosuppression Antiinflammatory/antiedema	2-4 mg/kg PO q24h 0.5-1 mg/kg PO q24h	2-6 mg/kg PO q24h Same
Procainamide	Myotonia	10-30 mg/kg PO q6h	None
Propofol	Anticonvulsant/anesthetic	4 mg/kg IV to effect	Same
Procarbazine (Matulane)	Treat GME	25-50 mg/m^2 PO q24h × 30 days, then q48h	None
Pyrimethamine	Toxoplasmosis	0.25-0.5 mg/kg PO q12h	Same
Pyridostigmine bromide (Mestinon)	Myasthenia gravis	1-3 mg/kg PO q8h	0.25-1 mg/kg PO q12h
Trimethoprim/sulfadiazine (Tribrissen)	Antibiotic	15 mg/kg PO q12h	Same
Xylazine (Rompun)	Emetic (cats)	None	0.44 mg/kg IM
Zonisamide (Zonegran)	Anticonvulsant	5-10 mg/kg PO q12h	

GME, Granulomatous meningoencephalomyelitis; *IM,* intramuscular; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.

PART TEN ▪ Joint Disorders

Susan M. Taylor

CHAPTER 68

Clinical Manifestations of and Diagnostic Tests for Joint Disorders



GENERAL CONSIDERATIONS

Disorders affecting the joints can be either noninflammatory or inflammatory (Box 68.1). Noninflammatory joint disorders including developmental, degenerative, neoplastic, and traumatic conditions are discussed in greater detail elsewhere (Rychel, 2010). Inflammatory joint disorders can be infectious or immune-mediated, and may affect one or multiple joints (polyarthritis). Immune-mediated polyarthritis is further classified as being erosive or nonerosive on the basis of physical examination and radiographic findings. Immune-mediated nonerosive polyarthritis (IMPA) is the most common type of polyarthritis recognized in dogs. It results from immune-complex deposition within the synovial membrane, causing a sterile synovitis. IMPA usually occurs as an idiopathic or primary isolated immune-mediated disorder, but it may also be a feature of the multisystemic immune-mediated disorder systemic lupus erythematosus (SLE) or may occur secondary to antigenic stimulation (reactive polyarthritis) in animals with chronic infection or neoplastic disease, or following administration of certain drugs. Some breed-associated immune-mediated syndromes of polyarthritis, polyarthritis/meningitis, or polyarthritis/myositis are also believed to be immune-mediated but have a genetic basis in dogs (see Chapter 64).

CLINICAL MANIFESTATIONS

Traumatic or developmental joint disorders typically involve only one or two joints, with lameness consistently described in the same limb(s). Animals with degenerative joint disease (DJD) typically exhibit low-grade chronic discomfort that causes lameness and a reluctance to exercise without systemic signs of illness and signs that are fairly consistent from day to day. In contrast, the pain associated with inflammatory arthritis—especially polyarthritis—is often much more severe than that of degenerative arthritis, and affected animals may refuse to walk or may cry in pain when moved or touched (Fig. 68.1). A shifting-leg lameness or "walking on egg shells" gait is commonly observed in dogs with polyarthritis. Some patients with polyarthritis are not obviously lame but have a vague history of decreased appetite, fever, weakness, stiffness, or exercise intolerance; in fact, polyarthritis is a common cause of persistent or cyclic fever in dogs (Battersby, 2006). Because some animals with polyarthritis do not have obvious lameness, joint pain, or detectable joint swelling or effusion, it is important to maintain a high index of suspicion for this disorder.

DIAGNOSTIC APPROACH

Animals with nonspecific pain, a stiff gait, reluctance to exercise, or fever of unknown origin should always be evaluated with a careful physical examination in an attempt to localize a region of pain or inflammation. Observation of the animal's posture and gait and thorough manipulation and palpation of the spine and all the muscles, bones, and joints of each limb are important. Palpation of the bones themselves will elicit pain in some animals with traumatic injuries and in dogs affected by panosteitis, hypertrophic osteodystrophy, osteomyelitis, or bone neoplasia. Palpation of affected muscles will be painful in animals with myositis or strain/sprain injuries. Spinal or cervical pain are expected with a variety of spinal cord or vertebral disorders, intracranial mass lesions, meningitis, or polyarthritis; inflammation of the intervertebral facetal joints can manifest as neck or back pain (see Box 58.8 and Box 64.1).

Most animals with joint inflammation experience obvious discomfort during joint manipulation. Flexing and extending a joint affected by degenerative or erosive inflammatory disease commonly reveals a restricted range of motion and crepitation, suggesting articular wear, the presence of

BOX 68.1

Classification of Common Joint Disorders in Dogs and Cats

Noninflammatory Joint Disease

Developmental
Degenerative
Traumatic
Neoplastic

Inflammatory Joint Disease

Infectious
Noninfectious (immune-mediated)
  Nonerosive
  Erosive

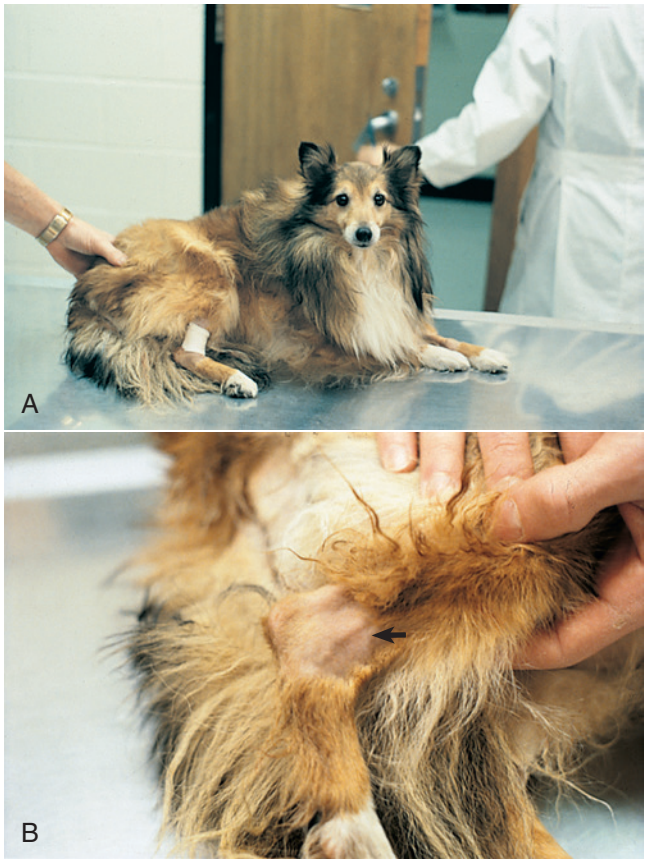


FIG 68.1
(A) A 7-year-old Shetland Sheepdog was referred for suspected paralysis. The dog was neurologically normal but refused to rise because of joint pain resulting from idiopathic immune-mediated polyarthritis. **(B)** The hock joint is visibly swollen.

osteophytes, or other periarticular changes. The stability of affected joints should be evaluated to assess the integrity of the supporting ligaments. Animals with nonerosive polyarthritis commonly have joint swelling and pain on manipulation of affected joints but the joints should not be

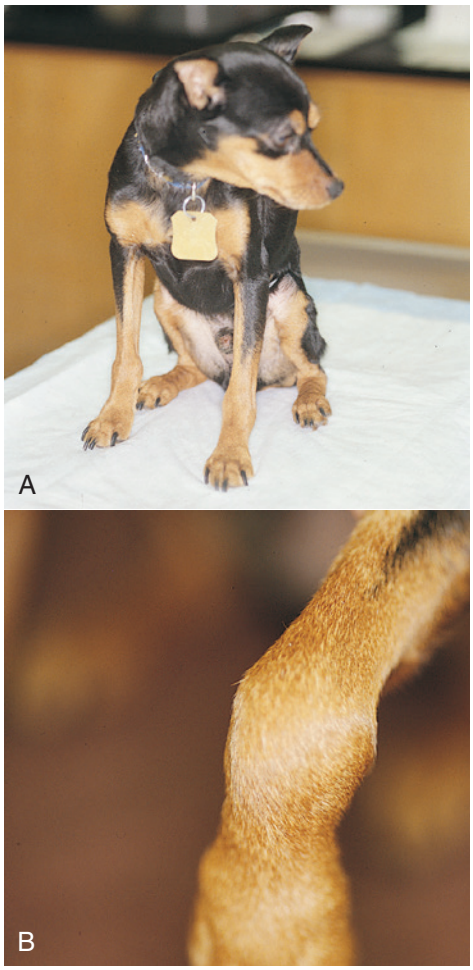


FIG 68.2
(A) A 4-year-old Miniature Pinscher was referred for intermittent fever and depression during the previous year. All joints are palpably and visibly swollen, particularly the carpus **(B).**

deformed or subluxated. (Fig. 68.2). *It is important to realize that approximately 25% of dogs with IMPA have no detectable joint swelling or pain, so normal joint palpation should not preclude further diagnostic evaluation for polyarthritis.*

Synovial fluid analysis is necessary to confirm a diagnosis of inflammatory arthritis. Synovial fluid should be collected and evaluated from multiple (three or more) joints in all dogs and cats with suspected polyarthritis and also those with apparently monoarticular disease whenever there is evidence of systemic or local inflammation. Synovial fluid analysis will differentiate inflammatory from noninflammatory joint disease (Table 68.1). When synovial fluid analysis reveals inflammation, infectious causes should be the first consideration. Infectious causes of arthritis include bacteria, *Mycoplasma* spp., bacterial L-forms, spirochetes, rickettsial agents, protozoa, and fungi (Table 68.2). Infectious agents may either directly invade the joint or cause clinical signs by triggering an immune-mediated polyarthritis due to circulating immune complex deposition (Sykes, 2006). Diagnostic tests used to differentiate infectious from immune-mediated

TABLE 68.1

Synovial Fluid Cytology in Common Joint Disorders

	WBC/μL	% PMN
Normal	200-3000	<10
Degenerative	1000-6000	0-12
Traumatic	Variable	<25
Septic	40,000-280,000	90-99
Immune-mediated disease		
Nonerosive immune	4000-370,000	15-95
Erosive arthritis (rheumatoid-like)	6000-80,000	20-80

PMN, Polymorphonuclear neutrophil leukocytes; *WBC,* white blood cells.

TABLE 68.2

Infectious Causes of Polyarthritis in Dogs and Cats

DOG	CAT
Direct inoculation with bacteria or hematogenous spread; *Staphylococcus, Streptococcus* (most common organisms cultured), others	Direct inoculation with bacteria or hematogenous spread; *Pasteurella multocida*, others
Borrelia burgdorferi	
Leishmania	
Ehrlichia spp., Rocky Mountain spotted fever, *Anaplasma* spp.	

causes of arthritis include a complete blood count (CBC); urinalysis; culture of urine, blood, and synovial fluid; and serology for tick-borne diseases. Thoracic radiographs and fungal serology may also be warranted. Once infectious causes of polyarthritis have been ruled out, immune-mediated conditions should be considered.

Noninfectious IMPA is common in dogs but uncommon in cats. Immune-mediated polyarthritis can occur as an idiopathic syndrome, as a feature of SLE, or secondary to systemic antigenic stimulation (reactive polyarthritis). In reactive polyarthritis, articular deposition of immune complexes causes synovitis. Reactive polyarthritis has been reported in association with chronic bacterial or fungal infections, neoplasia, and administration of drugs or vaccines (Sykes, 2006). An extensive diagnostic evaluation is sometimes required to rule out reactive polyarthritis (e.g., CBC, thoracic and abdominal radiographs, ophthalmologic examination, bacterial culture of urine and blood, lymph node aspirates, cardiac ultrasonography, abdominal ultrasound). Normal results on all of these tests warrant a diagnosis of idiopathic IMPA. Diagnostic testing for SLE is indicated if there is evidence of multiple organ involvement. Testing for SLE should include a CBC, platelet count, urine protein/creatinine ratio, antinuclear antibody (ANA) titer, and organ-specific tests such as measurement of creatine kinase for suspected myositis.

Because most dogs with IMPA have nonerosive disease, radiographs are not always performed during the initial diagnostic evaluation. If dogs with presumed IMPA do not respond quickly and completely to treatment, or if joints are unstable or deformed on palpation, radiography should be employed to evaluate for evidence of erosive disease affecting the articular surfaces, focal "punched out" lesions of lysis in subchondral bone, and proliferation and calcification of periarticular soft tissues. Erosive polyarthritis is characterized by progressive joint inflammation, destruction, and deformity and is an uncommon immune-mediated disorder in dogs. Serologic testing for rheumatoid factor (RF) (see p. 1204) and synovial membrane biopsy (see p. 1194) aid in the diagnosis of this rare disorder.

Polyarthritis is uncommon in cats. Infectious arthritis may be caused by bacteria, *Mycoplasma* spp., calicivirus infection, fungi, and some tick-borne pathogens (Lemetayer and Taylor, 2014). Forms of nonerosive immune-mediated polyarthritis include idiopathic/primary IMPA, reactive polyarthritis, rheumatoid arthritis, and (rarely) SLE. Two uncommon erosive immune-mediated disorders causing joint damage and destruction in cats are periosteal proliferative polyarthritis and rheumatoid-like polyarthritis.

DIAGNOSTIC TESTS

MINIMUM DATABASE

A minimum database (CBC, serum biochemistry profile, and urinalysis) should be normal in animals with noninflammatory joint disease. In dogs and cats with polyarthritis, it is common to identify a leukocytosis, hyperglobulinemia, and mild hypoalbuminemia. Thrombocytopenia is common in polyarthritis caused by tick-borne pathogens. Organisms may be identified within red or white blood cells in animals with some infectious causes of polyarthritis (Fig. 68.3). Proteinuria and hypoalbuminemia may be present in dogs with concurrent glomerulonephritis. Cats with polyarthritis should always be tested for feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody. Normal clinical pathologic findings do not rule out polyarthritis.

SYNOVIAL FLUID COLLECTION AND ANALYSIS

Synovial fluid collection and analysis is the most useful test for establishing a diagnosis in dogs and cats with joint disease. It is of greatest value in confirming that a specific joint is abnormal and in differentiating inflammatory from noninflammatory disease. Synovial fluid collection and analysis may also provide information regarding a specific diagnosis.

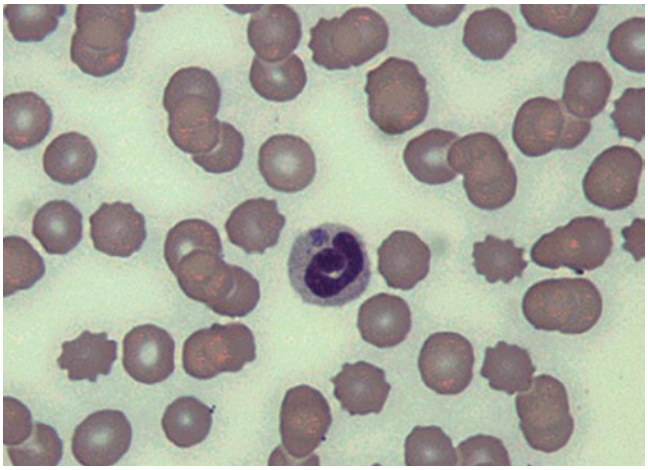


FIG 68.3
Anaplasma phagocytophilum morula in peripheral blood neutrophil from a dog with polyarthritis.



FIG 68.4
Arthrocentesis is performed using a small-gauge needle attached to a 3-mL syringe.

Collection Method

Arthrocentesis requires little in the way of expertise or equipment, involves minimal risk to the animal, is inexpensive to perform, and has a high diagnostic yield. In dogs, light tranquilization or sedation is usually administered for pain relief and restraint. General anesthesia is recommended for collection of synovial fluid in cats. Immunologically mediated disease tends to be most prominent in the distal small joints, but reports differ on whether the hock or carpal joints are most likely to be diagnostic in dogs with primary IMPA (Colopy et al., 2010; Stull et al., 2008). Whenever polyarthritis is suspected, synovial fluid should be analyzed from at least three to four joints, including at least one carpus, one hock, and one stifle. The joints that are clinically most severely affected should always be sampled. Elbows and shoulders should be tapped in animals with poorly localized forelimb lameness. When they are swollen or painful, the smaller metacarpophalangeal and interphalangeal joints can also be sampled. Even if only one joint is clinically affected, synovial fluid should be analyzed from multiple joints if polyarthritis is suspected clinically.

Arthrocentesis should be performed using sterile technique (sterile gloves, needles, and syringes). The hair should be clipped from the area and the skin surgically scrubbed. Arthrocentesis in dogs and cats typically requires a 25-gauge needle attached to a 3-mL syringe (Fig. 68.4). A 22-gauge, 1- to 1½-inch needle is used for the shoulder, elbow, and stifle joints of dogs, depending upon joint size. Large dogs may require a 3-inch spinal needle to enter the hip joint.

Landmarks for arthrocentesis vary according to personal preference, but some recommended approaches are outlined in Fig. 68.5. After aseptic preparation, the joint should be stabilized by an assistant and flexed and extended while the joint space is palpated using a gloved finger. For most joints, the joint space is easiest to access with the joint in moderate flexion. The needle is attached to the syringe and then introduced into the joint space. Once the tip of the needle is in the joint space, gentle negative pressure is applied to the syringe. Only a very small amount of joint fluid (one to three drops) is needed for determination of viscosity and cytologic examination to estimate cell count and to determine the differential white blood cell (WBC) count (Video 68.1). Once fluid is obtained, the negative pressure on the syringe is released before withdrawal of the needle through the skin to decrease the chance of blood from cutaneous vessels entering the syringe. The appearance of blood at any time during the procedure should prompt immediate release of suction and withdrawal of the needle. Synovial smears should be prepared immediately (Fig. 68.6); one drop of synovial fluid is placed onto each slide, and a second slide is used to make a smear. Additional drops of synovial fluid should be submitted for culture and sensitivity. Selection of the most appropriate joint to culture is based on clinical findings or on the gross characteristics of the joint fluid (cloudy, discolored, loss of viscosity). Fluid from at least one joint should be submitted for culture even if IMPA is suspected clinically. When synovial fluid from one or more joints appears grossly abnormal, it may be worthwhile to perform a second arthrocentesis on the most abnormal joint to collect a larger volume of fluid for culture. For aerobic culture, synovial fluid should be submitted in a sterile tube or on a sterile swab. If anaerobic infection is suspected, synovial fluid should be placed in an anaerobic culture tube containing transport medium (e.g., Port-a-Cul). When there is a limited sample volume, both aerobic and anaerobic bacteria can be isolated from an anaerobic culture tube.

Analysis of Gross Appearance

Normal synovial fluid is clear and colorless. Cloudiness or turbidity is observed when red blood cells (RBCs) or WBCs enter the joint in high numbers. A color change may be an indication of blood contamination or a pathologic condition. Hemorrhage from an earlier puncture attempt or an ongoing disease process typically results in a diffuse red discoloration

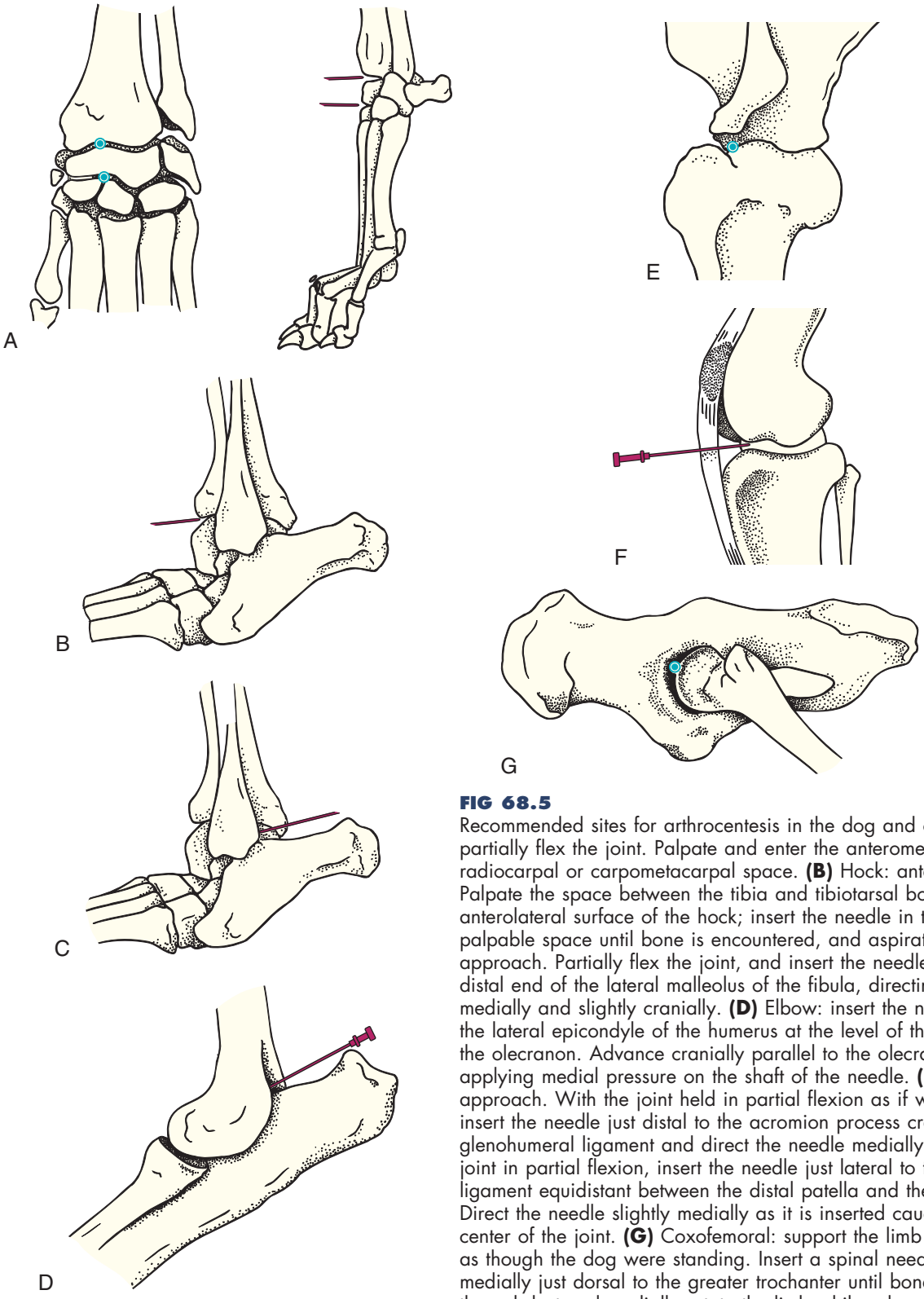


FIG 68.5
Recommended sites for arthrocentesis in the dog and cat. **(A)** Carpus: partially flex the joint. Palpate and enter the anteromedial aspect of the radiocarpal or carpometacarpal space. **(B)** Hock: anterior approach. Palpate the space between the tibia and tibiotarsal bone on the anterolateral surface of the hock; insert the needle in the shallow palpable space until bone is encountered, and aspirate. **(C)** Hock: lateral approach. Partially flex the joint, and insert the needle just caudal to the distal end of the lateral malleolus of the fibula, directing the needle medially and slightly cranially. **(D)** Elbow: insert the needle just medial to the lateral epicondyle of the humerus at the level of the dorsal edge of the olecranon. Advance cranially parallel to the olecranon process while applying medial pressure on the shaft of the needle. **(E)** Shoulder: lateral approach. With the joint held in partial flexion as if weight bearing, insert the needle just distal to the acromion process cranial to the glenohumeral ligament and direct the needle medially. **(F)** Stifle: with the joint in partial flexion, insert the needle just lateral to the straight patellar ligament equidistant between the distal patella and the tibial tuberosity. Direct the needle slightly medially as it is inserted caudally towards the center of the joint. **(G)** Coxofemoral: support the limb parallel to the table as though the dog were standing. Insert a spinal needle straight in medially just dorsal to the greater trochanter until bone is encountered, then abduct and medially rotate the limb while advancing the needle ventrally and caudally.

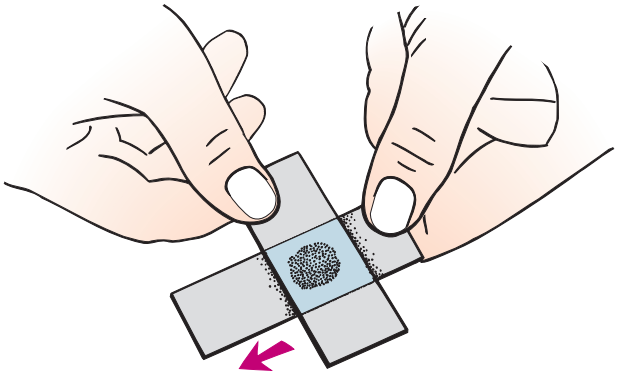


FIG 68.6
Preparing a smear of synovial fluid. A drop of fluid is placed onto a slide. A second slide is used to gently spread the fluid using a pull smear technique.

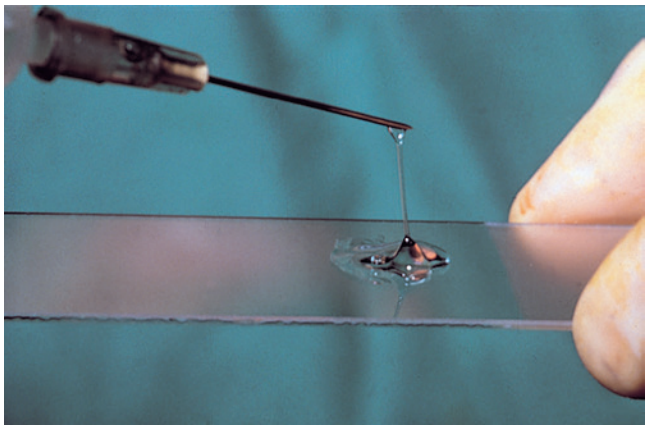


FIG 68.7
Normal synovial fluid is clear and viscous.

of the synovial fluid, whereas blood from a traumatic tap is not usually homogeneously mixed with the joint fluid. A yellowish fluid (xanthochromia) may indicate previous hemorrhage into the joint and is occasionally seen in degenerative, traumatic, and inflammatory joint diseases.

Normal synovial fluid is very viscous. It forms a long string (>2.5 cm) when allowed to drop from the tip of a needle onto a slide (Fig. 68.7, see Video 68.1). A thin or watery consistency indicates that the synovial fluid is deficient in polymerized hyaluronic acid. This may occur after dilution by serum or through degradation of hyaluronic acid by an intense intra-articular inflammatory reaction.

Analysis of Microscopic Appearance

Cytologic evaluation is the most important aspect of synovial fluid analysis. Usually only a few drops of synovial fluid are collected, and estimates of cell numbers are made from a stained direct smear of the fluid. One drop of fluid can be placed on a slide and a second slide used to spread the fluid to make a thin smear (see Fig. 68.6). This smear should be air-dried and then stained with Diff-Quik or Wright-Giemsa

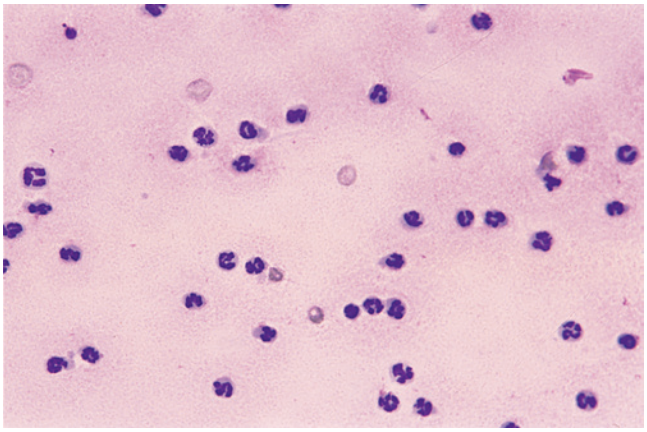


FIG 68.8
Synovial fluid with an increased nucleated cell count consisting primarily of neutrophils from an adult dog with idiopathic immune-mediated polyarthritis.

stain. Because normal synovial fluid contains fewer than 3000 WBCs/μL, no more than three WBCs should be observed per high-dry power (40×) field on a stained smear. Simple microscopic scanning of a stained slide of synovial fluid allows the clinician to estimate cell numbers as normal, mildly increased, or greatly increased.

Normal synovial fluid contains a mixture of large and small mononuclear cells that frequently contain many vacuoles and granules. An occasional neutrophil may be observed, but these cells should represent less than 10% of the total. Blood contamination during synovial fluid collection will result in approximately 1 neutrophil for every 500 RBCs contaminating the fluid. The presence of platelets indicates recent intra-articular hemorrhage or significant blood contamination. Hemosiderin-laden macrophages and erythrophagia confirm prior hemorrhage.

DJD causes a slightly increased cell count (<6000 cells/μL) and an increased volume of synovial fluid, but almost all of the cells are mononuclear cells (see Table 68.1). An increase in the number of neutrophils within a joint indicates inflammation of the synovial lining. The more inflamed the synovium, the greater the number of WBCs in the synovial fluid and the greater the percentage of neutrophils (Fig. 68.8).

In addition to the actual or estimated WBC count and WBC differential, cytologic evaluation of the cells in the joint fluid is important. Neutrophils in the synovial fluid of dogs and cats with immune-mediated disease should have a normal appearance. In acute or severe cases of septic arthritis, bacteria may be observed within the neutrophils, which may be toxic, ruptured, or degenerate. Organisms may occasionally be observed within the cells in the synovial fluid of animals with polyarthritis caused by rickettsial infections *(Ehrlichia canis, Ehrlichia ewingii, Anaplasma phagocytophilum)* or leishmaniasis. In dogs with SLE-induced polyarthritis, lupus erythematosus (LE) cells or ragocytes may rarely be seen within the synovial fluid (Fig. 68.9).

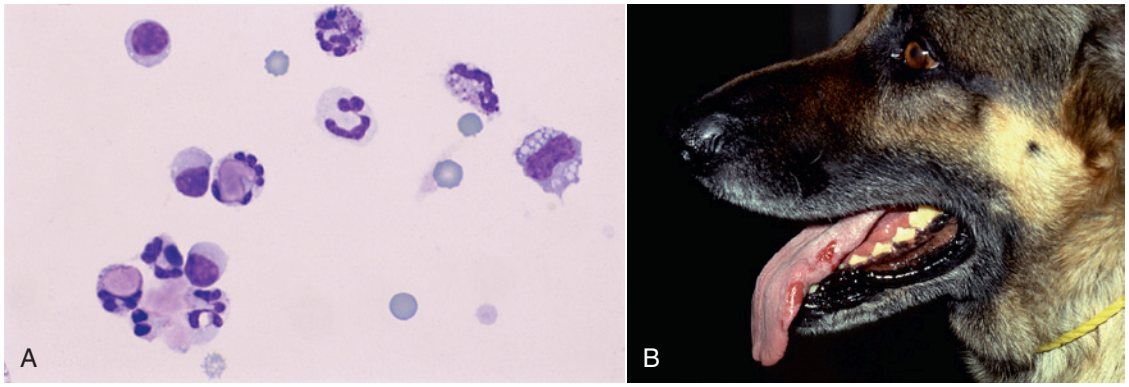


FIG 68.9
Synovial fluid from an adult German Shepherd dog with polyarthritis. **(A)** Some of the cells are lupus erythematosus (LE) cells containing phagocytized, opsonized, amorphous nuclear material. Finding these LE cells supports a diagnosis of systemic lupus erythematosus (SLE). **(B)** This dog also has proteinuria, tongue ulcers caused by vasculitis, and a positive antinuclear antibody test.

SYNOVIAL FLUID CULTURE

Bacteria are the most common cause of joint infection. Septic arthritis can often be diagnosed on the basis of the appearance of toxic changes within neutrophils and identification of bacteria on stained smears of synovial fluid (Clements, 2005). Some organisms (e.g., *Mycoplasma* spp.) do not induce characteristic cytologic abnormalities, so any joint fluid with an increased nucleated cell count and a high percentage of neutrophils warrants a culture. Synovial fluid should be submitted for aerobic and anaerobic culture and for specific *Mycoplasma* spp. culture. Because direct bacterial culture of synovial fluid is positive in less than half of all cases of septic arthritis, failure to grow bacteria in synovial fluid does not rule out septic arthritis. The diagnostic yield can be greatly improved (50%-100% positive) if infected synovial fluid is collected and inoculated into broth-enrichment media (e.g., thioglycolate blood culture bottles) and incubated for 24 hours prior to culture. Microbiologic culture of blood, urine, and synovial membrane biopsy specimens should also be considered to improve the chance of recovering a clinically relevant pathogen.

SYNOVIAL MEMBRANE BIOPSY

Performing synovial membrane biopsy can support a diagnosis already suspected on the basis of history, physical examination, radiographic studies, and synovial fluid analysis. It may also be used to collect a sample for microbiologic culture in cases of suspected septic arthritis. Examination of the synovial membrane is especially valuable in the diagnosis of neoplasia and in differentiating infectious arthritis from immune-mediated disorders.

Synovial membrane biopsies may be obtained by needle biopsy or surgical arthrotomy. Surgical excision of a wedge of synovial membrane allows visualization of the entire joint and selection of a specific site from which to obtain the biopsy. Needle biopsy of the synovial membrane is quick and minimally traumatic, but samples are small and easily obtained only from the stifle joint.

RADIOGRAPHY

Radiography is an important component of the initial diagnostic evaluation when only one joint is clinically affected or when joint palpation reveals crepitation, instability, or a restricted range of motion. Physical examination findings should be used to determine which joints should be radiographed, and two views (i.e., lateral and anterior/posterior) should be made of each joint. Radiographic abnormalities of the joints and periarticular region are expected in animals with DJD, chronic septic arthritis, and erosive immune-mediated arthritis. Radiographs of the carpus are abnormal in up to 75% of dogs with erosive polyarthritis at the time of first evaluation for polyarthritis. In dogs with presumed nonerosive IMPA and dogs with infectious polyarthritis, radiographs are generally not recommended if the response to treatment is rapid and complete, because the only abnormalities observed are mild effusion, joint capsule distention, and associated soft tissue swelling.

Radiographs of the thorax and abdomen and abdominal ultrasound are often recommended in dogs and cats with polyarthritis to evaluate for underlying infectious or neoplastic disease that could lead to reactive polyarthritis. In addition, radiographs of the spine should be performed in dogs with concurrent neck or back pain to screen for diskospondylitis as a cause for reactive polyarthritis.

Radiography is an important tool but has limited utility. Many of the bony changes seen with DJD and erosive immune-mediated disease are not apparent for weeks to months after the onset of signs. Although positive findings contribute a great deal to the diagnosis, negative findings should be interpreted with caution. Sequential radiographic studies may be warranted.

IMMUNOLOGIC AND SEROLOGIC TESTS

Lyme Disease Titers

Infection with the spirochete *Borrelia burgdorferi,* the etiologic agent for Lyme disease, causes primary infectious synovitis as well as immunologically mediated synovitis resulting from immune complex deposition. Affected dogs develop an antibody response that can be detected using an indirect fluorescent antibody (IFA) test or an enzyme-linked immunosorbent assay (ELISA). High serum titers are common in dogs with clinical signs of Lyme disease and also in asymptomatic dogs in endemic areas. A positive antibody titer merely indicates exposure to the organism and cannot be used to diagnose active disease. A surface peptide (C6) is expressed when Bb is transmitted to dogs but is not expressed in the tick, in tissue culture, or in Lyme vaccines. Therefore antibodies against C6 prove that natural exposure to *B. burgdorferi* has occurred. A quantitative version of this test (Lyme Quant C6 Test, IDEXX, Westbrook, Maine) is available, but positive results still indicate exposure rather than clinical disease. A diagnosis of Lyme disease polyarthritis must rely on a combination of the history (i.e., recent exposure to an area in which the disease is enzootic), clinical signs, identification of polyarthritis through arthrocentesis elimination of other known causes of polyarthritis, serologic testing, and response to therapy (see p. 1200).

Rickettsial Titers

Serologic testing plays an important role in the diagnosis of Rocky Mountain spotted fever (RMSF), canine monocytotropic ehrlichiosis, canine granulocytotropic anaplasmosis, and bartonellosis (see Chapter 95 for more discussion of rickettsial diseases and Chapter 94 for more discussion of bartonellosis). Demonstration of a rising titer is necessary to make the diagnosis of acute RMSF, with a fourfold increase between acute and convalescent titers expected. Demonstration of antibody against *E. canis, E. ewingii,* and *A. phagocytophilum* indicate prior exposure, with antibody levels remaining increased for months after successful treatment.

Systemic Lupus Erythematosus

Tests used to diagnose SLE include the ANA titer and the LE cell test. These tests should only be used when clinical criteria for diagnosis of SLE have been met (see Chapter 71). The ANA titer is positive when circulating antibodies to nuclear material are present in the blood. These antibodies are the most prominent of the autoantibodies associated with canine and feline SLE. The ANA test is a sensitive indicator for the diagnosis of SLE and is positive in 55% to 90% of SLE cases. The ANA is constant from day to day and is less steroid labile than the LE cell test. Unfortunately, a positive ANA test is not specific for SLE, and false-positive results may be seen in dogs and cats with many other systemic inflammatory or neoplastic diseases. The LE cell test requires identification of an LE cell, which is a neutrophil that has phagocytized, opsonized nuclear material. The cytoplasm of these cells is filled with amorphous purple material (see Fig. 68.9). The LE cell test is labor intensive, requires an experienced technician, and rapidly becomes negative after administration of corticosteroids, so it is rarely performed in clinical practice.

Rheumatoid Factor

The laboratory test for RF detects serum agglutinating antibody directed against the patient's own immunoglobulin (Ig) G. The reliability of the test increases with the severity and chronicity of the disease. The test is reported to be positive in 20% to 70% of dogs with erosive (rheumatoid-like) arthritis. Any disease associated with systemic inflammation and immune complex generation and deposition can result in weak false-positive results.

Suggested Readings

Battersby IA, et al. Retrospective study of fever in dogs: laboratory testing, diagnoses, and influence of prior treatment. *J Small Anim Pract*. 2006;47:370.

Clements DN, et al. Type I immune-mediated polyarthritis in dogs: 39 cases (1997-2002). *J Am Vet Med Assoc*. 2004;224:1323.

Clements DN, et al. Retrospective study of bacterial infective arthritis in 31 dogs. *J Small Anim Pract*. 2005;46:171.

Johnson KC, Mackin A. Canine immune-mediated polyarthritis, Part 1: pathophysiology. *J Am Anim Hosp Assoc*. 2012;48:12.

Johnson KC, Mackin A. Canine immune-mediated polyarthritis, Part 2: diagnosis and treatment. *J Am Anim Hosp Assoc*. 2012;48:71.

Lemetayer J, Taylor SM. Inflammatory joint disease in cats: diagnostic approach and treatment. *J Feline Med Surg*. 2014;16:547.

MacWilliams PS, Friedrichs KR. Laboratory evaluation and interpretation of synovial fluid. *Vet Clin North Am Small Anim Pract*. 2003;33:153.

Rychel JK. Diagnosis and treatment of osteoarthritis. *Top Companion Anim Med*. 2010;25:20.

Stull JW, et al. Canine immune-mediated polyarthritis: clinical and laboratory findings in 83 cases in western Canada. *Can Vet J*. 2008;49:1195.

Sykes JE, et al. Clinicopathologic findings and outcome in dogs with infective endocarditis: 71 cases (1992-2005). *J Am Vet Med Assoc*. 1735;228:2006.

Taylor SM. Arthrocentesis. In: Taylor SM, ed. *Small animal clinical techniques*. 2nd ed. St Louis: Elsevier; 2016.

CHAPTER 69

Disorders of the Joints



GENERAL CONSIDERATIONS

The diagnostic approach to dogs and cats with joint disease is discussed in detail in Chapter 68. Joint disorders are characterized as inflammatory or noninflammatory on the basis of synovial fluid analysis. The most common noninflammatory joint disease is degenerative joint disease (DJD). Inflammatory joint disorders can be due to either infectious or immune-mediated causes. Animals with immune-mediated polyarthritis (IMPA) usually have primary idiopathic immune-mediated disease, but immune complex–mediated polyarthritis may also occur secondary to prolonged systemic antigenic stimulation (reactive polyarthritis; see Chapter 68). Most IMPA syndromes are nonerosive. Disorders causing radiographic evidence of bone destruction (erosive disease) are rare.

NONINFLAMMATORY JOINT DISEASE

CANINE DEGENERATIVE JOINT DISEASE

Etiology

DJD, or osteoarthritis, is a chronic progressive disorder of joints that results in articular cartilage loss, osteophyte formation, and periarticular fibrosis. DJD can affect any size, breed, and age of dog, and any joint may be affected, including smaller joints such as the vertebral facets and metacarpophalangeal and metatarsophalangeal joints. Most DJD occurs secondary to joint instability, trauma, or developmental orthopedic diseases that damage articular cartilage, but primary DJD can occur as an intrinsic problem of cartilage homeostasis associated with aging. Although considered noninflammatory on the basis of synovial fluid cytology, inflammatory mediators are involved in the clinical manifestations and progression of DJD. An estimated 20% of the adult canine population in North America is affected by DJD in at least one joint.

Clinical Features

The clinical signs of DJD are usually insidious in onset and confined to the musculoskeletal system, with no associated systemic signs. Lameness and stiffness may initially be prominent only after periods of overexertion and may worsen in cold and damp weather. Mildly affected dogs may "warm out" of their lameness with exercise. As DJD progresses, fibrosis and pain lead to decreased exercise tolerance, persistent lameness, and, in severe cases, muscular atrophy. Either a single joint or multiple joints may be affected.

Diagnosis

DJD is usually diagnosed on the basis of history, physical examination findings, and characteristic radiographic features. Clinical examination may reveal pain in the affected joint(s), decreased range of motion, crepitation on flexion and extension of the affected joint(s), and sometimes appreciable joint swelling. Radiographic changes characteristic of DJD include joint effusion, periarticular osteophyte formation, subchondral bone sclerosis, joint space narrowing, and bone remodeling (Fig. 69.1). A predisposing condition is often identified, such as trauma, rupture of supporting ligaments, poor conformation, or a congenital deformity. Animals with DJD do not exhibit the fever, leukocytosis, and depression commonly seen in animals with inflammatory joint disease.

Synovial fluid from a joint with DJD may be slightly less viscous than normal. The total nucleated cell count (TNCC) is normal or slightly increased, but it rarely exceeds 5000 cells/μL. Mononuclear cells usually constitute at least 80% of the cells, and neutrophils are rare (<10%). Acute joint injury or ligament rupture occasionally incites a more inflammatory response, with moderate increases in synovial fluid neutrophil count for days to weeks following injury.

Treatment

The goals of treatment in dogs with DJD are to alleviate discomfort and prevent further joint degeneration. Surgical intervention may be necessary to eliminate joint instability or to correct anatomic defects. Options such as femoral head/neck ostectomy, joint arthrodesis, intra-articular regenerative stem cell therapy, or joint replacement surgery may be considered to relieve discomfort when response to medical therapy is inadequate.

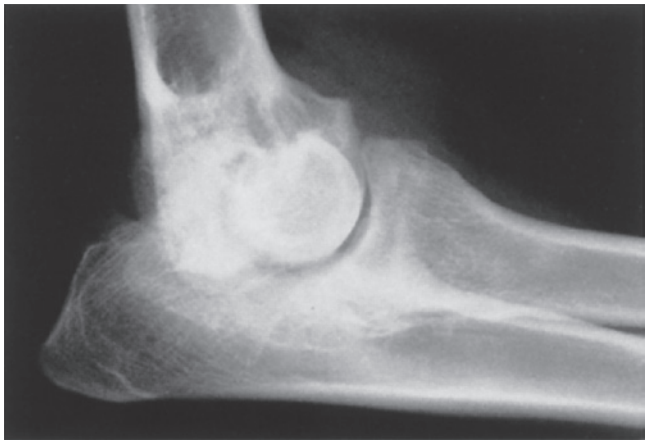


FIG 69.1
Close-up mediolateral radiograph of left elbow joint of a 14-month-old female German Shepherd dog with severe degenerative changes secondary to a fragmented coronoid process.

Medical treatment is symptomatic and nonspecific. Weight reduction may decrease the stresses acting on the joint. Rest often helps decrease the discomfort associated with acute exacerbations of disease. High-impact exercise, such as running and jumping, should be discouraged, whereas low-impact exercise done in moderation, such as swimming, leash walking, and walking on an underwater treadmill is recommended to maintain mobility and muscle strength. Other forms of rehabilitation therapy may include passive range-of-motion exercises, cryotherapy (ice compresses), muscle and joint massage, ultrasound, laser therapy, and electrical stimulation. Dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and antioxidants (vitamin E, vitamin C, beta carotene, zinc, selenium) or feeding commercial "joint diets" containing these supplements may decrease the inflammation and pain of DJD.

Pharmacologic therapies may be used to decrease further degradation of the articular cartilage, inhibit release of inflammatory mediators, and control pain. The nonsteroidal antiinflammatory drugs (NSAIDs) are often recommended because of their antiinflammatory and analgesic effects. The primary action of most NSAIDs is reversible inhibition of cyclooxygenase, preventing synthesis of the prostaglandins responsible for pain and inflammation. Selective inhibition of two forms of cyclooxygenase (COX-1 and COX-2) may explain some of the differences in efficacy and toxicity among the available NSAID agents. Preferential inhibition of COX-2 with relative sparing of COX-1 by an NSAID may be associated with improved control of inflammation and decreased potential for gastric irritation and ulceration or renal toxicity. Renal function should be assessed before prescribing any NSAID, after 7 days of treatment, and then at least every 6 months during chronic administration. Owners should also be instructed to monitor for inappetence, vomiting, or melena, which could indicate gastrointestinal toxicity. Because the clinical response to each NSAID varies between dogs, it is reasonable to switch drugs when the response to one drug is inadequate (Table 69.1). When switching from one NSAID to another, a washout period of at least 3 days without NSAID administration is recommended to prevent toxicity. In dogs that are intolerant of NSAIDs or those that require further analgesia, oral tramadol (2-5 mg/kg q8-12h), gabapentin (2.5-10 mg/kg oral [PO] q8-24h), or amantadine (3-5 mg/kg PO q24h) can be helpful in pain management.

Oral and injectable chondroprotective agents and nutraceuticals may improve cartilage biosynthetic activity, decrease synovial inflammation, and inhibit intra-articular degradative enzymes. Oral glucosamine and chondroitin sulfate can be administered separately or in combination. An orally administered combination of glucosamine HCl, chondroitin sulfate, and manganese ascorbate has also been recommended (Cosequin RS [regular strength], 1-2 tablets q24h in cats or small dogs; Cosequin DS [double strength], 2 to 4 tablets q24h in large dogs [Nutramax Labs, Edgewood, MD]). Polysulfated glycosaminoglycans (Adequan) or pentosan polysulfate may be beneficial when administered intramuscularly (see Table 69.1). Hyaluronic acid is a nonsulfated glycosaminoglycan that can be administered as an intra-articular injection to improve synovial viscosity and decrease inflammation. To achieve the maximum theoretic benefit from all these products, they should be administered before DJD has occurred; therefore they may be indicated for treating dogs that have sustained trauma or undergone surgery known to have damaged articular cartilage. Clinical trials are necessary to evaluate their efficacy.

FELINE OSTEOARTHRITIS

Cats are smaller and more agile than most dogs, and their clinical manifestations of discomfort are often subtle. Clinically significant DJD involving the elbow and hip joints is, however, very common in aging cats. Signs include reduced activity, decreased appetite, weight loss, irritability, and occasionally lameness. Diagnosis is based on physical findings and radiographic features. Treatment of DJD in cats is similar to that recommended in dogs and includes weight loss, rehabilitation therapy, and administration of chondroprotective medications, nutraceuticals, and analgesics. NSAIDs are potentially more toxic in cats than in dogs due to deficient glucuronidation pathways leading to a prolonged duration of effect so they should only be administered to normotensive, normovolemic adult cats with no history of renal or hepatic disease. Meloxicam has been shown to be safe and effective when administered chronically to cats with DJD, and many cats have a good clinical response to very low doses of meloxicam (0.1 mg/kg/day PO × 4 days, then 0.1 mg/cat/day). Other commonly prescribed analgesic medications include buprenorphine (0.01-0.03 mg/kg bid to tid via buccal mucosa), gabapentin (5-10 mg/kg bid-tid), tramadol (2 mg/kg bid PO), and amantadine (3-5 mg/kg PO q24h).

TABLE 69.1

Dosages of Selected Drugs for Treating Degenerative Joint Disease in Dogs

GENERIC NAME	DRUG NAME	DOSE
Nonsteroidal Antiinflammatory Drugs (NSAIDs)		
Acetylsalicylic acid	(Aspirin)	10-20 mg/kg PO q8-12h
Carprofen	(Rimadyl)	2.2 mg/kg PO q12h
Deracoxib	(Deramaxx)	1-2 mg/kg PO q24h
Etodolac	(Etogesic)	10-15 mg/kg PO q24h
Firocoxib	(Previcox)	5 mg/kg PO q24h
Meloxicam	(Metacam)	0.2 mg/kg PO once, then 0.1 mg/kg PO q24h
Piroxicam	(Feldene)	0.3 mg/kg PO q48h
Disease-Modifying Chondroprotective Agents		
Chondroitin sulfate		15-20 mg/kg PO q12h
Glucosamine		15-20 mg/kg PO q12h
Pentosan polysulfate	(Pentosan 100)	3 mg/kg IM q7d
Polysulfated glycosaminoglycans	(Adequan)	3-5 mg/kg IM q4d for 8 tx, then q30d
Analgesics		
Tramadol		2-5 mg/kg PO q8-12h
Gabapentin	(Neurontin)	2.5-10 mg/kg PO q8-12h
Amantadine		3-5 mg/kg PO q24h

IM, Intramuscular; *PO,* oral; *tx,* treatments.

INFECTIOUS INFLAMMATORY JOINT DISEASES

SEPTIC (BACTERIAL) ARTHRITIS

Etiology

Septic arthritis can result from a blood-borne infection, from direct inoculation of a joint, or by local spread from adjacent infected tissue. Bacterial infection of multiple joints suggesting hematogenous spread of bacteria is uncommon except in immunosuppressed animals and neonates with omphalophlebitis. Monoarticular septic arthritis is much more common than polyarticular and usually follows direct inoculation of bacteria into a single joint as a result of surgery, a bite wound, trauma, or foreign body penetration. Most septic joints with no physical or historical evidence of direct inoculation have radiographic evidence of preexisting osteoarthritis, potentially causing increased synovial vascularity and predisposing to hematogenous bacterial infection. *Staphylococcus* spp., *Streptococcus* spp., and coliform organisms are most often incriminated in dogs, and *Pasteurella* spp. are the most common cause in cats. Septic arthritis, regardless of the cause, is more common in dogs than cats, is most common in large-breed dogs, and more frequently affects males than females.

Clinical Features

Animals with septic polyarthritis are often systemically ill, febrile, and depressed. The affected joints are usually very painful, especially when manipulated, and may be palpably distended with synovial fluid. The periarticular soft tissues may be inflamed and edematous. Septic arthritis most commonly involves the elbow or stifle joints.

Diagnosis

To confirm a diagnosis of septic arthritis, bacteria must be identified in cytologic preparations of synovial fluid or cultured in synovial fluid, synovial membrane, blood, or urine from an animal with appropriate clinical signs and inflammatory synovial fluid. Synovial fluid obtained by arthrocentesis from infected joints is often yellow, cloudy, or bloody and less viscous than normal as a result of dilution and degradation of synovial mucin by bacterial hyaluronidase and the enzymes released from the inflammatory cells within the joint. Smears of synovial fluid should be made for Gram staining and cytologic evaluation. Because it is common for synovial fluid from infected joints to clot rapidly, a portion of the fluid should be immediately placed in an anticoagulant (i.e., ethylenediaminetetraacetic acid [EDTA]) tube for future cytologic evaluation if an adequate sample volume is obtained. In animals with septic arthritis, there is a marked

increase in the number (40,000-280,000/μL) of nucleated cells in the synovial fluid, with neutrophils predominating (usually >90%). In very acute or severe cases, it is common to see bacteria within the cells, and the neutrophils may be toxic, ruptured, or degranulated. Organisms that do not cause rapid destruction of articular cartilage (i.e., streptococci, *Mycoplasma*) may not cause remarkable toxic or degenerative changes in synovial fluid neutrophils. In chronic infections or in animals that have received prior treatment with antibiotics, bacteria may no longer be evident and neutrophils may appear healthy.

Synovial fluid should be cultured for aerobic and anaerobic bacteria. Direct bacterial culture of synovial fluid is positive in less than half of all animals with septic arthritis; improved diagnostic yield may be obtained by inoculating synovial fluid into blood culture medium (9:1 ratio) and incubating it for 24 hours at 37° C before inoculation. Bacteria can also be recovered from cultures of synovial membrane biopsy, blood, or urine specimens.

Radiographic changes of the involved joints in septic arthritis may initially be minimal and nonspecific, and limited to thickening of the joint capsule, widening of the joint space, and irregular thickening of periarticular soft tissues (Fig. 69.2). In chronic infections, cartilage degeneration, periarticular new bone formation, a marked periosteal reaction, and subchondral bone lysis may be observed (Fig. 69.3).

If septic arthritis is suspected and the animal has no history of direct inoculation of the joint with bacteria, diagnostic evaluation for a source of bacteremia should be performed, although often the cause cannot be identified. Radiographs of the thorax, abdomen, and spine, as well as cardiac and abdominal ultrasonography, are especially helpful in identifying a focal site of infection. Culture of material from any suspected site of infection should be performed if possible.

Treatment

The goals of therapy are to rapidly resolve the bacterial infection and remove intra-articular accumulations of enzymes and fibrin debris. Identifiable systemic sources of infection should also be eliminated. In an animal suspected of having septic arthritis, antibiotics should be administered as soon as possible after all samples are collected. Until culture results are available, a broad-spectrum, β-lactamase-resistant antibiotic such as a first-generation cephalosporin (e.g., cephalexin, 20-40 mg/kg PO q8h) or Clavamox (Zoetis; 12-25 mg/kg PO q8h) is indicated. Initially the antibiotic can be administered parenterally, followed by long-term oral administration. Quinolones should be used if gram-negative organisms are suspected; retinal toxicity is a potential concern in cats receiving quinolones, but pradofloxacin has an improved safety profile. Metronidazole should be added if anaerobic infection is suspected. Animals with acute septic

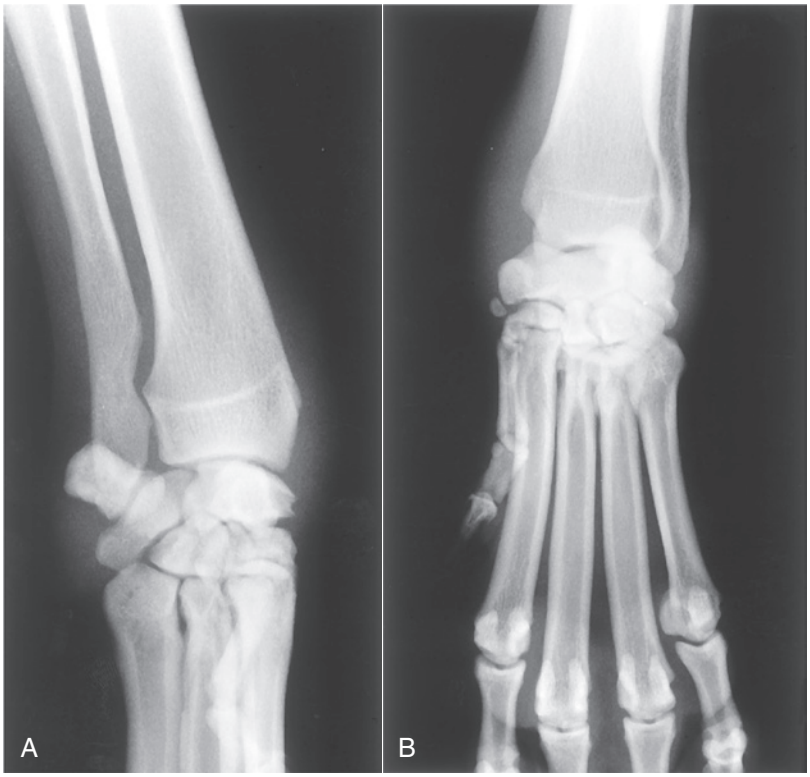


FIG 69.2
Lateral **(A)** and dorsopalmar **(B)** radiographs of the swollen left carpus of a 2-year-old Bullmastiff with a 1-week history of lameness caused by septic arthritis. Surgical exploration revealed two porcupine quills within the infected joint.

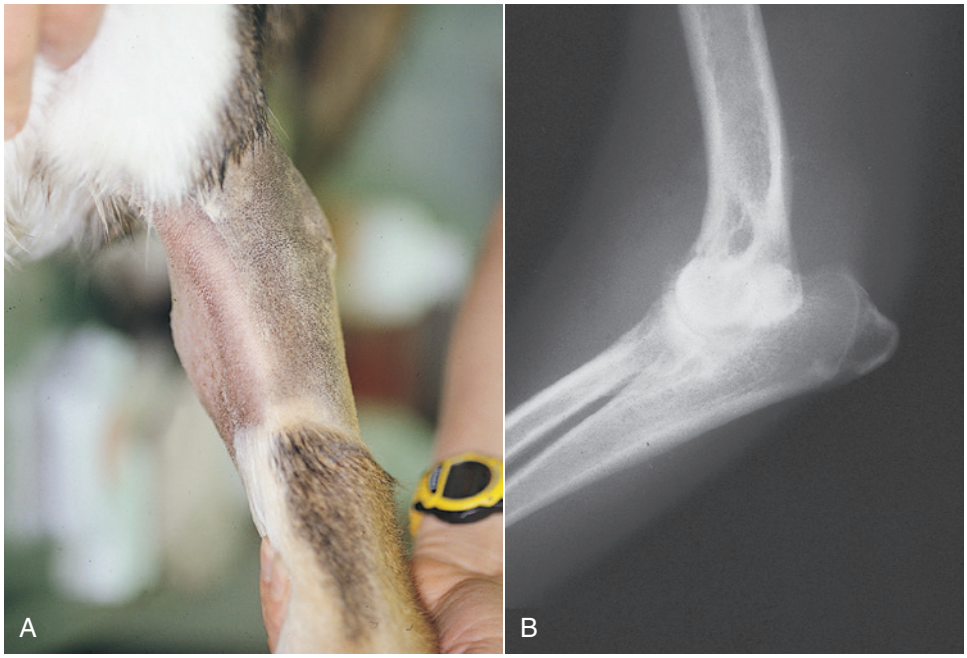


FIG 69.3
(A) Very swollen elbow in a Husky-cross dog with a 3-month history of non–weight-bearing lameness not responding to antibiotics. **(B)** Radiographs reveal marked swelling within the joint and diffuse periosteal proliferation. Synovial fluid showed septic inflammation, and surgical exploration revealed a single porcupine quill within the joint. The dog recovered completely.

arthritis can initially be treated conservatively with systemic antibiotics; however, if dramatic improvement is not seen within 3 days, surgery should be performed. Chronic infections, suspected intra-articular foreign bodies, postoperative joint infections, and infection in immature animals with open growth plates should all be treated with immediate surgical debridement and lavage. A minimum of 6 weeks of antibiotic therapy is administered, and cage rest is recommended to facilitate healing of articular cartilage.

Prognosis

The prognosis for a return to normal function depends on the severity of the damage to the articular cartilage at the time the infection is brought under control. Secondary DJD commonly occurs.

MYCOPLASMA POLYARTHRITIS

Mycoplasma spp. are normal inhabitants of the conjunctival membranes, pharynx, upper respiratory, and urogenital tracts of most species, and are generally considered nonpathogenic. *Mycoplasma gatea* and *Mycoplasma felis* have, however, been associated with erosive and nonerosive polyarthritis and tenosynovitis in cats. Mycoplasma polyarthritis occurs primarily in immunosuppressed or debilitated cats but has rarely been reported in apparently immunocompetent cats.

Mycoplasma polyarthritis typically results from hematogenous spread of the bacteria to the joints. Clinical signs include lameness, joint pain, depression, and fever. Synovial fluid analysis reveals an increase in nondegenerate neutrophils with no visible organisms. Routine aerobic and anaerobic cultures of joint fluid are negative because successful culture of *Mycoplasma* requires specific transport media and sample handling. Inflammatory joint fluid from cats should always be specifically cultured for *Mycoplasma spp,* and empirical treatment with oral doxycycline (5-10 mg/kg q12h) for 3 weeks is recommended before treating with immunosuppressant drugs for presumed idiopathic IMPA. Cats with polyarthritis should also be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), and radiographs should be made of the affected joints to investigate for erosive changes. Treatment of Mycoplasma arthritis with doxycycline, enrofloxacin, or pradofloxacin should result in rapid clinical improvement, but treatment for 6 to 8 weeks may be necessary to prevent relapse.

RICKETTSIAL POLYARTHRITIS

Nonerosive polyarthritis has been recognized in association with several tick-borne rickettsial diseases, including Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii, Ehrlichia canis, Ehrlichia ewingii,* and *Anaplasma phagocytophilum*. The polyarthritis that occurs in these disorders is believed to be due at least in part to immune complex deposition in the joints (reactive polyarthritis). Most infected dogs have other systemic signs of illness. Joint pain and effusion may be noted, and increased numbers of nondegenerate

neutrophils are identified in the joint fluid; occasionally, *Ehrlichia* or *Anaplasma* morulae can be identified in cytologic preparations of joint fluid. Fever and polyarthritis may be the only clinical abnormalities in dogs with ehrlichiosis and anaplasmosis, although concurrent hematologic abnormalities such as thrombocytopenia and anemia are common. Serologic testing for *E. canis, E. ewingii,* and *A. phagocytophilum* is widely available, but positive results merely indicate prior exposure and not necessarily active infection. Also, because polyarthritis often occurs early in acute ehrlichiosis and anaplasmosis, it is common for symptomatic dogs to have negative serologic results. Convalescent titers (10-14 days later) might be required to document infection.

Dogs with polyarthritis caused by RMSF typically show a variety of clinical signs resulting from widespread vasculitis, including fever, petechiae, lymphadenopathy, neurologic signs, edema of the face or extremities, and pneumonitis. Hematologic abnormalities, including thrombocytopenia, are common. Diagnosis is made on the basis of the results of serologic testing and demonstration of a fourfold increase in serum immunoglobulin (Ig)G concentrations over 2 to 3 weeks.

Acute rickettsial infections causing polyarthritis are best treated with oral doxycycline (5 mg/kg q12h). Empirical antibiotic treatment is warranted in all dogs with confirmed polyarthritis from endemic areas, especially if there is concurrent thrombocytopenia or other evidence to support rickettsial infection. Concurrent glucocorticoid therapy (prednisone, 0.5-2 mg/kg PO q24h) may be necessary in some dogs with confirmed rickettsial polyarthritis if antimicrobial therapy alone does not eliminate the fever, lameness, and joint swelling. Antibiotic treatment should continue for at least 3 weeks.

LYME DISEASE

Etiology

Infection by the tick-borne spirochete *Borrelia burgdorferi* (Bb) can cause illness (Lyme disease) in dogs. Ticks of the genus *Ixodes* transmit the spirochete, requiring at least 50 hours of tick attachment for transmission. Although serologic evidence of exposure is common in dogs throughout North America, most reports of canine Lyme disease have occurred in dogs from the northeastern and mid-Atlantic states, with Minnesota, Wisconsin, California, and Oregon accounting for most of the remaining cases.

Clinical Features

Most dogs bitten by ticks infected with Bb develop an antibody response but remain asymptomatic. Acute polyarthritis is the most common form of Lyme borreliosis diagnosed, and it occurs in fewer than 5% of naturally infected dogs. Clinical features of Lyme polyarthritis include shifting leg lameness, joint swelling, fever, lymphadenopathy, and anorexia. Cytologic examination of synovial fluid reveals neutrophilic inflammation. Cardiac, renal, and neurologic manifestations (e.g., seizure, behavior change) have also been attributed to Bb infection in dogs. There are reports of dogs with Bb antibodies developing a unique progressive renal disorder characterized by immune-mediated glomerulonephritis, tubular necrosis, and lymphocytic-plasmacytic interstitial nephritis. This disorder, which is often called Lyme nephritis, is most common in Labrador and Golden Retrievers and Shetland Sheepdogs, and causes progressive uremia, proteinuria, peripheral edema, body cavity effusions, and often death. Because of the high rate of seropositivity in endemic areas and the frequency of concurrent infection with other tick-borne diseases, it is difficult to determine how common Lyme disease is in clinical practice. The rate of veterinary diagnosis of canine Lyme polyarthritis certainly far exceeds its actual prevalence. Bacterial DNA was detected by polymerase chain reaction (PCR) in dogs with naturally occurring anterior cranial cruciate rupture but not in dogs with experimentally induced cranial cruciate rupture. Whether Lyme borreliosis plays a part in the pathogenesis of cranial cruciate rupture in dogs is unclear (Muir et al., 2007).

Diagnosis

Fever, lameness, and anorexia in dogs from endemic areas should raise the suspicion of Lyme disease. Synovial fluid analysis confirms polyarthritis. Attempts to culture Bb from the blood, urine, and synovial fluid of affected dogs are usually unsuccessful. Lyme disease polyarthritis should be diagnosed only if the animal has a history of recent potential exposure, the synovial fluid is confirmed to be inflammatory and sterile, serologic testing is positive, infection with other tick-borne diseases is eliminated, and a prompt and permanent response to appropriate antibiotic therapy is seen. The diagnosis can be supported by identifying *Borrelia* organisms in biopsy specimens of tissues prepared using special stains and monoclonal antibodies.

Treatment

Antibiotics are the treatment of choice. Oral doxycycline (5 mg/kg q12h), amoxicillin (22 mg/kg PO q12h), ampicillin (22 mg/kg PO q8h), Clavamox (12.5-25 mg/kg PO q8-12h), and cephalexin (20-40 mg/kg PO q8h) are all effective. Treatment during the acute stage of the disease should result in rapid clinical improvement (i.e., within 2-3 days). Treatment for at least 4 weeks is advised. Failure to recognize acute disease or institution of inappropriate treatment can allow chronic disease to develop, including relapsing polyarthritis, glomerulonephritis, and cardiac abnormalities.

Prevention

The prevention of Lyme disease is discussed in Chapter 93.

LEISHMANIASIS

Leishmaniasis is a chronic systemic disease caused by a protozoan parasite found mainly in Central and South America, Africa, India, and the Mediterranean. In the United States, *Leishmania* spp. are endemic in Ohio, Oklahoma, and Texas.

Clinical abnormalities develop 3 months to 7 years after infection and typically consist of vague signs, including weight loss, lymphadenopathy, and splenomegaly. Hyperglobulinemia, hypoalbuminemia, and proteinuria are expected. Polyarthritis causing lameness and exercise intolerance is common. Many affected dogs will have erosive disease with radiographic evidence of periarticular lysis and periosteal proliferation. Diagnosis is made when organisms are identified within macrophages in lymph node or splenic aspirates or in joint fluid (see Chapter 98).

FUNGAL ARTHRITIS

Fungal infection of the joints is very rare. When it does occur, it is usually as an extension of fungal osteomyelitis caused by *Coccidioides immitis, Blastomyces dermatitidis,* or *Cryptococcus neoformans.* More commonly a reactive, immunologically mediated, culture-negative polyarthritis occurs in dogs and cats with systemic fungal infections.

VIRAL ARTHRITIS

Calicivirus

Natural calicivirus infection and attenuated live calicivirus vaccination have been associated with development of transient polyarthritis in 6- to 12-week-old kittens. Clinical signs include lameness, stiffness, and fever that usually resolve spontaneously after 2 to 4 days (Fig. 69.4). Some kittens go on to develop overt calicivirus infection, with glossal and palatine vesicles or ulcers and signs of upper respiratory tract disease. Synovial fluid analysis reveals a mildly to greatly increased nucleated cell count, with small mononuclear cells and macrophages predominating, some of which contain phagocytosed neutrophils. Two specific strains of calicivirus have been implicated. Attempts to isolate the virus from affected joints has been unrewarding, although the virus can be found in the oropharynx of some infected cats. The polyarthritis in these kittens is likely to be immune complex mediated (reactive polyarthritis) rather than infectious.



FIG 69.4
Presumed calicivirus polyarthritis in a 10-week-old kitten exhibiting swollen joints, lameness, and fever 6 days after modified-live virus vaccination.

NONINFECTIOUS POLYARTHRITIS: NONEROSIVE

Noninfectious inflammatory (immune-mediated) joint diseases are very common in the dog but rare in the cat. IMPA is classified as either erosive or nonerosive on the basis of the presence or absence of radiographically evident joint destruction. Erosive disorders are very rare (<1% of canine polyarthritis cases). Nonerosive IMPA is believed to be mediated through immune complex formation and deposition in the synovial membrane. Immune-mediated nonerosive polyarthritis occurs secondary to antigenic stimulation from chronic infection, neoplasia, or drugs (i.e., reactive polyarthritis), as an idiopathic syndrome, and as a feature of systemic lupus erythematosus (SLE). Breed-associated syndromes of polyarthritis or polyarthritis/meningitis or polyarthritis/myositis also exist and are thought to have a genetic basis.

REACTIVE POLYARTHRITIS

Reactive polyarthritis accounts for some 25% of all nonerosive IMPAs cases and has been documented in association with chronic bacterial, fungal, or rickettsial infections; neoplasia; and drug administration. When it occurs secondary to chronic infection, the joints themselves are not infected, but immune complex deposition causes immune mediated synovitis. Reactive polyarthritis has been documented in dogs with endocarditis, foreign body abscesses or granulomas, diskospondylitis, heartworm disease, pancreatitis, prostatitis, pyelonephritis, pneumonia, other chronic bacterial and rickettsial infections, and a variety of tumors (Fig. 69.5). Drugs that have been implicated in causing reactive polyarthritis include sulfadiazine-trimethoprim, phenobarbital, erythropoietin, penicillin, cephalexin, and routine vaccinations. Rarely, gastrointestinal disorders such as inflammatory bowel disease, salmonellosis, and chronic active hepatitis have also been associated with reactive polyarthritis.

Because many animals with reactive polyarthritis have vague or minimal clinical signs referable to their underlying disease, they may be presented for veterinary evaluation when their joint inflammation makes them reluctant to walk. Therefore it is important to perform a thorough physical examination of every animal with polyarthritis and obtain a complete history regarding medication administration and the presence or absence of systemic signs. Once infectious causes of polyarthritis have been eliminated, screening tests (i.e., complete blood count [CBC], biochemical panel, urinalysis, thoracic and abdominal radiography, abdominal ultrasonography, culture of urine and blood, lymph node aspirates, cardiac ultrasonography) may be required to identify underlying chronic infections or neoplasia (Fig. 69.6).



FIG 69.5
(A) Two-year-old German Shepherd dog/Labrador Retriever cross with reactive polyarthritis. The dog was seen because of a 3-month history of shifting leg lameness and weight loss. There was joint swelling and pain and a grade IV/VI diastolic cardiac murmur. Synovial fluid was inflamed but sterile. **(B)** A cardiac ultrasound study suggested infective endocarditis of the aortic valve, which was confirmed by postmortem evaluation.

Serology or PCR testing may be necessary to evaluate for systemic infections known to cause reactive polyarthritis (*Bartonella, Anaplasma* and *Ehrlichia* spp).

Clinical signs in dogs with reactive polyarthritis typically include cyclic fevers, stiffness, and lameness. Synovial fluid analysis reveals an increase in both white blood cell (WBC) count and the percentage of neutrophils in affected joints, but synovial fluid culture is negative. Radiographically, the only finding is joint swelling.

Treatment must be directed at eliminating the underlying disease or antigenic stimulus whenever possible. If this can be achieved, polyarthritis usually resolves without additional therapy. Short-term low-dose glucocorticoid therapy (prednisone, 0.25-1 mg/kg PO q24h) or NSAID therapy may be warranted to control synovitis in severe cases.

IDIOPATHIC IMMUNE-MEDIATED NONEROSIVE POLYARTHRITIS

Nonerosive noninfectious polyarthritis in which a primary or underlying disease cannot be identified is referred to as *idiopathic immune-mediated polyarthritis*. This disorder can be diagnosed only by ruling out the other causes of polyarthritis, but it is the most common form of polyarthritis diagnosed in dogs (Box 69.1). It is especially common in sporting and large breeds. Dogs of any age can be affected, but the incidence peaks at 2.5 to 4.5 years. Idiopathic immune-mediated nonerosive polyarthritis is uncommon in cats.

BOX 69.1

Classification of Polyarthritis in Dogs

Infectious

Bacterial
Mycoplasma
Rickettsial
Lyme borreliosis
Leishmaniasis
Fungal
Viral

Noninfectious, Nonerosive

Idiopathic immune-mediated polyarthritis (IMPA)
Systemic lupus erythematosus (SLE)
Reactive polyarthritis (bacterial, fungal, parasitic, neoplastic, enterohepatic, drug reaction, vaccine induced)
Breed-associated syndromes
  Polyarthritis (Akita, Newfoundland, Weimaraner)
  Polyarthritis/meningitis (Akita, Beagle, Bernese Mountain dog, Boxer, German Shorthaired Pointer)
  Polyarthritis/polymyositis (Spaniels)
  Familial Shar-Pei fever
Lymphoplasmacytic synovitis

Noninfectious, Erosive

Rheumatoid-like arthritis
Erosive polyarthritis of Greyhounds

Clinical Features

The most common manifestations of idiopathic IMPA are cyclic fever, stiffness, and lameness. Multiple joints are usually involved, with the small distal joints (i.e., carpus, hock) affected most frequently. Approximately 20% to 50% of affected dogs lack palpable joint effusion or joint pain. Cervical pain and vertebral hypersensitivity are sometimes present, reflecting either intervertebral facetal joint involvement or the presence of concurrent steroid-responsive meningitis-arteritis (see Chapter 64). Some affected dogs are not obviously lame but are evaluated because of a vague history of decreased appetite or fever of unknown origin.

Diagnosis

Idiopathic IMPA is diagnosed on the basis of the results of synovial fluid analysis, failure to identify an infectious cause, and the absence of evidence to support a diagnosis of SLE or reason to suspect reactive polyarthritis (see Fig. 69.6). A CBC can be normal or inflammatory. Hyperglobulinemia

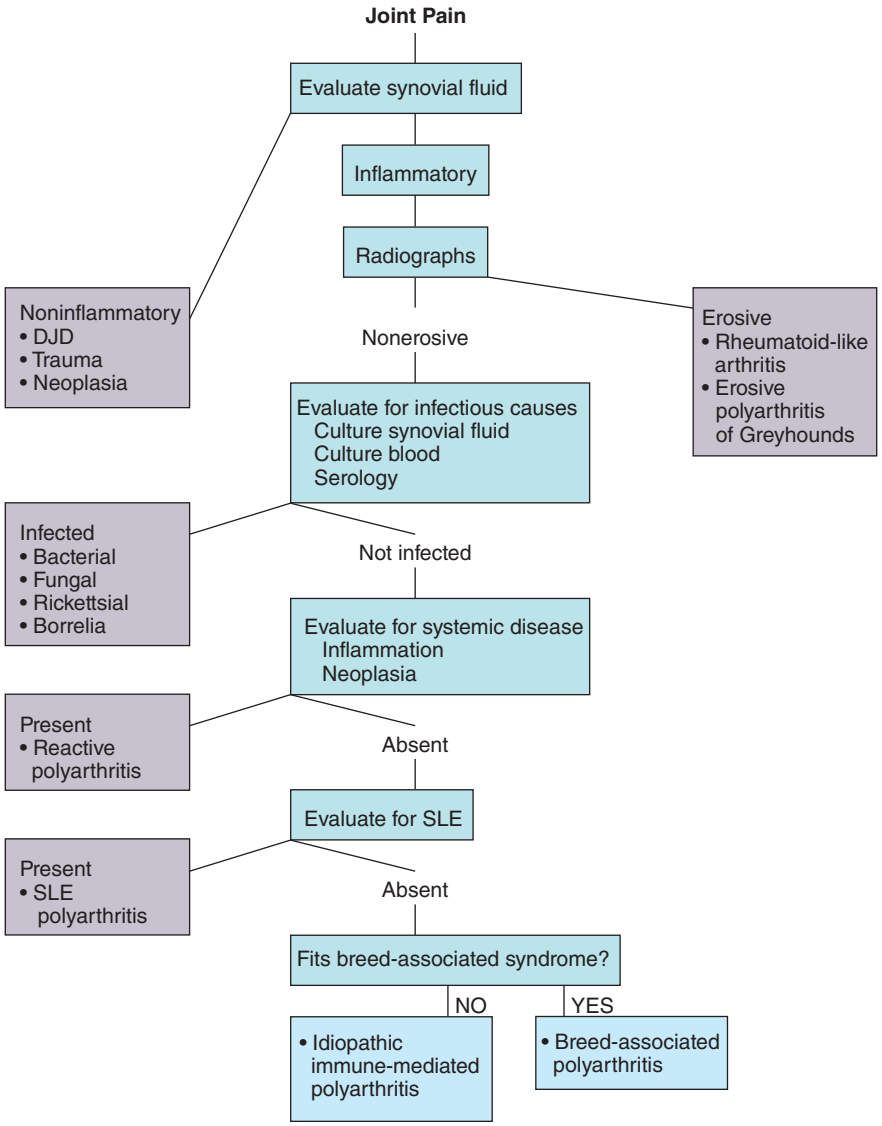


FIG 69.6
Algorithm for diagnostic evaluation of dogs with joint pain.

and hypoalbuminemia are common, reflecting ongoing systemic inflammation. Radiographs are either normal or demonstrate joint and periarticular swelling with no bone or cartilage abnormalities. Synovial fluid usually has decreased viscosity and may be turbid. Nucleated cell counts are increased (4000-370,000 cells/μL), with nondegenerate neutrophils predominating (usually >80%). In animals with less severe or waxing and waning disease and animals that have received glucocorticoids, there may be a lower synovial fluid WBC count and a lower percentage of neutrophils (15%-80%). Blood, urine, and synovial fluid cultures are negative for bacteria and *Mycoplasma* spp.

Treatment

In areas endemic for infectious causes of polyarthritis, empirical treatment with doxycycline is usually instituted while awaiting the results of diagnostic testing for infectious agents. A rapid and complete response makes a diagnosis of idiopathic IMPA less likely. Glucocorticoids are the initial treatment of choice for dogs with idiopathic IMPA. Prednisone treatment alone results in remission in 50% of cases. Immunosuppressive doses are initially administered, and the dosage is gradually decreased every 3 to 4 weeks if the animal is clinically normal and the inflammation in the synovial fluid has subsided (Box 69.2). The gold standard for response to therapy is resolution of synovial inflammation, so, ideally, arthrocentesis should be used to monitor response to therapy. Synovial fluid should be monitored carefully during treatment, and resolution of inflammation should be demonstrated prior to each decrease in drug dose. Repeated arthrocentesis may rarely be associated with mild mononuclear joint inflammation but does not cause neutrophilic inflammation in healthy dogs (Berg et al., 2009). If a dog with IMPA can be maintained on a low alternate-day

BOX 69.2

Treatment Recommendations for Canine Idiopathic Immune-Mediated Polyarthritis

1. Prednisone 2 mg/kg q12h orally for 3-4 days
2. Prednisone 2 mg/kg q24h orally for 14 days
3. Assess clinical response and synovial fluid cytology:
   - If clinical signs have resolved, the dose of prednisone is gradually tapered, evaluating clinical response and synovial fluid before each dose reduction:
     1 mg/kg q24h × 4 weeks
     1 mg/kg q48h × 4 weeks
     0.5 mg/kg q48h × 4 weeks
     0.25 mg/kg q48h × 8 weeks
   - If clinical signs of joint inflammation are present at any recheck, return to step 2 and add azathioprine (2 mg/kg/day PO) to treatment. Continue prednisone taper after signs resolve and synovial fluid is normal.

dose of prednisone (0.25 mg/kg PO q48h) for 2 months and the synovial fluid is not inflammatory, it is often possible to discontinue all therapy. However, approximately 50% of affected dogs will need at least alternate-day low-dose prednisone therapy for the remainder of their lives. In dogs receiving a stable dose of medication, synovial fluid should be evaluated every 4 to 6 months.

Additional immunosuppressive drugs should be administered to dogs with persistent inflammation of synovial fluid despite prednisone therapy and to dogs that cannot be maintained on a low dose of prednisone without relapse. Azathioprine (Imuran) is often used for this purpose, and it may also be used as initial treatment in dogs that are known to not tolerate prednisone therapy. Azathioprine (2.2 mg/kg) is administered PO once daily for 4 to 6 weeks. The frequency of administration can be decreased to every other day and then discontinued if the animal is doing well clinically and synovial fluid inflammation has resolved; however, some dogs will require lifelong azathioprine therapy. In most dogs azathioprine is well tolerated, with myelosuppression the most common adverse effect. A CBC and platelet count should be performed initially every 2 weeks and then every 4 to 8 weeks during treatment. See Chapter 72 for more information on azathioprine treatment. Azathioprine, leflunomide, mycophenolate mofetil, cyclosporine, and cyclophosphamide have all be shown to be effective add-on treatments for idiopathic IMPA in dogs. Cats with idiopathic IMPA can be treated with cyclosporine, leflunomide, chlorambucil, or methotrexate if prednisolone alone is ineffective.

Idiopathic nonerosive IMPA is easy to control in most patients. If the polyarthritis is refractory to treatment, the patient should be reevaluated for infectious disease, reactive polyarthritis, and erosive disease prior to considering alternative or additional immunosuppressive agents (Table 69.2). In addition to medical treatment, management should initially include restricted exercise, followed by regular gentle exercise and weight control. Chondroprotective agents, omega-3 fatty acids, and antioxidants may also prove beneficial. (See Chapters 72 and 73 for more information on immunosuppressive treatment.)

TABLE 69.2

Drugs Used in the Treatment of Immune-Mediated Polyarthritis in Dogs

DRUG	DOSAGE
Prednisone	Variable
Azathioprine (Imuran [GlaxoSmithKline, Philadelphia, PA])	2.2 mg/kg PO q24-48h
Cyclosporine (Atopica [Novartis, Greensboro, NC])	2.5-5 mg/kg PO q12h Target blood level 400 ng/mL
Leflunomide (Arava [Aventis Pharma, Bridgewater, NJ])	3-4 mg/kg q24h Target trough blood level 20 µg/mL
Cyclophosphamide (Cytoxan [Bristol-Myers-Squibb, Princeton, NJ])	50 mg/m^2 PO q48h
Chlorambucil (Leukeran [GlaxoSmithKline])	Dogs: 0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen
Methotrexate (Rheumatrex [Wyeth, Philadelphia, PA])	2.5 mg/m^2 PO q48h

PO, Oral.

Prognosis

The prognosis for animals with idiopathic immune-mediated nonerosive polyarthritis is good in most cases. Approximately 80% of dogs respond well to initial treatment, and 50% of these dogs can be weaned off therapy after 3 to 4 months. An occasional dog is very difficult to control initially or keep in remission. In such cases reevaluation of the diagnosis should be considered to make sure a diagnosis of erosive polyarthritis or SLE has not been missed. Dogs that require long-term (4-5 years) high-dose immunosuppressive drug therapy for polyarthritis may develop symptomatic DJD secondary to chronic low-grade synovial inflammation and the detrimental effects of glucocorticoids on cartilage synthesis and repair.

SYSTEMIC LUPUS ERYTHEMATOSUS–INDUCED POLYARTHRITIS

SLE is a multisystemic immune-mediated disorder in which autoantibodies against tissue proteins and DNA result in circulating immune complexes that, when deposited in tissues, induce inflammation and organ damage (see Chapter 73).

Although SLE is a relatively uncommon cause of polyarthritis in dogs compared with idiopathic IMPA, its effects on other organ systems can be devastating, which makes accurate diagnosis important. SLE is most commonly diagnosed in dogs 2 to 4 years old. German Shepherd dogs and Shetland Sheepdogs may be predisposed, but any breed of dog may be affected.

Clinical Features

The clinical manifestations of SLE depend on the organs involved and include intermittent fever, polyarthritis, glomerulonephritis, skin lesions, hemolytic anemia, immune-mediated thrombocytopenia, myositis, and polyneuritis. Polyarthritis is the most common manifestation, occurring in 70% to 90% of dogs diagnosed with SLE. Some affected dogs show no signs referable to their joint disease, and polyarthritis is detected when synovial fluid is examined as part of a workup for fever or polysystemic immune-mediated disease. More often, dogs with SLE polyarthritis show generalized stiffness, joint swelling, or shifting leg lameness. SLE causes a sterile nonerosive polyarthritis, with distal joints (i.e., hocks, carpi) usually more severely affected than proximal joints. Synovial fluid analysis reveals an increased WBC count (5000-350,000/mL) consisting primarily of nondegenerate neutrophils (>80%). In rare instances, lupus erythematosus (LE) cells or ragocytes are detected in the synovial fluid (see Fig. 68.9).

Diagnosis

SLE should be considered in any dog with noninfectious polyarthritis. A thorough physical examination, CBC, platelet count, biochemistry profile, urinalysis, fundic examination, and protein/creatinine ratio determination should be performed to search for other manifestations of this disease. Laboratory tests that may aid in the diagnosis of SLE polyarthritis include the LE cell test and the antinuclear antibody (ANA) test. An animal is diagnosed with SLE if there are two or more of the major clinical abnormalities known to be associated with SLE (e.g., polyarthritis, glomerulonephritis, hemolytic anemia, thrombocytopenia, leukopenia, polymyositis, dermatitis) and either the ANA or LE test is positive. When two or more of the common clinical syndromes are recognized but none of the serologic tests is positive, the dog is determined to have an SLE-like multisystemic immune-mediated disease. See Chapter 73 for more information on the diagnosis of SLE.

Treatment

Treatment for SLE-associated polyarthritis is the same as that used for idiopathic IMPA; however, addition of other cytotoxic drugs (e.g., azathioprine, cyclosporine) is usually necessary to induce or maintain remission. See Chapter 73 for more information on treatment of SLE.

Prognosis

The prognosis for dogs with SLE is guarded to poor. Relapse is common regardless of the drug protocol used, and long-term and often lifelong immunosuppressive therapy is necessary to control the disease. Relapses may involve different organ systems and clinical signs than at initial presentation (e.g., hemolytic anemia initially and polyarthritis at relapse).

BREED-SPECIFIC POLYARTHRITIS SYNDROMES

There are a number of breed-specific IMPA syndromes in dogs. A heritable polyarthritis has been documented in Akitas younger than 1 year of age, and a similar disease is reported sporadically in Newfoundlands and Weimaraners. Many of these dogs have concurrent meningitis resembling the meningeal vasculitis syndromes seen in other breeds (see Chapter 64). ANA tests are negative in these animals, and generally they respond poorly to routine immunosuppressive therapy so more aggressive immunosuppressive treatment is recommended. In contrast, polyarthritis that accompanies meningeal vasculitis in Boxers, Bernese Mountain Dogs, German Shorthaired Pointers, and Beagles often responds completely to immunosuppressive therapy.

Familial polyarthritis with concurrent myositis has been rarely reported in Spaniel breeds. Affected dogs are exercise intolerant and exhibit a crouched stance at rest. Widespread muscle atrophy is common, occasionally leading to muscle fibrosis, contracture, and reduced mobility. Muscle enzymes (creatine kinase [CK], aspartate aminotransferase [AST]) may be increased. Response to therapy is often poor.

FAMILIAL CHINESE SHAR-PEI FEVER

Familial Chinese Shar-Pei fever, also known as Shar-Pei Autoinflammatory Disease (SPAID), is an inherited inflammatory disease that occurs in nearly 25% of all Shar-Peis. The disorder was initially thought to be due to a genetic mutation that increased production of hyaluronic acid (HA) by dermal fibroblasts, causing mucinosis and triggering an inflammatory response (Olsson et al., 2011). More recent genetic studies have identified a missense mutation in affected dogs that works directly to strongly promote proinflammatory reactions. The disease is usually first manifested prior to 18 months of age and is characterized initially by intermittent episodes of inflammation and fever lasting 24 to 36 hours. Some 50% of affected dogs develop periarticular swelling around the hock joints during the febrile episodes, and some dogs develop polyarthritis, particularly of the hocks. Affected dogs are at increased risk for systemic amyloidosis, often leading to renal or hepatic failure. Renal amyloid deposition is primarily medullary, so not all dogs will exhibit proteinuria. Hyperglobulinemia and increased serum concentrations of the cytokine interleukin-6 are common. Glomerulonephritis, pyelonephritis, renal infarcts, and systemic thromboembolic disease may occur. This disorder is inherited as an autosomal incompletely dominant trait. Treatment relies on symptomatic control of fever and inflammation. Oral administration of colchicine (0.03 mg/kg q24h) may decrease amyloid deposition.

LYMPHOPLASMACYTIC SYNOVITIS

Lymphoplasmacytic synovitis is present in some dogs with partial and complete tears of the cranial cruciate ligament, but the relationship between the immune-mediated response and the ligament rupture is uncertain. Partial tears or ruptures of the cruciate ligament commonly initiate an inflammatory reaction directed against the collagen of the ligament, resulting in mildly inflammatory synovial fluid and synovial fluid antibodies directed against type 1 and type 2 collagen. An alternative theory is that lymphoplasmacytic synovitis is a primary immune-mediated disorder that causes joint laxity and instability, eventually leading to rupture of the cranial cruciate ligament. Some investigators have estimated that perhaps as many as 10% to 25% of cruciate ruptures in dogs are caused by this immunologic disorder, but this is a controversial claim.

Dogs diagnosed with lymphoplasmacytic synovitis are the same dogs typically presented for cruciate ligament rupture, with Rottweilers, Newfoundlands, Staffordshire Bull Terriers, and Labrador Retrievers most commonly affected. Clinical signs are limited to acute or chronic lameness involving one or both stifles. Cruciate ligament rupture at the time of diagnosis may be partial or complete, and often there is no history of trauma. Arthroscopy or magnetic resonance imaging (MRI) may be required to confirm the diagnosis of partial rupture. Affected animals are in good body condition and are not systemically ill; CBC is normal. Synovial fluid is thin and turbid, with an increased nucleated cell count (5000-20,000 cells/μL, but occasionally > 200,000/μL). Lymphocytes and plasma cells predominate (60%-90%) in the synovial fluid. Biopsy of ligament and synovium should be performed at the time of surgical exploration and repair in all dogs with nontraumatic cruciate ligament ruptures. Characteristic histopathologic changes in the synovial lining include lymphocytic and plasmacytic infiltration and villous hyperplasia. Surgical stabilization of the stifle and treatment with NSAIDs usually result in rapid resolution of clinical signs. Some dogs will have persistent effusion and discomfort that responds well to immunosuppressive treatment with prednisone and/or azathioprine, initiated a minimum of 3 days after NSAID therapy is discontinued.

NONINFECTIOUS POLYARTHRITIS: EROSIVE

CANINE RHEUMATOID-LIKE POLYARTHRITIS

A disorder resembling human rheumatoid arthritis (RA) is a rare cause of erosive polyarthritis and progressive joint destruction in dogs. Small and toy breeds are most commonly affected (mean body weight 8 kg). Cocker Spaniels and Shetland Sheepdogs may be predisposed. The age of onset is variable (i.e., 9 months to 13 years), but most affected dogs are young or middle-aged at the time of diagnosis. Initially, the disease is indistinguishable from idiopathic nonerosive polyarthritis, but the joints are destroyed over time (months to years), with distal joints most severely affected.

Etiology

The pathogenesis of canine RA-like polyarthritis is poorly understood. Antibodies directed against IgG (i.e., rheumatoid factors [RFs]) form and complex with IgG within the synovium. This results in complement activation and the chemotactic attraction of plasma cells, lymphocytes, and neutrophils into the joint fluid. The synovial membrane thickens and develops a fibrous, vascular granulation tissue (pannus) that invades articular cartilage, tendons, ligaments, and subchondral bone. Proteolytic enzymes are released that erode the articular cartilage and subchondral bone, leading to joint collapse and radiographically visible "punched-out" subchondral bone lesions. Articular and periarticular inflammation and instability lead to joint subluxation and luxation, resulting in joint deformity.

Clinical Features

Affected dogs initially have signs indistinguishable from those of other forms of polyarthritis. A low-grade fever, depression, anorexia, and reluctance to exercise are common. Joint-related clinical signs such as joint pain and stiff gait are prominent. Signs may be sporadic initially, and stiffness is generally worse after rest and improves with mild exercise. The joints may appear normal or be swollen and painful. The joints most commonly affected are the carpi, hocks, and phalanges, although stifles, elbows, and shoulders can also be affected. As the disease progresses, clinical examination reveals crepitus, laxity, luxation, and deformity of affected joints, especially the carpus bilaterally (Fig. 69.7). Unilateral or bilateral anterior cruciate ligament rupture is also common.

Radiographic features may be subtle at the time of initial diagnosis, with intracapsular swelling the only consistent



FIG 69.7
Complete collapse of both carpi, resulting in luxation and severe distortion of the forelimbs in a Dachshund with rheumatoid arthritis. (Courtesy Dr. D. Haines, University of Saskatchewan.)



FIG 69.8
Radiographs of both carpal joints of a 9-year-old female Shih Tzu. Both carpi are severely deformed secondary to erosive rheumatoid-like polyarthritis. The intercarpal spaces have thinned laterally, and there are focal radiolucent cyst-like areas of subchondral bone destruction and regional soft tissue swelling. There is dislocation of the radius and ulna from the carpus bilaterally.

finding. Later, characteristic changes consist of focal, irregular, radiolucent, cyst-like areas of subchondral bone destruction (Fig. 69.8); joint space collapse; and joint subluxation and luxation. Erosive changes are common in the carpus at the time of diagnosis (75% of affected dogs) and are evident radiographically in all affected dogs within 1 year of diagnosis. Whenever RA is suspected, carpi should be radiographed bilaterally.

Diagnosis

RA-like polyarthritis should be suspected in any dog with erosive polyarthritis once infectious causes have been eliminated. The synovial fluid in affected joints is thin, cloudy, and hypercellular, with an increased TNCC similar to dogs with nonerosive idiopathic IMPA (mean 7200 WBCs/μL). Neutrophils are usually the predominant cell (20%-95%; average 74%), but mononuclear cells may sometimes predominate. Lymphocyte numbers are often increased in synovial fluid from dogs with erosive polyarthritis. Culture of synovial fluid is negative. Whenever possible, the synovial fluid should be collected during a period when the dog is most symptomatic, because the cyclical nature of the disease occasionally makes diagnosis difficult.

Serologic tests for circulating RF are positive in 20% to 70% of affected dogs (see Chapter 68). Weak false-positive results are common in dogs with other systemic inflammatory diseases. Synovial biopsy may help establish the diagnosis, revealing synovial thickening, hyperplasia, and proliferation with pannus formation. The pannus is composed primarily of proliferating activated synoviocytes, lymphocytes, plasma cells, macrophages, and neutrophils. Culture of the synovial biopsy is negative. RA is diagnosed on the basis of the typical clinical findings and radiographic features, characteristic synovial fluid features, a positive RF test result, and the typical histopathologic changes seen in a synovial biopsy specimen.

Treatment

Early treatment of RA is important to prevent irreversible changes and progressive disease. Medical treatment usually includes immunosuppressive drugs and chondroprotective agents. Initially, most dogs are treated with oral prednisone (2-4 mg/kg q24h for 14 days, then 1-2 mg/kg q24h for 14 days) and azathioprine (2.2 mg/kg PO q24h), administered as described for the treatment of refractory idiopathic nonerosive polyarthritis. Oral chondroprotective agents (see Table 69.1) should be administered concurrently. Subjective improvement has also been observed in dogs receiving injectable chondroprotective agents (e.g., Adequan).

If there is a good response to treatment, based on both resolution of clinical signs and synovial fluid inflammation, the glucocorticoid dose should be decreased to 1 to 2 mg/kg orally every 48 hours, and treatment with azathioprine is continued. If the response to treatment is inadequate after 1 month of treatment with glucocorticoids and azathioprine, more aggressive immunosuppressive therapy should be considered (see Table 69.2). Few published data exist regarding treatment of RA in dogs, so choice of immunosuppressive agents is usually based on individual clinical experience and response to therapy. Leflunomide has been reported to be

effective as monotherapy in some dogs with idiopathic polyarthritis and is well tolerated. Leflunomide is administered at an initial dose of 3 to 4 mg/kg PO q24h, and the dose is adjusted to maintain a trough plasma level of 20 mg/mL. (See Chapter 72 for more information on immunosuppressive treatment.)

Some therapeutic success may be expected if treatment is initiated before joint damage is severe. In most cases, however, damage to the articular cartilage is severe before the diagnosis is made. Many dogs require additional therapy with analgesics such as tramadol to control joint discomfort. RA is a relentlessly progressive disorder, and even with appropriate therapy most dogs show deterioration with time. Surgical procedures can occasionally be used to improve joint stability and pain. Synovectomy, arthroplasty, joint replacement, and arthrodesis may decrease pain and improve function.

EROSIVE POLYARTHRITIS OF GREYHOUNDS

An erosive IMPA occurs in Greyhounds from 3 to 30 months of age. This disorder is primarily seen in Australia and Great Britain. The proximal interphalangeal joints, carpi, hocks, elbows, and stifles are most commonly affected. Clinical signs include generalized stiffness, joint pain or swelling, and a single or multiple-limb lameness that may be intermittent. The synovial membrane is infiltrated with lymphocytes and plasma cells, and synovial fluid analysis also reveals an increase in lymphocytes. There is extensive necrosis of deep articular cartilage zones, with relative sparing of the superficial surface cartilage. *Mycoplasma spuman* was isolated from one affected Greyhound, so it is important to rule out infectious causes of polyarthritis in affected dogs; trial therapy with antibiotics may be warranted. Therapy is as for refractory idiopathic immune-mediated nonerosive polyarthritis. Response to treatment is variable.

FELINE EROSIVE IMMUNE MEDIATED POLYARTHRITIS

Two uncommon immune mediated disorders cause joint damage and destruction in cats. One is a periosteal proliferative polyarthritis characterized by marked periosteal new bone formation and the second is a deforming arthritis resembling RA in humans and dogs. When first described, both of these disorders were thought to be variants of one disorder referred to as chronic progressive polyarthritis (CPP). All of the originally reported cases were male cats, all were positive for antibodies against feline syncytium-forming virus (FeSFV), and approximately 60% were infected with FeLV or FIV or both. There was speculation that CPP was caused by chronic immune stimulation secondary to FeSFV infection in immunosuppressed genetically predisposed cats. FeSFV is, however, a widespread retrovirus of cats, and experimental infection with FeSFV does not cause polyarthritis, so the association between this virus and the manifestations of CPP is uncertain.

FELINE PERIOSTEAL PROLIFERATIVE POLYARTHRITIS

Periosteal proliferative polyarthritis occurs most often in young adult male cats, but female cats can also be affected. Clinical signs include fever, stiff gait, joint pain, lymphadenopathy, and edema of the skin and soft tissues overlying the joints, particularly the carpus and hock. Synovial fluid analysis reveals a neutrophilic pleocytosis, and culture is negative. Initially, the radiographic changes are mild and include periarticular soft tissue swelling and mild periosteal proliferation. With time, the periosteal proliferation worsens and periarticular osteophytes, subchondral cysts, and collapse of the joint space may be noted. A treatment trial with doxycycline to rule out infectious polyarthritis should be considered prior to institution of immunosuppressive treatment. Treatment with glucocorticoids (prednisolone or prednisone) lessens the severity of signs and may slow progression of disease, but it is not curative. About half of treated cats have a reasonable quality of life when treated lifelong with glucocorticoids and analgesics. There may be further improvement when more potent immunosuppressive drugs are administered. (Table 69.3)

FELINE RHEUMATOID-LIKE ARTHRITIS

Feline rheumatoid-like arthritis has an insidious onset, with the slow development of lameness, stiffness, and joint deformity over weeks to months. Middle-aged and older cats are affected, and Siamese cats may be predisposed. Systemic illness and fever do not usually occur, so most affected cats are not examined until severe joint deformities are evident (Lemetayer et al., 2014). Synovial fluid analysis reveals mild to moderate mixed inflammation. Radiographically there are severe subchondral central and marginal erosions, and periarticular swelling that initially progresses to extensive bone destruction and gross joint deformities. Rheumatoid-like arthritis should be suspected in cats with erosive, deforming polyarthritis once infectious causes have been eliminated

TABLE 69.3

Drugs Used in the Treatment of Immune-Mediated Polyarthritis in Cats

Prednisolone	2 mg/kg q12h initially, then taper
Cyclosporine	2.5-5.0 mg/kg PO q12h
Leflunomide	10 mg/cat PO q24h
Chlorambucil	2 mg/cat PO q48h
Methotrexate	2.5 mg/m^2 PO q48h
Leflunomide/Methotrexate Protocol for Rheumatoid-Like Arthritis:	
Leflunomide	10 mg/cat PO q24h until improvement Then 10 mg/cat PO twice weekly
Methotrexate	2.5 mg/cat PO q12h for 3 doses once a week until improvement Then 2.5 mg/cat PO weekly

and a treatment trial with doxycycline has been ineffective. Serologic tests for circulating RF (using the canine Rose-Waaler or ELISA test) are positive in most literature reports of cats with rheumatoid-like arthritis, but a positive test is not essential for diagnosis (Hanna, 2005).

Rheumatoid-like arthritis is an aggressive, destructive, and irreversible disease. Most cats have only a minimal response to treatment with NSAIDs or glucocorticoids. There have, however, been reports of remarkable improvement in cats treated with methotrexate in combination with leflunomide (Hanna, 2005) (see Table 69.3). Treatment with other potent immunosuppressive agents should also be considered. Concurrent treatment with analgesics such as amantadine (3 mg/kg PO q24h), amitriptyline (0.5-2 mg/kg PO q24h), or gabapentin (2-10 mg/kg PO q24h) may make affected cats more comfortable.

Suggested Readings

Agut A, et al. Clinical and radiographic study of bone and joint lesions in 26 dogs with leishmaniasis. *Vet Rec*. 2003;153:648.

Berg RIM, et al. Effect of repeated arthrocentesis on cytologic analysis of synovial fluid in dogs. *J Vet Intern Med*. 2009;23:814.

Bleedorn JA, et al. Synovitis in dogs with stable stifle joints and incipient cranial cruciate ligament rupture: a cross-sectional study. *Vet Surg*. 2011;40:531.

Clements DN, et al. Type I immune-mediated polyarthritis in dogs: 39 cases (1997-2002). *J Am Vet Med Assoc*. 2004;224:1323.

Clements DN, et al. Retrospective study of bacterial infective endocarditis in 31 dogs. *J Small Anim Pract*. 2005;46:171.

Colopy SA, et al. Efficacy of leflunomide for treatment of immune mediated polyarthritis in dogs: 14 cases (2006-2008). *J Am Vet Med Assoc*. 2010;236:312.

Danielson F, et al. Inflammatory response in dogs with spontaneous cranial cruciate ligament rupture. *Vet Comp Orthop Traumatol*. 2005;17:237.

Foley J, et al. Association between polyarthritis and thrombocytopenia and increased prevalence of vectorborne pathogens in Californian dogs. *Vet Rec*. 2007;160:159.

Greene CE, et al. *Ehrlichia* and *Anaplasma* infections. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 4th ed. Philadelphia: Elsevier; 2006.

Hanna FY. Disease modifying treatment for feline rheumatoid arthritis. *Vet Comp Orthop Traumatol*. 2005;18:94.

Jacques D, et al. A retrospective study of 40 dogs with polyarthritis. *Vet Surg*. 2002;31:428.

Littman MP, et al. ACVIM Small Animal Consensus statement on Lyme disease in dogs: diagnosis, treatment and prevention. *J Vet Intern Med*. 2006;20:422.

Johnson KC, Mackin A. Canine immune-mediated polyarthritis, Part 1: pathophysiology. *J Am Anim Hosp Assoc*. 2012;48:12.

Johnson KC, Mackin A. Canine immune-mediated polyarthritis, Part 2: diagnosis and treatment. *J Am Anim Hosp Assoc*. 2012;48:71.

Lemetayer J, Taylor S. Inflammatory joint disease in cats: diagnostic approach and treatment. *J Feline Med Surg*. 2014;16:547.

Muir P, et al. Detection of DNA from a range of bacterial species in the knee joints of dogs with inflammatory knee arthritis and associated degenerative anterior cruciate ligament rupture. *Microb Pathog*. 2007;42:47.

Olsson M, et al. A novel unstable duplication upstream of HAS2 predisposes to a breed-defining skin phenotype and a periodic fever syndrome in Chinese Shar-Pei dogs. *PLoS Genet*. 2011;7:e1001332. [Epub Mar 17, 2011].

Rhoades AC, et al. Comparison of the efficacy of prednisone and cyclosporine for treatment of dogs with primary immune mediated polyarthritis. *J Am Vet Med Assoc*. 2016;248:395.

Rondeau MP, et al. Suppurative, nonseptic polyarthropathy in dogs. *J Vet Intern Med*. 2005;19:654.

Rychel JK. Diagnosis and treatment of osteoarthritis. *Top Companion Anim Med*. 2010;25:20.

Vanderweerd C, et al. Systematic review of efficacy of nutraceuticals to alleviate clinical signs of osteoarthritis. *J Vet Intern Med*. 2012;26:448.

Drugs Used in Joint Disease

DRUG NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Acetylsalicylic acid (aspirin)	Analgesia, antiinflammatory	10-20 mg/kg PO q8h	10 mg/kg PO q48h
Amantadine	Analgesia	3-5 mg/kg PO q24h	3 mg/kg PO q24h
Amoxicillin	Antibiotic	22 mg/kg PO q12h	Same
Amoxicillin with clavulanic acid (Clavamox)	Antibiotic	12-25 mg/kg PO q8h	Same
Ampicillin	Antibiotic	22 mg/kg PO q8h *or* 22 mg/kg IV, SC, IM q6h	Same
Azathioprine (Imuran)	Immunosuppression	2.2 mg/kg PO q24-48h	Not recommended
Buprenorphine (injectable)	Analgesia	0.01-0.03 mg/kg IM q8h	0.01-0.03 mg/kg on oral mucosa q8h
Carprofen (Rimadyl)	Analgesia, antiinflammatory	2.2 mg/kg PO q12h	None

Continued



Drugs Used in Joint Disease—cont'd

DRUG NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Cefotaxime	Antibiotic	20-40 mg/kg IV q6h	Same
Ceftriaxone	Antibiotic	25 mg/kg, IV or SC, q24h	Same
Cephalexin (Keflex)	Antibiotic	20-40 mg/kg PO q8h	Same
Chlorambucil (Leukeran)	Immunosuppression	0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen	0.1-0.2 mg/kg PO q24-72h or 2 mg/cat q48-72h
Chondroitin sulfate	Chondroprotective	15-20 mg/kg PO q12h	Same
Colchicine	Antiinflammatory	0.03 mg/kg PO q24h	Same
Cyclophosphamide (Cytoxan)	Immunosuppression	50 mg/m^2 PO q48h	Same
Cyclosporine (Atopica)	Immunosuppression	2.5-5 mg/kg PO q12h	Same
Deracoxib (Deramaxx)	Analgesia Antiinflammatory	1-2 mg/kg PO q24h	None
Doxycycline	Antibiotic	5-10 mg/kg PO, IV q12h	Same
Enrofloxacin (Baytril)	Antibiotic	5-20 mg/kg PO or SC q24h or divided q12h	5 mg/kg PO or SC q24h; use pradofloxacin
Etodolac (Etogesic)	Analgesia, antiinflammatory	10-15 mg/kg PO q24h	None
Firocoxib (Previcox)	Analgesia, antiinflammatory	5 mg/kg PO q24h	None
Gabapentin (Neurontin)	Analgesia	2-10 mg/kg PO q8-12 h	2-10 mg/kg PO q8-24 h
Glucosamine	Chondroprotective	15-20 mg/kg PO q12h	Same
Leflunomide (Arava)	Immunosuppression	3-4 mg/kg PO q24h	10 mg/cat q24h
Meloxicam (Metacam)	Analgesia, antiinflammatory	0.2 mg/kg PO once, then 0.1 mg/kg PO q24h	0.05-0.1 mg/kg q24h × maximum 4 d then 0.1 mg/cat/24h
Methotrexate (Rheumatrex)	Immunosuppression	2.5 mg/m^2 PO q48h	Same
Metronidazole (Flagyl)	Antibiotic	10-15 mg/kg PO q8h 7.5 mg/kg IV q8h	Same Same
Pentosan polysulfate (Pentosan 100)	Chondroprotective	3 mg/kg IM q7d	None
Piroxicam (Feldene)	Analgesia, antiinflammatory	0.3 mg/kg PO q48h	Same
Polysulfated glycosaminoglycans (Adequan)	Chondroprotective	3-5 mg/kg IM q4d for 8 tx, then q30d	Same
Pradofloxacin (Veraflox)	Antibiotic	3-4.5 mg/kg PO q24h (tablets only)	3-4.5 mg PO q24h (tablets); 5-7.5 mg/kg PO q24h (oral suspension)
Prednisolone Prednisone	Immunosuppression Antiinflammatory	2-4 mg/kg PQ q24h 0.5-1 mg/kg PO q24h 2-4 mg/kg PO q24h	4-6 mg/kg PO q24h 1 mg/kg PO q24h 4-6 mg/kg PO q24h; use prednisolone instead
	Antiinflammatory	0.5-1 mg/kg PO q24h	Same
Tramadol	Analgesia	2-5 mg/kg PO q8-12h	1-5 mg/kg PO q8-12h

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous; *tx,* treatments.

PART ELEVEN ▪ Immune-Mediated Disorders

Andrew Woolcock and J. Catharine R. Scott-Moncrieff

CHAPTER 70

Pathogenesis of Immune-Mediated Disorders



GENERAL CONSIDERATIONS AND DEFINITION

Immune-mediated disorders occur when the protective immune response is activated inappropriately, resulting in organ or cellular injury. Pathologic immune reactions may occur in response to infectious pathogens and contribute to the clinical disease presentation for that pathogen (e.g., the hemolytic anemia associated with *Mycoplasma haemofelis* infection) or be stimulated by otherwise innocuous foreign substances (e.g., the allergic reactions that occur to house dust) or by self-antigens (primary autoimmunity). Autoimmunity is defined as a condition characterized by a specific humoral or cell-mediated immune response against constituents of the body's own tissues (self-antigens or autoantigens). The term *primary autoimmune disease* is reserved for disorders in which no underlying cause can be identified and the cause of the autoimmunity is believed to be an underlying immune system dysfunction or imbalance. The term *secondary autoimmunity* (also termed *secondary immune-mediated disease*) is used to describe immune-mediated disorders in which an underlying reason for the autoimmune response can be identified. Examples of secondary causes of autoimmunity include infection, exposure to certain drugs or toxins, neoplasia, and vaccine administration.

IMMUNOPATHOLOGIC MECHANISMS

Immunopathologic injury occurs as a result of a hypersensitivity reaction, for which there are four major mechanisms (Table 70.1). Each mechanism may be either part of an appropriate response to a foreign antigen or an inappropriate response that can lead to allergic or immune-mediated disease. The immune response can be rapid, representing the innate immune system, with an adaptive immune response that follows. This adaptive immune response is mediated primarily by T-lymphocytes. Depending on the most appropriate immune response, inflammatory cytokines mediate a Th1 (cell-mediated) or Th2 (humoral) lymphocytic response which, in turn, activates the appropriate immune cells for the antigen encountered. More than one mechanism may be involved in some immune-mediated disorders.

Type I hypersensitivity involves the humoral immune system, immunoglobulin E (IgE), and mast cells. Exposure of the immune system to antigens by way of the skin, respiratory tract, or gastrointestinal tract leads to activation of antigen-specific subsets of T-helper lymphocytes and initiation of B-cell differentiation to plasma cells. Plasma cells secrete IgE, which attaches to receptors on mast cells. On future exposure to the same antigen, cross-linking of the IgE molecules on the mast cells occurs, which leads to mast cell degranulation. The potent inflammatory mediators that are released lead to vasodilation, edema, eosinophil chemotaxis, pruritus, and bronchoconstriction. Some drugs (e.g., doxorubicin) can induce mast cell degranulation independent of IgE (i.e., anaphylactoid reaction). Examples of diseases mediated primarily by a type I response include allergic bronchitis (feline asthma) and acute anaphylactic reactions.

Type II (cytotoxic) hypersensitivity involves the binding of antibody (IgG or IgM) and/or complement to specific molecules on the surface of a cell. This binding typically results in destruction of the cell or receptors on the cell. Less commonly, antibodies may induce a biologic effect such as stimulation of the thyroid-stimulating hormone receptor and induction of hyperthyroidism in humans with Graves disease. The target of antibody binding may be normal self-antigens, infectious agents bound to the cell surface, or nonbiologic antigens such as drugs bound to the cell surface (hapten mediated). Antibodies to self-antigens may be formed due to cell damage, resulting in exposure of previously hidden antigens, similarity between self-antigens and foreign antigens such as infectious agents and drugs, and primary immune system dysfunction or imbalance. Classic

TABLE 70.1

Mechanisms of Immunopathologic Injury

TYPE OF MECHANISM	IMMUNE SYSTEM EFFECTORS	ORGAN SYSTEMS COMMONLY AFFECTED	EXAMPLES
Type I (immediate)	Humoral immune system (T-helper cells and B cells), IgE, mast cells, inflammatory mediators	Skin, respiratory tract, gastrointestinal tract	Acute anaphylactic reactions, atopy, allergic bronchitis (feline asthma)
Type II (cytotoxic)	Humoral immune system, IgG and IgM	Hematologic, neuromuscular junction, skin	Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, myasthenia gravis, pemphigus foliaceous
Type III (immune complex)	Soluble immune complexes	Kidney, joints, skin	Glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis
Type IV (delayed type)	Sensitized T lymphocytes, cytokines, neutrophils, and macrophages	Endocrine glands, muscle, skin	Lymphocytic thyroiditis, myositis

examples of diseases mediated by type II mechanisms include immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, pemphigus foliaceous, and myasthenia gravis. Antibodies involved in type II responses are usually tissue specific, and the consequences of antibody binding vary from tissue to tissue. For example, in immune-mediated hemolytic anemia, antibody binding results in either intravascular or extravascular red blood cell hemolysis, whereas in pemphigus foliaceous, antibody binding results in disruption of keratinocyte adhesion and vesicle formation. In myasthenia gravis, antibodies directed against acetylcholine receptors cross-link and internalize the receptors, which results in failure of neuromuscular transmission.

Type III (immune complex) hypersensitivity involves the formation and deposition of soluble immune complexes (predominantly IgG) within tissues. Deposition of immune complexes in tissues results in complement fixation and a localized inflammatory response characterized by mast cell degranulation, platelet activation, and neutrophil chemotaxis. Phagocytosis of immune complexes by macrophages causes release of more inflammatory cytokines. In the presence of antibody excess, the inflammatory reaction typically remains localized at the site of the initiating antibody; in the presence of antigen excess, however, soluble immune complexes enter the circulation and become deposited in vascular beds in the kidney, joints, eye, and skin. The location and extent of antibody deposition depend on a number of variables, including complex size, charge, degree of glycosylation, and Ig subclass. Classic examples of diseases mediated by type III mechanisms include infections (e.g., feline infectious peritonitis), glomerulonephritis, systemic lupus erythematosus (SLE), and rheumatoid arthritis.

Type IV (delayed-type) hypersensitivity involves the cell-mediated immune system. Exposure to either soluble or cell-associated antigen results in sensitization of specific subsets of T cells. Reexposure to the same antigen results in activation of sensitized lymphocytes, subsequent release of cytokines, and recruitment of neutrophils and macrophages. Cytotoxic destruction of target cells may also occur by this mechanism. Activation of sensitized lymphocytes requires 24 to 72 hours to occur, which is why this type of response is termed "delayed." Persistence of the antigen can result in formation of multinucleate giant cells and tissue granulomas. Examples of diseases mediated by type IV immune responses include the protective immune response to intracellular microbes (e.g., leishmaniasis), contact hypersensitivity, polymyositis, and immune-mediated thyroiditis.

PATHOGENESIS OF IMMUNE-MEDIATED DISORDERS

In normal animals the adaptive immune system should be tolerant of self. A number of mechanisms prevent B and T lymphocytes from becoming self-reactive. Most autoreactive B and T cells are deleted during maturation in the thymus, and those that escape to the periphery are either directed against cryptic epitopes, undergo peripheral deletion by apoptosis, are rendered anergic in the peripheral circulation, or are actively suppressed by regulatory T cells. When autoimmunity occurs, these mechanisms responsible for tolerance break down. Factors that may play a role in loss of tolerance include genetics, environmental factors, age, hormonal influences, and other diseases that lead to perturbations of the immune system.

Genetics clearly play an important role in the development of autoimmune disease. In some autoimmune diseases, certain breeds of dog are at increased risk

TABLE 70.2

Suspected Autoimmune Disorders of Various Organ Systems in Dogs and Cats

ORGAN SYSTEM	DISEASE	POSTULATED IMMUNOPATHOLOGIC MECHANISM	BREED PREDISPOSITION
Hematologic	Immune-mediated hemolytic anemia	Type II	American Cocker Spaniel, Bichon Frise, Miniature Pinscher, Miniature Schnauzer, Rough-Coated Collie, English Springer Spaniel, Finnish Spitz
	Pure red cell aplasia	Type II	
	Immune-mediated thrombocytopenia	Type II	Cocker Spaniel, Poodle (all varieties), German Shepherd Dog, and Old English Sheepdog
	Idiopathic neutropenia	Type II	
Joints	See Table 73.7	Type III	
Skin	Various	Types II, III, and IV	
Eye	Uveitis, retinitis	Type III	
	Uveodermatologic syndrome	Type IV (suspected)	Akita, Samoyed, Siberian Husky, Shetland Sheepdog
Kidney	Glomerulonephritis	Type III	Bernese Mountain dog, Bull Terrier, Cocker Spaniel, Dalmatian, Doberman, Shar-Pei, Soft-coated Wheaten Terrier
Respiratory tract	Allergic rhinitis	Type I	
	Allergic bronchitis (asthma)	Type I	
	Pulmonary infiltrates with eosinophils	Type I	Husky, Malamute
Gastrointestinal tract	Feline stomatitis/gingivitis, lymphocytic plasmacytic enteritis, anal furunculosis (perineal fistula)	Type IV	German Shepherd dog
Neurologic system	Myasthenia gravis	Type II	Abyssinian, Somali
	Myositis	Type IV	Boxer, Newfoundland
	Polyradiculoneuritis	Unknown	
	Granulomatous meningoencephalomyelitis	Unknown	
	Polyarteritis	Unknown	Beagle
Endocrine glands	Thyroiditis (hypothyroidism)	Type IV	Beagle, Golden Retriever
	Adrenalitis (hypoadrenocorticism)		Standard Poodle, Leonberger, Duck Tolling Retriever
	Insulitis (diabetes mellitus)		Keeshond
Multisystemic immune disease	Systemic lupus erythematosus	Type III	German Shepherd dog

(Table 70.2). Autoimmunity is also reported more commonly in some families than others. Examples of immune-mediated diseases in dogs in which genetics clearly predispose to the disease include SLE, immune-mediated hemolytic anemia, and thyroiditis. The inbreeding that occurs in many dog breeds exacerbates the effects of such familial traits. Purebred dogs represent up to 90% of the cases of primary immune-mediated hemolytic anemia, further supporting a familial component to the immunopathologic disease. Familial autoimmunity is not as well documented in the cat, although the Abyssinian and Somali breeds are at increased risk of myasthenia gravis. The underlying genetic changes that result in such predispositions are not yet well characterized in the dog and cat.

Environmental factors are believed to be important in the development of autoimmunity; exposure to infectious agents either during natural infection or as a result of vaccination is the most common factor identified. Other

possible environmental factors include environmental toxins and drug exposure. Some drugs have been clearly linked to induction of autoimmunity, and many other drugs can likely cause idiosyncratic autoimmune reactions. Examples include the risk of systemic immune disease (polyarthritis, glomerulonephritis, cutaneous lesions, retinitis, polymyositis, anemia, and thrombocytopenia) in Doberman Pinschers treated with trimethoprim-sulfadiazine and development of immune-mediated hemolytic anemia in some cats treated with thioureylene drugs such as propylthiouracil and methimazole. Myasthenia gravis has also been reported in cats treated with methimazole.

Mechanisms by which infectious agents may induce autoimmunity include molecular mimicry, exposure of cryptic antigens after cellular damage, nonspecific polyclonal activation by superantigens, production of interferon-γ that induces major histocompatibility complex class II expression on cells that do not usually express them (e.g., thyroid follicular cells), and the innocent bystander effect in which the immune response is directed against a microbial antigen or other antigen on the surface of the cell. A complicating factor is that some infections (e.g., ehrlichiosis, borreliosis, and many other vector-borne diseases) may either mimic an autoimmune disease or cause true autoimmunity, and clinically differentiating the two can be difficult. This is clinically relevant because the clinician is faced with a decision whether to include immunosuppressive drugs in the treatment protocol.

The role of vaccination in the precipitation of autoimmunity is unclear. Currently the evidence is weak and based on anecdotal observation of a temporal association of immune-mediated disease with vaccination in some studies but not others. A cause-and-effect relationship has been difficult to establish definitively because of the high frequency of vaccination and the low prevalence of reported adverse effects. Specific evidence for association of individual disease syndromes with vaccination is discussed in the sections on individual diseases. Altered immunoregulation and evidence of immune-mediated disease may also occur in other underlying diseases such as lymphoid neoplasia or IgA deficiency, and after chemotherapy administration.

ORGAN SYSTEMS INVOLVED IN AUTOIMMUNE DISORDERS

Any organ system in the body may be targeted by immune-mediated disease processes (see Table 70.2). The most common systems involved in the dog and cat are the joints, skin, kidney, and hematologic system, although, in general, immune-mediated diseases are less common in the cat than the dog. Other organs commonly involved in immune-mediated diseases are the eye, neurologic system, gastrointestinal tract, respiratory tract, and endocrine glands (see Table 70.2). Some immune-mediated diseases such as SLE involve multiple organ systems, although not all organ systems may be involved in every animal. Dogs with systemic immune-mediated disorders frequently present with one manifestation of the disorder (e.g., immune-mediated hemolytic anemia) and later relapse with another (e.g., immune-mediated thrombocytopenia, polyarthritis). In some of these cases, the underlying disorder may be SLE, but this is not always the case.

Many canine and feline diseases involve immune-mediated mechanisms. The autoimmune disorders discussed in detail in the following chapters focus on the more common autoimmune diseases, especially those in which the treatment of choice is immunosuppression. Other disorders in which the pathogenesis is immune mediated, but in which immunosuppression is not part of the treatment (e.g., hypothyroidism from thyroiditis), are discussed in the parts on diseases of the appropriate organ system.

Suggested Readings

Carr AP, et al. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. *J Vet Intern Med*. 2002;16:504.

Chabanne L, et al. Canine systemic lupus erythematosus. Part I. Clinical and biologic aspects. *Compendium (small animal/exotics)*. 1999;21:135.

Day MJ. *Clinical immunology of the dog and cat*. ed 2. London: Manson; 2012:78.

Duval D, et al. Vaccine associated immune-mediated hemolytic anemia in the dog. *J Vet Intern Med*. 1996;10:290.

Goggs R, et al. Predicting outcome in dogs with primary IMHA: results of a multicenter case registry. *J Vet Intern Med*. 2015;29(6):1603.

Miller SA, et al. Case control study of blood type, breed, sex, and bacteremia in dogs with immune-mediated hemolytic anemia. *J Am Vet Med Assoc*. 2004;224:232.

CHAPTER 71

Diagnostic Testing for Immune-Mediated Disease



CLINICAL DIAGNOSTIC APPROACH

The diagnostic approach to a dog or cat with suspected immune-mediated disease depends on the clinical presentation and organ(s) involved. A complete history, including questions regarding environmental or drug exposures, previous medical history, exposure to infectious agents, and vaccination history, should be obtained. A thorough physical examination should also be performed. The next step is to define the extent of the problem and rule out other more common and/or secondary causes of the clinical signs. A typical minimal database includes a complete blood count (CBC), serum biochemical profile, and urinalysis. Because many immune-mediated diseases are characterized by fever and leukocytosis, ruling out infectious agents as the primary cause of the clinical signs is important before pursuing other less common causes. The diagnostic evaluation for immune-mediated disease is similar to that for fever of unknown origin (see Chapter 90). Bacterial culture of the urine, blood, or both—testing for common viral pathogens such as feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis—and diagnostic imaging (thoracic and abdominal radiographs, abdominal ultrasonography) are important. Investigation for vector-borne diseases such as ehrlichiosis, anaplasmosis, bartonellosis, borreliosis, and leishmaniasis, as well as more fastidious organisms such as mycoplasma and L-forms, is usually only considered once more common bacterial and viral infections have been excluded because these tests are more expensive and the results are often not immediately available. The specific infectious agents tested for depend on whether the patient is a dog or cat, as well as the disease presentation and geographic location, because many infectious diseases have regional distributions.

If infection is ruled out or considered unlikely, further diagnostic evaluation should focus on organs identified as potentially involved according to the physical examination and results of the minimal database and diagnostic imaging. Chronic inflammatory and neoplastic causes should be investigated as part of this organ-specific evaluation. Organ-specific diagnostic tests may include evaluation of joint or cerebrospinal fluid (CSF), quantification of urine protein excretion, and biopsy of affected organs. (These tests are discussed in more detail in the sections on specific diseases.)

Specific tests of immune dysfunction are indicated once infectious and neoplastic diseases have been excluded and when the organ system(s) of interest has been identified. For example, in a dog with regenerative anemia the clinician should consider doing a direct antiglobulin (Coombs) test, whereas in a dog with erosive polyarthritis a test for rheumatoid factor (RF) would be indicated. Immune panels that include a selection of tests with different indications are rarely necessary and may result in excessive testing and results that are difficult to interpret; in addition, the tests are often positive in dogs with infectious diseases. For example, a positive Coombs test has little relevance in a dog that is not anemic.

SPECIFIC DIAGNOSTIC TESTS

SLIDE AGGLUTINATION TEST

The slide agglutination test is used to detect the presence of spontaneous agglutination of red blood cells (RBCs). Spontaneous agglutination (autoagglutination) is a three-dimensional clustering of RBCs that occurs from cross-linking of RBC surface-associated antibodies. Autoagglutination occurs as a result of the presence of either high-titer immunoglobulin (Ig) G or IgM on the RBC membrane. Agglutination must be distinguished from rouleaux formation (stacking of RBCs that occurs most often in the presence of high globulin concentrations). To evaluate for the presence of agglutination, 1 drop of saline should be added to 5 to 10 drops of blood and mixed. The RBC suspension is then evaluated both by macroscopic and microscopic examination at a temperature as close to 37° C as possible. The temperature is important because clinically insignificant cold-acting agglutinins are common in normal dogs. A positive slide agglutination test does indicate the presence

of surface-associated antibodies, but it does not distinguish primary from secondary immune-mediated hemolytic anemia (IMHA) (see Chapter 73).

COOMBS TEST (DIRECT ANTIGLOBULIN TEST)

The direct Coombs test, or direct antiglobulin test (DAT), detects the presence of antibody and/or complement bound to patient RBC membranes. The test is used for diagnosis of IMHA. The DAT uses anti–dog antiglobulin antibody or anti–cat antiglobulin antibody produced in a different species (usually goats or rabbits); the reagents are species specific. The DAT is usually performed on ethylenediamine tetraacetic acid (EDTA) anticoagulated blood at body temperature (37° C). Most frequently a combined Coombs reagent containing goat anti–canine IgG, IgM, and complement component C3 is used. Addition of the Coombs reagent to washed patient RBCs results in agglutination if more than approximately 100 IgG antibody or C3 molecules are bound to the RBCs. Because the end point of the test is agglutination, the test cannot be interpreted if spontaneous agglutination persists after washing the RBCs. Results of the DAT may be reported in various forms depending on the laboratory: positive or negative, 1+ to 4+ agglutination, or as the lowest dilution of the reagent that results in agglutination. Modifications of the DAT that may improve diagnostic performance include use of monospecific antisera (usually IgG, IgM, and C3); using more dilutions of the reagents than typically performed to avoid a prozone effect; and testing at 4° C, as well as 37° C. Use of monospecific antisera has been shown to improve sensitivity of the DAT for diagnosis of IMHA in dogs, but the reported patterns vary between investigators and this technique is not available in commercial laboratories. Using more dilutions of reagent can potentially improve the sensitivity of the DAT because it allows detection of the prozone effect in which a lack of reactivity is observed with high concentrations of antibody. Another modification of the DAT involves performing the test at 4° C to identify cold-acting agglutinins. This test is best used in animals with clinical signs of cold agglutinin disease (e.g., ear or tail tip necrosis) because nonspecific RBC agglutination occurs at 4° C in some healthy dogs; however, this technique can be useful to increase the sensitivity of the Coombs test in cats. Although these modifications of the Coombs test have been shown to increase sensitivity of the DAT for diagnosis of IMHA by some investigators, it is important to remember that test results should always be interpreted in the context of the clinical and hematologic data. A diagnosis of IMHA should not be based on the Coombs test alone. Both false-positive and false-negative results may occur with the DAT (Box 71.1).

In some dogs with IMHA that have spontaneous agglutination, agglutination will resolve after washing of the RBCs. In this scenario a DAT may still be indicated because resolution of a previously positive DAT may be useful for disease monitoring. Recognizing that a positive Coombs test does not distinguish primary from secondary IMHA is also important (see Chapter 73). Other more sensitive techniques such as enzyme-linked antiglobulin tests, flow cytometric techniques, and antiglobulin gel tests have also been used to detect the presence of antibody on RBCs; however, these tests are not yet widely available in commercial laboratories.

ANTIPLATELET ANTIBODIES

Detection of platelet surface–associated antibody (direct antibody) or serum platelet bindable antibody (indirect antibody) may be useful in evaluation of dogs and cats with suspected immune-mediated thrombocytopenia. Tests for antiplatelet antibody are most commonly performed by using flow cytometric techniques. Detection of platelet surface–associated IgG (direct) is more sensitive than detection of serum platelet–bindable antibodies (indirect), presumably because the majority of antiplatelet antibody is bound to platelets rather than free in the circulation. The direct assay has a sensitivity of greater than 90% in dogs with confirmed idiopathic thrombocytopenic purpura (ITP). Because of the high sensitivity of the direct assay, a negative result for platelet surface–associated antibody makes a diagnosis of ITP unlikely. Detection of antiplatelet antibodies by either the direct or indirect technique implies an immune-mediated pathogenesis for thrombocytopenia but is not specific for primary immune-mediated thrombocytopenia. Many infectious and neoplastic diseases, as well as drug exposure, may

BOX 71.1

Causes of False-Positive and False-Negative Results for the Direct Antiglobulin (Coombs Test)

False-Positive Result	False-Negative Result
Chronic inflammatory disease	Technical problems (washing, dilution, centrifugation errors)
Technical problems (contamination, overcentrifugation)	Delay in running test (e.g., mail-in samples)
Poor sample quality (clotted samples, use of serum separator tubes, collection from dextrose-containing infusion lines)	Contamination or repeated freezing of reagents
	Low quantities of antibody present on cell
Septic patient	
Clinically insignificant, naturally occurring cold autoantibody	
Hypergammaglobulinemia	
Interference by drugs (e.g., amiodarone in dogs)	

cause thrombocytopenia by immune-mediated mechanisms; therefore blood samples from such patients may be positive for platelet-associated antibody. A flow cytometric assay for platelet surface–associated IgG for both dogs and cats is currently available at Kansas State University. The test requires 2 mL of EDTA blood and currently costs $71.50 plus shipping. Blood samples should be shipped overnight on ice.

ANTINUCLEAR ANTIBODY TEST

Measurement of antinuclear antibody (ANA) is useful in the evaluation of dogs and cats with suspected systemic lupus erythematosus (SLE). SLE should be suspected in patients with evidence of an immune-mediated process affecting a minimum of two organ systems (see Chapter 73). Antinuclear antibodies are heterogenous antibodies directed against nuclear antigens. They are typically detected by immunofluorescent staining of frozen sections of rat liver or tissue culture monolayers of human epithelial cell lines. Results are reported as a titer that is the highest dilution of patient serum that causes definitive immunofluorescent nuclear staining. Various patterns of nuclear staining (diffuse, speckled, peripheral, and nucleolar) can be identified, but the clinical significance of the various staining patterns is still under investigation in dogs and cats. Measurement of ANA antibodies is sensitive for diagnosis of SLE in dogs and cats, although ANA-negative cases of SLE do occur. In one study of 75 dogs with SLE, 100% had a positive ANA titer. In most cases the ANA titer was greater than 1:256, and the magnitude of the titer correlated with disease severity. Other studies have demonstrated lower sensitivity of the ANA for diagnosing SLE. The variability in diagnostic sensitivity probably arises from differences in stringency in the diagnostic criteria for confirming a diagnosis of SLE and variability among laboratories in assay sensitivity and specificity. Many normal animals have low positive titers for ANA, so a cutoff for a significant positive titer should be established for each individual laboratory. The cutoff titer varies depending on the substrate and techniques used by the laboratory. Low positive ANA titers may also occur after exposure to certain drugs and in animals with chronic inflammatory or neoplastic diseases. ANAs are detected in 10% to 20% of dogs with seroreactivity to *Bartonella vinsonii, Ehrlichia canis,* and *Leishmaniasis infantum*. Dogs with seroreactivity to multiple pathogens are more likely to be ANA positive. Chronic or high-dose corticosteroid treatment may decrease the ANA titer.

LUPUS ERYTHEMATOSUS TEST

The lupus erythematosus (LE) test is a highly specific test for SLE but is rarely used clinically because it lacks sensitivity, and the ANA test is more sensitive and less time consuming. LE cells are neutrophils that contain phagocytosed nuclear material. The test is performed in vitro. Blood collected from the patient is allowed to clot and is damaged in order to release free nuclei. If ANA is present it binds to nuclear material. The resulting complex is phagocytosed by neutrophils and can be identified as an LE cell by visual inspection. LE cells may also rarely be identified in vivo in blood, bone marrow, or joint fluid and, when present, are highly suggestive of SLE. The LE cell test is more sensitive to the effects of steroids than is the ANA titer. The test has been reported to be positive in the blood of 30% to 90% of dogs with SLE but may also be positive in other immune or neoplastic disorders. This test is not used frequently in practice.

RHEUMATOID FACTOR

RF is antibody directed against an individual's own IgG. The antibody is directed against sites on the Fc portion of immunoglobulin molecules that become exposed only after antibody binds to antigen. The test is used as one of the diagnostic criteria for rheumatoid arthritis; however, the utility of the test is limited by a lack of sensitivity and specificity. The most common technique for detection of RF is the Rose-Waaler test, which uses sheep RBCs sensitized to rabbit IgG. If RF is present in patient serum, agglutination occurs. The test is performed on refrigerated serum. Samples should not be frozen because RF activity may be destroyed. Only 40% to 75% of dogs with rheumatoid arthritis are positive for RF, so a negative titer does not rule out the disease. In addition, any disease with longstanding immune complex formation may eventually cause RF, so a positive titer should not be the sole criterion for a diagnosis of rheumatoid arthritis.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is a molecule that is rapidly produced as part of the nonspecific acute-phase response to most forms of inflammation. This production, principally by hepatocytes, is stimulated by cytokines originating from the site of inflammation. CRP is a very sensitive biomarker of inflammation. It increases rapidly in response to inflammatory cytokines, and does not demonstrate diurnal or post-prandial variation. Biologically, CRP binds to a variety of ligands, can bind complement proteins, and can activate the classical complement pathway similar to antibody binding.

The CRP concentration is a useful but nonspecific biochemical marker of inflammation. CRP concentrations have been shown to be increased in many inflammatory diseases of the dog and cat including sepsis, pancreatitis, IMHA, inflammatory bowel disease, rickettsial diseases, chronic valvular disease, and certain neoplasia. Thus CRP values are not specific for diagnosis of immune-mediated diseases but are a sensitive marker of inflammation that can be useful for monitoring treatment response.

CRP is consistently increased in dogs with primary IMHA, and CRP concentrations decrease in response to immune-suppressive treatment. Measurement of CRP is not useful for predicting outcome or survival in primary IMHA, and therefore it may not be any more useful than standard hematologic monitoring in this disease. CRP concentration is used to monitor therapy in people with rheumatoid arthritis, and so it has been investigated in dogs with immune-mediated polyarthritis (IMPA). As would be expected, all

dogs with IMPA had increased CRP concentrations at the time of diagnosis; 82% of dogs demonstrated a significant decrease in CRP concentrations within 5 days of corticosteroid therapy. CRP concentrations measured at 1 to 2 weeks following initiation of treatment were predictive that continued treatment with immune-suppressive medications would still be required to manage IMPA at the 6-month follow up. CRP concentrations also correlated with resolution of clinical signs by 1 to 2 weeks following initiation of corticosteroid therapy. Therefore, although measurement of CRP is not useful for diagnosis of IMPA, it should be considered as a monitoring tool in lieu of repeated arthrocentesis in dogs that are clinically responding well to treatment.

IMMUNOFLUORESCENCE AND IMMUNOHISTOCHEMISTRY

In many type II and type III immune-mediated diseases, the presence of antibody in fixed tissues (e.g., kidney, skin) can be detected by immunofluorescence or immunoperoxidase techniques. Numerous variations on these methods exist, but, in general, sections of tissue are labeled with a primary antibody (e.g., rabbit anti–dog IgG) and then a secondary antibody is added (e.g., anti–rabbit IgG), which has been conjugated to either fluorescein or the enzyme peroxidase. If antibodies are present in the tissue sample, apple green fluorescence is seen under ultraviolet light with immunofluorescent staining. In the case of immunoperoxidase peroxide, when a substrate is added in the presence of hydrogen peroxide, deposition of a brown color can be visualized with the light microscope. Tissue samples for immunofluorescence testing should be collected in Michel's medium. Routinely fixed tissue can be used for immunohistochemistry. Common uses for immunofluorescence staining include evaluation of renal biopsies in dogs with suspected glomerulonephritis, detection of antibodies directed against megakaryocytic cells in the bone marrow, and evaluation of skin biopsies from patients with suspected immune-mediated skin disease.

AUTOIMMUNE PANELS

Many laboratories offer an immune panel that typically includes a CBC and platelet count, Coombs test, ANA, and RF. It would be unusual for all these tests to be appropriate in an individual patient (Table 71.1). In addition to the cost of running such a panel, the significance of a positive test may be difficult to determine in patients in which the test was initially not indicated, and some of these tests can be positive in dogs and cats with infectious diseases. For these reasons the clinician is encouraged to pick individual tests rather than automatically choosing an autoimmune panel in a dog or cat with suspected autoimmune or immune-mediated disease.

TABLE 71.1

Clinical Indications for Use of Diagnostic Tests in Suspected Immune-Mediated Disease

CLINICAL SYNDROME	POTENTIAL IMMUNE-MEDIATED CONDITIONS TO CONSIDER	TESTS INDICATED TO CONFIRM	LIMITATIONS
Anemia (regenerative or nonregenerative)	Immune-mediated hemolytic anemia, pure red cell aplasia	Coombs test, slide agglutination test, review of CBC smear for spherocytes or ghost cells Bone marrow aspirate and core (if anemia is nonregenerative)	A negative Coombs test result does not rule out immune-mediated hemolytic anemia; false-positive Coombs test results may also occur
Thrombocytopenia	Immune-mediated thrombocytopenia, infectious causes of thrombocytopenia, megakaryocytic aplasia	Platelet-associated antibody, platelet-bindable antibody, bone marrow aspirate and core	Positive platelet-associated antibody test does not distinguish primary from secondary immune-mediated thrombocytopenia
Anemia and thrombocytopenia	IMHA, Evans syndrome	Coombs test Slide agglutination test Review of slide for spherocytes or ghost cells Platelet-associated antibody, platelet-bindable antibody, bone marrow aspirate and core	May be hard to distinguish blood loss anemia from hemolytic anemia in dogs with severe thrombocytopenia; Coombs test may be positive after transfusion
Shifting leg lameness, joint pain, or effusion	Polyarthritis SLE, immune-mediated polyarthritis, rheumatoid arthritis	Synovial fluid collection, radiographs of joints, RF, ANA (if other organ systems involved)	Negative RF does not rule out rheumatoid arthritis; in early rheumatoid arthritis erosive changes may not be present

TABLE 71.1

Clinical Indications for Use of Diagnostic Tests in Suspected Immune-Mediated Disease—cont'd

CLINICAL SYNDROME	POTENTIAL IMMUNE-MEDIATED CONDITIONS TO CONSIDER	TESTS INDICATED TO CONFIRM	LIMITATIONS
Proteinuria	Glomerulonephritis	Urinalysis; protein/creatinine ratio; renal biopsy for histopathology, immunofluorescence, electron microscopy	Need to rule out inflammation arising from the lower urinary tract before interpreting protein/creatinine ratio
Two of the previous clinical syndromes together or in combination with dysfunction of other organ system	SLE	ANA, LE preparation	LE has very low sensitivity for diagnosis of SLE; ANA titer is more sensitive, but some dogs with SLE may have a negative ANA

ANA, Antinuclear antibody; *CBC,* complete blood count; *IMHA,* immune-mediated hemolytic anemia; *LE,* lupus erythematosus; *SLE,* systemic lupus erythematosus.

Suggested Readings

Dircks BH, et al. Underlying diseases and clinicopathologic variables of thrombocytopenic dogs with and without platelet-bound antibodies detected by use of a flow cytometric assay: 83 cases (2004-2006). *J Am Vet Med Assoc*. 2009;235:960.

Eckersall PD, et al. Acute phase proteins: biomarkers of infection and inflammation in veterinary medicine. *Vet J*. 2010;185(1):23–27.

Fournel C, et al. Canine systemic lupus erythematosus I: a study of 75 cases. *Lupus*. 1992;1:133.

Lewis DC, et al. Canine idiopathic thrombocytopenia. *J Vet Intern Med*. 1996;10:207.

Smee NM, et al. Measurement of serum antinuclear antibody titer in dogs with and without systemic lupus erythematosus: 120 cases (1997-2005). *J Am Vet Med Assoc*. 2007;230:1180.

Smith BE, et al. Antinuclear antibodies can be detected in dog sera reactive to *Bartonella vinsonii* subsp., *berkhoffii, Ehrlichia canis,* or *Leishmania infantum* antigens. *J Vet Intern Med*. 2004;18:47.

Wardrop KJ. The Coombs' test in veterinary medicine: past, present, and future. *Vet Clin Pathol*. 2005;34:325.

Wardrop KJ. Coombs' testing and its diagnostic significance in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2012;42:42.

CHAPTER 72

Treatment of Primary Immune-Mediated Diseases



PRINCIPLES OF TREATMENT OF IMMUNE-MEDIATED DISEASES

Immunosuppressive drugs are the mainstay of treatment for patients with immune-mediated disease; however, it is critical that any underlying disease is also identified and treated to achieve a good response. In patients with secondary immune-mediated disease, effective treatment of underlying disease may minimize the duration of required immunosuppressive therapy. The aim of treatment of immune-mediated diseases is to control the immune-mediated process while minimizing the adverse effects of the drugs used. In many situations short-term adverse effects must be tolerated initially to achieve disease remission. For long-term management, it is critical that medications are tapered to the lowest possible dose to minimize adverse effects. If this is not possible or if the initial drug chosen is not effective for disease management, alternate or additional therapy should be considered. Monitoring the patient carefully to assess response to treatment before each dose reduction is critical, and drug tapering should be individualized depending on the underlying disease process, other concurrent illness, and the sensitivity of the patient to the drugs chosen. For example, in immune-mediated hemolytic anemia (IMHA), monitoring the complete blood count (CBC), reticulocyte count, and the Coombs test is adequate, whereas in dogs with immune-mediated polyarthritis, repeated joint taps for synovial fluid analysis before dose reduction may be necessary. There is wide interpatient variability in sensitivity to immunosuppressive drugs, particularly glucocorticoids, and these individual variations need to be taken into account during treatment.

Supportive care and aggressive monitoring for potential complications of immunosuppressive drug therapy are also critical. Detection and treatment of complications of therapy can improve long-term outcome and minimize adverse sequelae. For example, patients receiving glucocorticoids should be carefully monitored for evidence of gastrointestinal hemorrhage, and animals receiving azathioprine should be monitored for hepatotoxicity and bone marrow suppression. Supportive care is necessary while waiting for the effects of immunosuppressive therapy to manifest. For example, dogs with IMHA, immune-mediated thrombocytopenia (ITP), and Evans syndrome may require several transfusions before immunosuppressive treatment adequately controls the immune-mediated destruction of red blood cells (RBCs) or platelets. Other forms of supportive care that may be necessary include care of the skin in animals that are recumbent, nutritional support, monitoring for and treatment of infection, ventilatory support, and prevention of gastrointestinal ulceration.

OVERVIEW OF IMMUNOSUPPRESSIVE THERAPY

The initial treatment for the majority of immune-mediated diseases is treatment with glucocorticoids. The reasons for using glucocorticoids as the first line of therapy include rapid onset of action, broad immune-suppressive effects, low risk of immediate toxicity, and low cost. Even in patients with concurrent conditions such as diabetes mellitus, in which long-term glucocorticoid treatment is relatively contraindicated, in most cases glucocorticoids should be used initially until alternative drugs that are less likely to complicate management of the concurrent disease have time to become effective. Exceptions to this include diseases such as myasthenia gravis and immune-mediated polyarthritis (see Chapter 73). Although glucocorticoids are used in the initial management of the majority of immune-mediated diseases, there are some immune-mediated diseases such as myasthenia gravis for which glucocorticoid treatment is avoided (see Chapter 73). In some immune-mediated diseases additional immunosuppressive drugs should be added at the start of treatment. These are diseases in which a positive response to glucocorticoids alone is unlikely. Examples include canine Evans syndrome; canine IMHA with multiple poor prognostic indicators (intravascular hemolysis, agglutination that persists after washing of RBCs, high bilirubin concentration); systemic lupus erythematosus (SLE); rheumatoid

arthritis (RA); and the polyarthritis syndrome of Akitas. In most other immune-mediated diseases, the response to glucocorticoids should be assessed before adding other immunosuppressive drugs. If immune-mediated disease has an underlying infectious cause, more caution should be used before adding another immunosuppressive drug. If response to glucocorticoids is inadequate or the adverse effects of glucocorticoids are unacceptable, adjunctive immunosuppressive medications should be considered. Adjunctive immunosuppressive medications should not be assumed to provide immediate additional suppression to the immune response. Some confusion exists in the veterinary literature about the length of time required for the adjunctive immunosuppressive medications to have a clinical effect. For example, in one study azathioprine inhibited blastogenic response of canine lymphocytes to mitogens after 7 days of treatment, although serum immunoglobulin concentrations were unchanged. The authors recommend that at least 7 days of therapy are necessary to gain clinical effect. If there is any concern for lack of clinical effect, several of the adjunctive immunosuppressive medications have pharmacokinetic or pharmacodynamic monitoring tests available to aid in guiding therapy.

Common adjunctive immunosuppressive medications include those that interfere with nucleotide synthesis such as azathioprine, mycophenolate, and leflunomide, as well as cytotoxic drugs like cyclosporine and chlorambucil. Historically, azathioprine has been the most common second-line immunosuppressive medication used in dogs; the authors consider azathioprine, cyclosporine, and mycophenolate to all be acceptable second-line immunosuppressive medications in dogs, although there is a larger body of literature in support of azathioprine. The risks and benefits of each should be considered when selecting an adjunctive immunosuppressive medication. Chlorambucil or cyclosporine would be the most appropriate second-line immunosuppressive medications to consider in cats. Drugs such as cyclophosphamide and leflunomide are typically considered third-line drugs. When adding a third-line drug, in most circumstances it should replace the second-line drug. Treatment with two or more adjunctive immunosuppressive drugs at the same time (e.g., azathioprine and cyclosporine together) is likely to cause much more severe immunosuppression and a high risk of secondary infection and should be avoided. Bacterial infections that may develop in dogs and cats on long-term immunosuppressive drugs include lower urinary tract infections, pyelonephritis, cholangiohepatitis, hepatic abscesses, and pyoderma; however, the overall prevalence of secondary infections in patients properly dosed with immunosuppressive drugs is low. Fungal infections such as candidiasis may also occur. These serious infections can be extremely difficult to manage once established and should therefore be prevented, if at all possible, by judicious use of immunosuppression and careful patient monitoring.

Some exceptions exist in which a typically adjunctive immunosuppressive is more appropriate as first-line or primary therapy. For example, cyclosporine is used as a first-line drug in treatment of perianal fistulas in dogs. These exceptions are discussed in the sections on the individual immune-mediated diseases (see Chapter 73).

GLUCOCORTICOIDS

Glucocorticoids (corticosteroids with primarily glucocorticoid activity) are the mainstay of treatment of most immune-mediated diseases because they are effective, rapid acting, and inexpensive. Several different glucocorticoid drugs are used in veterinary medicine, and they vary according to duration, potency, and route of administration. Glucocorticoids are characterized by their biologic half-life as measured by duration of suppression of the hypothalamic pituitary adrenocortical axis (Table 72.1). Short-acting glucocorticoids such as hydrocortisone and cortisone have a biologic half-life of less than 12 hours. Intermediate-acting steroids such as prednisone, prednisolone, methylprednisolone, and triamcinolone have a biologic half-life of 12 to 36 hours; and betamethasone, dexamethasone, and flumethasone have a biologic half-life of 48 hours or longer. The duration of effect of a glucocorticoid preparation is also influenced by the chemical form of the steroid. Parenteral glucocorticoid preparations are either esters or free steroid alcohols. Highly soluble esters (e.g., dexamethasone sodium phosphate, prednisolone sodium succinate) and solutions of free steroid alcohols in polyethylene glycol (dexamethasone, flumethasone) have a duration of action similar to the biologic half-life, but long-acting suspensions of insoluble steroid esters (e.g., methylprednisolone acetate suspension, triamcinolone acetonide suspension) are absorbed slowly from the injection site, which markedly prolongs the duration of effect. Long-acting suspensions of glucocorticoids do not achieve high plasma concentrations and are therefore not ideal for use in management of immune-mediated diseases. Oral preparations are usually composed of the free steroid alcohol; because absorption from the gastrointestinal tract is quite rapid, the duration of effect is similar to the biologic half-life. The antiinflammatory effects of corticosteroids correlate with their glucocorticoid activity, whereas undesirable adverse effects such as sodium retention and edema formation are due to their mineralocorticoid activity. Most synthetic steroids such as prednisone and dexamethasone have higher glucocorticoid and lower mineralocorticoid activity than hydrocortisone. Prednisone has four times the potency of hydrocortisone but 0.3 times the mineralocorticoid activity; dexamethasone has 30 times the potency of hydrocortisone (≈8 times the potency of prednisone) with no mineralocorticoid activity.

In most patients with immune-mediated disease, the ideal route of glucocorticoid administration is oral; however, in animals that are vomiting or that have diseases that interfere with swallowing or gastrointestinal absorption, intravenous administration of either prednisolone or dexamethasone may be necessary. The use of long-acting parenteral drugs for treatment of immune-mediated disease is not recommended

TABLE 72.1

Comparison of the Properties of Synthetic Glucocorticoids

COMPOUND	DURATION OF ACTION*	ANTIINFLAMMATORY POTENCY	EQUIVALENT DOSE (mg)	MINERALOCORTICOID POTENCY	APPROPRIATE FOR ALTERNATE-DAY USE
Cortisone	Short	0.8	5.0	0.8	No
Hydrocortisone	Short	1.0	4.0	1.0	No
Prednisone/ prednisolone	Intermediate	4.0	1.0	0.3	Yes
Methylprednisolone	Intermediate	5.0	0.8	0	Yes
Triamcinolone	Intermediate (up to 48 h)	5.0	0.8	0	No
Flumethasone	Long	15.0	0.3	0	No
Dexamethasone	Long	30.0	0.15	0	No
Betamethasone	Long	35.0	0.12	0	No

*Short = <12 hours; intermediate = 12 to 36 hours; long = >48 hours.
Reprinted from Behrend EN et al.: Pharmacology, indications, and complications. *Vet Clin North Am Small Anim Pract* 1997;27:187.

because of the failure to achieve high plasma concentrations and the long duration of effect.

Glucocorticoids bind to a cytosolic glucocorticoid receptor, which then moves to the nucleus, binds to DNA, and influences gene transcription. Cellular effects include stabilization of cell membranes, inhibition of phospholipase A_2 with resultant inhibition of the cyclooxygenase and lipoxygenase pathways, decreased release of cytokines interleukin (IL)-1 and IL-6, and downregulation of Fc receptor expression on macrophages. The early effects of corticosteroids are believed to predominantly result from a rapid decrease in the phagocytic activity of splenic and hepatic macrophages, whereas the long-term effects result primarily from suppression of cell-mediated immunity. How much suppression of antibody production occurs in steroid-resistant species such as the dog and cat is controversial, but effects on B lymphocytes likely occur from suppression of T-helper cells required for full antibody response to an antigen. Effects of corticosteroids that make them useful drugs in the treatment of various immune-mediated diseases are shown in Box 72.1.

BOX 72.1

Actions of Corticosteroids That Play a Role in Treatment of Immune-Mediated Disease

- Inhibition of macrophage and neutrophil phagocytosis and chemotaxis
- Decreased neutrophil margination and migration
- Decreased lymphocyte proliferation
- Decreased numbers of circulating lymphocytes
- Altered cytokine production (decreased production of T-cell cytokines)
- Decreased cellular response to inflammatory mediators
- Inhibition of complement pathways
- Inhibition of immune complex passage through basement membranes
- Decreased prostaglandin and leukotriene synthesis
- Altered expression of phenotypic markers on canine lymphocytes
- Induction of lymphocyte apoptosis (in vitro)

For treatment of most immune-mediated diseases, an intermediate-acting corticosteroid such as prednisone is considered the treatment of choice because transition to an alternate day schedule will decrease long-term adverse effects of glucocorticoids. Prednisone undergoes hepatic metabolism to prednisolone. The two drugs have historically been considered clinically identical except in the presence of hepatic failure; however, prednisone has much lower bioavailability in cats than prednisolone. Thus prednisolone is the authors' preferred drug for immunosuppression in cats. In healthy dogs the relative bioavailability of prednisone is 65% that of prednisolone, so prednisolone rather than prednisone should also be considered in dogs, especially if there is any concern about gastrointestinal absorption or glucocorticoid efficacy (Boothe, 2012). Glucocorticoid resistance is a major cause of glucocorticoid treatment failure in humans. It is hypothesized that a similar phenomenon occurs in dogs and cats, but the incidence of this problem in dogs is unknown (Whitley et al., 2011). Decreased bioavailability due to poor gastrointestinal absorption or use of prednisone rather than prednisolone could mimic glucocorticoid resistance.

The typical starting dose for prednisolone/prednisone in dogs is 2 mg/kg/day PO, usually given in two divided doses. In individual cases, higher doses may be required (2-4 mg/kg/day orally). Cats are more resistant to the effects of glucocorticoids than are dogs. In cats, doses of 2 to 4 mg/kg/day of oral prednisolone or 4 mg/week per cat of dexamethasone are

recommended. For immunosuppressive therapy with other glucocorticoids, the dose is based on the drug's comparative potency to prednisone. For example, the dose of dexamethasone should be approximately eight times less than the dose of prednisone for an equivalent effect. Other than this difference in potency, no evidence currently suggests that dexamethasone is more effective than prednisone or prednisolone in the treatment of immune-mediated disease. The most common reason for choosing dexamethasone rather than prednisone is for parenteral administration in patients that are vomiting or cannot tolerate oral medication. Dexamethasone has a longer biologic half-life than prednisone or prednisolone, so it is not suitable for chronic use.

Although glucocorticoids are extremely useful in the management of immune-mediated disease, long-term adverse effects may be debilitating to the animal and intolerable to the owner. Common adverse effects include polyuria, polydipsia, panting, weakness, dermatologic changes, predisposition to infection, gastrointestinal hemorrhage, and muscle atrophy (Fig. 72.1). Glucocorticoids may also cause insulin resistance, hyperglycemia, vacuolar hepatopathy, and hypercoagulability as assessed by thromboelastography. Individual patients vary in their tolerance of the side effects of glucocorticoid therapy, with larger dogs often being particularly sensitive. Cats seem to be much less likely to have debilitating adverse effects of glucocorticoid treatment than dogs.

Strategies to minimize the adverse effects of glucocorticoid therapy include using the lowest dose possible, using shorter-acting rather than longer-acting steroids, and switching to alternate-day therapy as soon as feasible. To maximize the likelihood of a good response, treatment should start with high doses initially, and the dose should then be slowly tapered rather than starting with a more conservative dose and increasing the dose if required. Tapering of the dose should be based on an objective measure of response to treatment (e.g., hematocrit or joint fluid analysis) and should be done slowly to minimize the chance of disease relapse. As a general rule when managing immune-mediated diseases, the glucocorticoid dose should not be tapered by more than 50% per month. Remission may be harder to achieve a second time if the disease is allowed to relapse because of premature dose reduction. If clinical signs of glucocorticoid treatment are intolerable, other immunosuppressive drugs should be added to the treatment protocol so that the dose of glucocorticoids can be tapered more rapidly and, if possible, ultimately discontinued.



FIG 72.1
Severe temporal muscle atrophy in a 7-year-old castrated male Weimaraner treated with immunosuppressive doses of prednisone for immune-mediated disease.

AZATHIOPRINE

Azathioprine (Imuran) is a thiopurine antimetabolite that is a sulfur analog of adenine. After absorption, azathioprine is converted into 6-mercaptopurine (6-MP) and then into a number of thiopurine antimetabolites within the liver. The active cytotoxic metabolites of azathioprine are the 6-thioguanine nucleotides, which compete with purines in the synthesis of nucleic acids. This results in formation of nonfunctional nucleic acid strands. DNA and RNA synthesis is inhibited, leading to decreased proliferation of rapidly dividing cells such as lymphocytes. Azathioprine has a preferential effect on T lymphocyte function and inhibits cell-mediated immunity and T lymphocyte–dependent antibody synthesis. Numbers of circulating monocytes are also decreased. In hepatic insufficiency, the immunosuppressive effects of azathioprine are diminished while concurrent administration of allopurinol results in increased concentration of active metabolites. The enzyme thiopurine methyltransferase (TPMT) is important in metabolism of 6-MP and its metabolites. TPMT is found in highest concentrations in the liver and kidney, but RBC activity is a convenient and accurate indirect indicator of whole body enzyme activity in humans. Variation in RBC TPMT activity has been correlated with clinical outcome. Patients with low activity are at increased risk of myelosuppression, whereas those with high activity may have an inadequate response to treatment with azathioprine.

Azathioprine is commonly used as a second-line drug in a variety of immune-mediated diseases, including IMHA, ITP, immune-mediated polyarthritis, inflammatory bowel disease, and SLE (see Chapter 73 for the specific indications for each of these diseases). Azathioprine at the typical starting dose of 2 mg/kg PO q24h is well tolerated in dogs. Adverse effects are uncommon, but bone marrow suppression, gastrointestinal upset, pancreatitis, and hepatotoxicity have been reported. A small percentage of canine patients experience life-threatening myelosuppression, characterized by neutropenia, thrombocytopenia, and sometimes anemia, when treated with azathioprine; in some dogs, only thrombocytopenia occurs. Hepatotoxicity, characterized by a primary increase in the alanine aminotransferase (ALT) concentration occurs in approximately 15% of dogs within 14 to 21 days after initiation of therapy. German Shepherds

were shown to be over-represented in the dogs experiencing this hepatotoxicity. Bone marrow suppression usually occurs within 1 to 4 months after initiation of therapy and is typically reversible within 7 to 14 days after discontinuation of therapy. Because of the potential for myelosuppression and hepatotoxicity, dogs receiving azathioprine should have a CBC evaluated and hepatic enzyme activities measured every 1 to 2 weeks for the first month of treatment and then every 1 to 3 months indefinitely. Lower doses of azathioprine (2 mg/kg PO q48h) should be considered in dogs that show evidence of myelosuppression at the typical 2 mg/kg daily dose. Preliminary studies of TPMT activity on dogs have not been useful in predicting which patients are likely to have adverse reactions from azathioprine. However, several breed variations were identified. Giant Schnauzers were shown to have decreased TPMT activity, whereas Alaskan Malamutes were shown to have increased TPMT activity. These variations have not been correlated with any decreased activity or increased risk of toxicity, respectively. *Azathioprine is not recommended for use in cats because severe neutropenia and thrombocytopenia have been reported to occur even at reduced doses.*

Azathioprine is typically used in conjunction with immunosuppressive doses of prednisone. If a positive response is observed to combined therapy, the prednisone dose should be tapered over a period of 2 to 4 months. During this time daily azathioprine should be continued at the same dose (if adverse effects are not seen). If complete discontinuation of prednisone is possible without disease relapse, then the dose of azathioprine can be gradually decreased. This is usually accomplished by initially changing the dose schedule to every other day and then to every third day before complete cessation of treatment. In patients for whom prior relapse of immune-mediated disease has already occurred, the clinician may choose to continue lifelong low-dose azathioprine treatment (2 mg/kg q48h). Of note, bone marrow suppression has been reported as long as 12 months after starting azathioprine treatment, so monitoring of CBC and hepatic enzymes should be continued for the duration of treatment.

CHLORAMBUCIL

Chlorambucil (Leukeran) is an alkylating agent used to treat lymphoid neoplasms as well as immune-mediated disease. Chlorambucil is a prodrug that is metabolized to the active metabolite, phenylacetic acid mustard. It can be used as an alternate immunosuppressive drug in dogs that do not tolerate the more commonly used cytotoxic drugs. Historically, chlorambucil has been used most commonly in cats with immune-mediated disease due to their intolerance of azathioprine. Due to its common use in chemotherapy protocols for gastrointestinal lymphoma, chlorambucil has gained popularity as an adjunctive treatment for other infiltrative gastrointestinal diseases, such as inflammatory bowel disease. The usual starting dose for treatment of immune-mediated diseases in both dogs and cats is 0.1 to 0.2 mg/kg PO q24h (see Table 72.2). Adverse effects include bone marrow suppression, gastrointestinal upset, and predisposition to infection.

CYCLOSPORINE (CICLOSPORIN)

Cyclosporine, a potent immunomodulating agent, is a cyclic polypeptide extracted from fungi. The major mode of action is by inhibition of the initial activation phase of CD4 T lymphocytes. Cyclosporine blocks the transcription of genes encoding several cytokines, in particular IL-2. This prevents the activation and proliferation of T lymphocytes and the secondary synthesis of other cytokines. Cyclosporine does not affect the humoral immune system; therefore treatment with cyclosporine should not influence response to vaccination.

Cyclosporine is approved for management of atopic dermatitis in dogs and cats, and is the treatment of choice for perianal fistulas in dogs. Cyclosporine has also been used to treat a variety of other immune-mediated diseases in dogs and cats. Cyclosporine is a common adjunctive medication used for the treatment of IMHA and pure red cell aplasia. Immunophenotyping of dogs with IMHA showed an upregulation of IL-2, which may help explain why cyclosporine is beneficial with this disease. In addition, cyclosporine has been investigated as a monotherapy for dogs with immune-mediated polyarthritis, with a high rate of remission. Cyclosporine has also been used in other, refractory immune-mediated diseases in dogs and cats such as ITP, inflammatory bowel disease, myasthenia gravis, granulomatous meningoencephalomyelitis, chronic stomatitis, and a variety of immune-mediated dermatologic diseases.

Cyclosporine is available as a veterinary-labeled product in a formulation that forms a microemulsion in an aqueous environment (Atopica, Novartis Animal Health, Basel, Switzerland). Two human products are available, one formulated in vegetable oil (Sandimmune, Sandoz) and one that is a microemulsion (Neoral, Sandoz). Caution should be used when prescribing the human products as the bioavailability is lower than that of the veterinary-labeled product. Also, the doses recommended for the different products are not interchangeable because bioavailability of the microemulsion is higher than that of the oil-based product, and there is less variability in absorption of the microemulsions. Because food intake delays drug absorption and increases variability of absorption, the microemulsion form of cyclosporine should be given 2 hours before or after feeding. Doses of cyclosporine depend on the product used and the disease being treated but range from 5 mg/kg q24h to 10 mg/kg PO q12h (Tables 72.2 and 72.3). Measurement of blood cyclosporine concentration for dose individualization is recommended; therapeutic drug monitoring is available through the Clinical Pharmacology Laboratory at Auburn University (Clinical Pharmacology Laboratory, 1500 Wire Road, 142-A McAdory Hall, Auburn University, AL 36849; clinpharm@auburn.edu). In addition, pharmacodynamic

TABLE 72.2

Immunosuppressive Drugs Used in Treatment of Immune-Mediated Diseases in Dogs and Cats

DRUG	DOSE (DOG)	DOSE (CAT)	ADVERSE EFFECTS	RECOMMENDED MONITORING
Prednisone	2-4 mg/kg/day	2-8 mg/kg/day	Signs of hyperadrenocorticism, gastrointestinal ulceration, predisposition to infection	History and physical examination, CBC, biochemical panel; monitor parameters of disease progression
Azathioprine	2 mg/kg/day initially. Dose can be decreased to every other day to reduce risk of toxicity	Not recommended	Bone marrow suppression, gastrointestinal upset, hepatotoxicity, pancreatitis	CBC, platelet count, liver enzymes biweekly for 2 months, then monthly
Chlorambucil	0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen	0.1-0.2 mg/kg PO q24h initially, then q24-72h	Myelosuppression	CBC and platelet count weekly initially; may decrease to biweekly or monthly once stable
Cyclosporine	5-10 mg/kg PO q12-24h Recommend using only Atopica® due to concerns for bioavailability of other products. Lower doses of 1-2.5 mg/kg q12h if in conjunction with ketoconazole (see Table 72.4)	3-5 mg/kg PO q12h Recommend using only Atopica® due to concerns for bioavailability of other products	Gastrointestinal upset, infection, gingival hyperplasia, papillomatosis, increased shedding	CBC and biochemical panel monthly
Vincristine	0.02 mg/kg IV as a single dose for treatment of ITP	NA	Myelosuppression, thrombophlebitis if allowed to extravasate outside vein	Daily CBC and platelet count to monitor response of platelets
hIVIG	0.25-1.5 g/kg as an IV infusion over 6-12 h (one dose only)	NA	Vomiting, mild thrombocytopenia in normal dogs	Monitor animal during administration by frequent TPR measurements, CBC and platelet count for disease monitoring
Mycophenolate mofetil	10 mg/kg PO q12h	10 mg/kg PO q12h	Gastrointestinal upset, hemorrhagic diarrhea	CBC and biochemical panel monthly
Leflunomide	2-4 mg/kg PO q24h	NA	Decreased appetite, lethargy, mild anemia, and hematemesis or hematochezia	

CBC, Complete blood count; *hIVIG,* human intravenous immunoglobin; *ITP,* immune-mediated thrombocytopenia; *NA,* not applicable; *TPR,* total parenteral nutrition.

monitoring is available to assess the degree of T-cell suppression achieved by a given dose of cyclosporine. This monitoring is available through the Pharmacodynamic Laboratory at Mississippi State University (Diagnostic Laboratory Services, 240 Wise Center Drive, Mississippi State, MS 39762; [662]312-8836). There is considerable interindividual variability in the concentration of cyclosporine required to achieve a therapeutic goal. Therefore following the guidelines of individual laboratories regarding the therapeutic range is important. However, clinical response is a very important

TABLE 72.3

Selected Studies of Dosing Recommendations and Therapeutic Monitoring for Dogs Treated With Cyclosporine

REFERENCE	NUMBER OF CASES	PRODUCT USED	EFFECTIVE DOSE	CLINICAL INDICATION	TARGET THERAPEUTIC RANGE (trough)*	INITIAL RESPONSE RATE
Mathews, 1997	20	Sandimmune	5 mg/kg q12h	Perianal fistulas	400-600 ng/mL	85%
Griffiths et al., 1999	6	Neoral	7.5 mg/kg q12h	Perianal fistulas	400-600 ng/mL	5/6
Olivry, 2002	31	Neoral	5 mg/kg q24h	Atopic dermatitis	Not reported	61%
Mouatt et al., 2002	16	Neoral	0.5-1 mg/kg q12h with ketoconazole 10 mg/kg q24h	Perianal fistulas	>200 ng/mL	93%
Patricelli et al., 2002	12	Neoral	2.5 mg/kg q12h or 4 mg/kg q24h with ketoconazole 5-11 mg/kg q24h	Perianal fistulas	400-600 ng/mL	8/12
O'Neill et al., 2004	19	Neoral	0.5-2 mg/kg q12h with ketoconazole 5.3-8.9 mg/kg q12h	Perianal fistulas	400-600 ng/mL	100%
Hardie et al., 2005	26	Neoral	4 mg/kg q12h	Perianal fistulas	Not measured	69%
Steffan, 2005	268	Atopica	5 mg/kg q24h	Atopic dermatitis	Not measured	58%
Allenspach et al., 2006	14	Atopica	5 mg/kg q24h	Inflammatory bowel disease	Peak concentrations 699 ± 326 ng/mL	12/14

*Except where indicated.

monitoring tool as positive clinical responses for some disorders may be observed at lower concentrations. Therefore therapeutic drug monitoring is most recommended in those patients where a clinical response has not been achieved, or where signs of toxicity are noted at lower doses than would be expected.

Numerous interactions between cyclosporine and other drugs occur because of shared metabolic pathways involving the cytochrome P450 enzyme system. Therapeutic monitoring is especially important in animals receiving concurrent therapy with such drugs (Table 72.4). In dogs treated with cyclosporine, concurrent ketoconazole administration (5-10 mg/kg q24h) can be used to decrease the required dose of cyclosporine, with resultant cost savings. This strategy has primarily been used in dogs with perianal fistulas and dogs undergoing organ transplantation; however, it could also be considered for other immune-mediated diseases, although the effectiveness is unproven. Similarly, concurrent itraconazole administration (10 mg/kg q24h) increased the bioavailability of orally administered cyclosporine in cats (Katayama et al., 2010). Therapeutic monitoring of the cyclosporine concentration is important when using this strategy.

Adverse effects of cyclosporine in dogs include gastrointestinal disturbance, predisposition to infection, gingival hyperplasia, papillomatosis, and increased shedding. A dermatosis from atypical staphylococcal infection (psoriasiform lichenoid–like dermatosis) has also been reported in dogs treated with cyclosporine. Affected dogs improved after antibiotic therapy and a decreased dose of cyclosporine. At the doses used to treat atopic dermatitis (5 mg/kg PO q24h), no difference in prevalence of bacterial infection was demonstrated between dogs treated with prednisone and those treated with cyclosporine. The risk of infection is increased in dogs treated with higher doses of cyclosporine, such as those used to prevent transplant rejection (20 mg/kg PO q24h), and when cyclosporine is combined with other immunosuppressive drugs such as prednisone and azathioprine. Cats treated with cyclosporine have adverse effects similar to what dogs have but may also develop anorexia, weight loss, bone marrow hypocellularity, and hepatic lipidosis.

LEFLUNOMIDE

Leflunomide is metabolized to teriflunomide, which inhibits its pyrimidine synthesis. Leflunomide also inhibits tyrosine kinases involved in cell differentiation and signal transduction. The drug inhibits T- and B-cell proliferation and has

TABLE 72.4

Pharmacokinetic Interactions With Cyclosporine

EFFECT OF THE CONCOMITANT THERAPY ON CYCLOSPORINE CONCENTRATION	WELL-DOCUMENTED REPORT OF INTERACTION WITH MARKED EFFECTS ON BLOOD LEVELS	ANECDOTAL REPORTS OF INTERACTION	DOCUMENTED EVIDENCE OF ABSENCE OF INTERACTION
Increase of concentrations	***Ketoconazole*** ***Fluconazole*** ***Itraconazole*** **Diltiazem** **Erythromycin** **Clarithromycin** Norfloxacin Phenytoin Metoclopramide *Vitamin E (with Sandimmune)*	Nafcillin Estradiol	
No change of concentrations	*Metoclopramide*		*Methylprednisolone* *Cimetidine* *Vitamin E (with Atopica)* Nonsteroidal antiinflammatory drugs Fluoroquinolones* β-Lactam antibiotics
Decrease of concentrations	Trimethoprim sulfonamides, St. John's wort	Clindamycin	

Drugs in *italics* documented in dogs or cats.
Text in **bold,** increase by >100%.
Regular text, increase or decrease by 50% to 100%.
*Except norfloxacin.
Modified from Guaguere E et al.: A new drug in the field of canine dermatology. *Vet Dermatol* 2004;15:61.

antiinflammatory effects. Leflunomide is most commonly used to treat RA in people. In dogs, leflunomide was first used as part of an immunosuppressive protocol for renal transplantation but is now also used as adjunctive treatment in dogs that are refractory to more traditional immunosuppressive drugs and in patients in which glucocorticoids are contraindicated. Published studies regarding leflunomide use in dogs are limited, but a retrospective study reporting its use as a monotherapy for immune-mediated polyarthritis in dogs was encouraging. Leflunomide has also been used for treatment of Evans syndrome, IMHA, and polymyositis.

Adverse effects are uncommon but include decreased appetite, lethargy, mild anemia, and hematemesis or hematochezia when used in conjunction with corticosteroids. An idiosyncratic thrombotic microangiopathy is also described in dogs but is reversible with discontinuation of the drug. The current recommended dose is 2 to 4 mg/kg PO q24h. Therapeutic monitoring for leflunomide is available through the Clinical Pharmacology Laboratory at Auburn University (Clinical Pharmacology Laboratory, 1500 Wire Road, 142-A McAdory Hall, Auburn University, AL 36849; clinpharm@auburn.edu).

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH) required for purine synthesis. MPA inhibits proliferation of B and T cells and decreases antibody production. Mycophenolate mofetil was developed as an alternative to azathioprine due to its similar mechanism of action and low risk of myelotoxicity. Mycophenolate has most commonly been used in transplantation medicine for prevention of rejection; however, it has become widely used in clinical veterinary medicine for immunosuppression, particularly for treatment of IMHA and ITP. Mycophenolate has also been used in refractory cases of mysathenia gravis, inflammatory bowel disease, and meningoencephalomyelitis of unknown etiology.

Advantages of mycophenolate include its availability as both an oral and parenteral product, which is appealing for anorectic patients. Other advantages include a low risk of toxicity. The most common adverse effects are gastrointestinal toxicity, which previously occurred in up to 67% of patients. Gastrointestinal toxicity, including hemorrhagic diarrhea, has the potential to be severe, but

has been found to be dose-dependent. Doses of greater than 15 mg/kg PO q12h are associated with higher risk of gastrointestinal toxicity. Mild suspected allergic reactions have been reported with use of the parenteral product. The current recommended dose in dogs is 10 mg/kg PO q12h. The concentration of MPA in the plasma of cats following administration of mycophenolate is highly variable, so the safety and efficacy of this drug is unknown in cats (Slovak et al., 2017).

SPLENECTOMY

Splenectomy is an adjunctive therapy recommended in the management of hematologic immune-mediated diseases such as IMHA and ITP. Splenectomy is theorized to decrease the number of mononuclear phagocytic cells available for phagocytosis of antibody-coated RBCs and platelets. It is typically recommended in dogs with IMHA or ITP resistant to medical therapy. There is evidence to support splenectomy in dogs with ITP that relapse after tapering of prednisone and azathioprine therapy. The merits of splenectomy in dogs with IMHA are less clear. One retrospective case series documented a positive clinical response after splenectomy in 10 dogs with IMHA that were not responding to immunosuppressive treatment. Nine of ten dogs survived to 30 days, and the hematocrit increased while transfusion requirements decreased after surgery. Interpretation of this study is difficult because most dogs were treated concurrently with corticosteroids, and the positive outcome could have been a delayed response to medical treatment. Potential risks of splenectomy include hemorrhage and thromboembolic complications. The spleen is also an important site of extramedullary hematopoiesis, so splenectomy has the potential to impair RBC regeneration.

HUMAN INTRAVENOUS IMMUNOGLOBULIN

Human intravenous immunoglobulin (hIVIG) is a preparation of polyspecific IgG obtained by pooling the plasma of a large number (>1000) of healthy human blood donors. hIVIG is available as either a solution or a lyophilized product, and a wide range of concentrations and vial sizes are available. Numerous commercial products are available and vary in price and availability (e.g., Gammagard S/D, Baxter Healthcare Corporation, Deerfield, Ill; Gamimune N, Bayer Pharmaceuticals, Leverkusen, Germany). hIVIG is the treatment of choice for immune-mediated thrombocytopenic purpura in people and is also used for the treatment of a wide variety of other immune-mediated diseases. Numerous mechanisms by which hIVIG modulates the immune system have been documented in humans, including decreased production of autoantibodies, possibly due to antiidiotypic antibodies in hIVIG, functional modulation of T cells, decreased natural killer cell activity, blockade of complement-mediated cell damage, and modulation of the release and function of proinflammatory cytokines. In dogs, hIVIG binds to Fc receptors on mononuclear phagocytes, thereby inhibiting phagocytosis. Whether other mechanisms also play a role is unknown. hIVIG has been used in veterinary medicine to treat IMHA, pure red cell aplasia, myelofibrosis, ITP, erythema multiforme, pemphigus foliaceus, and toxic epidermal necrolysis. Doses of hIVIG that have been used in dogs range from 0.25 to 1.5 g/kg; hIVIG is administered as an intravenous infusion over 6 to 12 hours. Mild thrombocytopenia and occasional vomiting have been reported in healthy dogs treated with hIVIG. The most serious concern for use of hIVIG in dogs and cats is that administration of an infusion containing human protein could lead to sensitization and potential anaphylaxis if the treatment is repeated. There are few reports of anaphylactic reactions in dogs or cats treated with hIVIG despite repeated administration in some case reports; however, anaphylaxis was reported to occur in a dog with myasthenia gravis treated with four doses of hIVIG. The other potential adverse effect documented in dogs is increased risk of thromboembolism. In a study of healthy dogs treated with hIVIG, a prothrombotic and proinflammatory effect was demonstrated (Tsuchiya et al., 2009). Risk of thromboembolism is also a concern in people treated with hIVIG, especially in those already at risk. A high prevalence of thromboembolism was reported in dogs with IMHA treated with hIVIG; however, whether this related to the underlying disease or the hIVIG treatment was not clear. The major limitation of hIVIG treatment is the expense; consequently prospective studies of hIVIG treatment in veterinary medicine have been limited, and the evidence for its efficacy in disorders other than canine ITP is weak. Immunoglobulin is currently most commonly used as an adjunctive treatment in dogs with severe ITP and as a rescue agent in dogs with immune-mediated diseases (IMHA, myasthenia gravis, dermatologic drug reactions, pemphigus foliaceus) that are not responding to conventional immunosuppressive agents. Because of the rapid but short-acting effect of hIVIG on phagocytosis, the most logical use is as a bridge to suppress phagocytosis in diseases such as IMHA and ITP while waiting for other immunosuppressive drugs to become effective; however, clinical studies to support this hypothesis are lacking except in canine ITP.

PENTOXIFYLLINE

Pentoxifylline belongs to the methylxanthine drug class and is a derivative of theobromine. Despite this derivation, the drug does not have cardiac or bronchodilatory effects. The major properties of pentoxifylline relate to its effects on the immune system and blood viscosity. Pentoxifylline improves the deformability of RBCs by unknown mechanisms. Pentoxifylline also has a number of immunomodulating effects, including inhibition of IL-1, IL-6, and tumor necrosis factor-α, as well as inhibition of B- and T-cell activation.

The pharmacokinetics of pentoxifylline have been described in the dog, and the current dose recommendation is 10 to 15 mg/kg PO q8h. In veterinary medicine, pentoxifylline has primarily been used for the management of cutaneous immune-mediated diseases, including dermatomyositis, SLE, and various forms of vasculitis. Whether the drug might be beneficial in other immune-mediated diseases is not known. Adverse effects in dogs are uncommon but may include vomiting, diarrhea, bone marrow suppression, and flushing.

VINCRISTINE

Vincristine is an alkaloid derived from the periwinkle plant. It is used as an antineoplastic and immunosuppressive agent. Vincristine binds to the microtubular structural protein tubulin, which is abundant within platelets. At low doses the drug causes a transient increase in circulating platelet numbers; at higher doses it can cause myelosuppression and thrombocytopenia. Proposed mechanisms for increased platelet numbers in normal dogs include stimulation of thrombopoiesis by circulating thrombopoietic factors (perhaps by concealing platelets from the thrombopoietic regulatory system) or by inducing acute fragmentation of mature megakaryocytes. In ITP, in which stimulation of thrombopoiesis is already maximal, the mechanisms for increased platelet numbers are most likely increased platelet release from the bone marrow and impaired platelet destruction from inhibition of phagocytosis, or interference with antibody binding to platelets. Decreased antibody synthesis seems less likely considering the short time course for the increase in platelet count (median 3 days for platelet recovery). Disruption of structure and function of platelets has been reported after exposure to vincristine in vitro and in vivo in dogs with lymphoma; however, the clinical significance of this finding is unclear.

The major indication for vincristine in treatment of immune-mediated disease is as adjunctive therapy for dogs with severe ITP. Vincristine-treated dogs with ITP have a more rapid increase in platelet number and shorter duration of hospitalization than dogs treated with prednisone alone. Vincristine is administered at 0.02 mg/kg IV as a single dose in conjunction with glucocorticoids. The advantages of vincristine are that it is readily available and inexpensive. Although bone marrow suppression may occur at higher doses, this has not been reported at the low single dose used for treatment of ITP. Care should be taken during intravenous administration because the drug is highly caustic if extravasation occurs.

Suggested Readings

Allenspach K, et al. Pharmacokinetics and clinical efficacy of cyclosporine treatment of dogs with steroid refractory inflammatory bowel disease. *J Vet Intern Med*. 2006;20:239.

Beale KM. Azathioprine for treatment of immune-mediated diseases of dogs and cats. *J Am Vet Med Assoc*. 1988;192:1316.

Beale KM, et al. Systemic toxicosis associated with azathioprine administration in domestic cats. *Am J Vet Res*. 1992;53:1236.

Behrend E, et al. Pharmacology, indications, and complications. *Vet Clin North Am Small Anim Pract*. 1997;27:187.

Bianco D, et al. A prospective randomized double blinded, placebo controlled study of human intravenous immunoglobulin for the acute management of presumptive primary immune mediated thrombocytopenia in dogs. *J Vet Intern Med*. 2009;23:1071.

Boothe DM. *Small animal clinical pharmacology and therapeutics*. 2nd ed. Philadelphia: Elsevier; 2012.

Colopy SA, et al. Efficacy of leflunomide for treatment of immune-mediated polyarthritis in dogs: 14 cases (2006-2008). *J Am Vet Med Assoc*. 2010;236:312.

Dewey CW, et al. Mycophenolate mofetil treatment in dogs with serologically diagnosed acquired myasthenia gravis: 27 cases (1999-2008). *J Am Vet Med Assoc*. 2010;236:664.

Flint SK, et al. Independent and combined effects of prednisone and acetylsalicylic acid on thromboelastography variables in healthy dogs. *Am J Vet Res*. 2011;72:1325.

Grau-Bassas ER, et al. Vincristine impairs platelet aggregation in dogs with lymphoma. *J Vet Intern Med*. 2000;14:81.

Griffiths LG, et al. Cyclosporine as the sole treatment for anal furunculosis: preliminary results. *J Small Anim Pract*. 1999;40:569.

Guaguere E, et al. A new drug in the field of canine dermatology. *Vet Dermatology*. 2004;15:61.

Hardie RJ, et al. Cyclosporine treatment of anal furunculosis in 26 dogs. *J Small Anim Pract*. 2005;46:3.

Heinrich NA, et al. Adverse events in 50 cats with allergic dermatitis receiving cyclosporin. *Vet Dermatol*. 2011;22:511.

Horgan JE, et al. Splenectomy as an adjunctive treatment for dogs with immune-mediated hemolytic anemia: ten cases (2003-2006). *J Vet Emerg Crit Care*. 2009;19:254.

Katayama M, et al. Effects of multiple oral dosing of itraconazole on the pharmacokinetics of cyclosporine in cats. *J Fel Med Surg*. 2010;6:512.

Mathews KA, et al. Randomized controlled trial of cyclosporine for treatment of perianal fistulas in dogs. *J Am Vet Med Assoc*. 1997;211:1249.

Miller E. The use of cytotoxic agents in the treatment of immune-mediated diseases of dogs and cats. *Semin Vet Med Surg (Small Anim)*. 1997;12:144.

Mouatt JG, et al. Cyclosporine and ketoconazole interaction for treatment of perianal fistulas in the dog. *Aust Vet J*. 2002;80:207.

Ogilvie GK, et al. Short-term effect of cyclophosphamide and azathioprine on selected aspects of the canine blastogenic response. *Vet Immunol Immunopath*. 1988;18:119.

Olivry T, et al. Randomized controlled trial of the efficacy of cyclosporine in the treatment of atopic dermatitis in dogs. *J Am Vet Med Assoc*. 2002;221:370.

O'Neill T, et al. Efficacy of combined cyclosporine A and ketoconazole treatment of anal furunculosis. *J Small Anim Pract*. 2004;45:238.

Patricelli AJ, et al. Cyclosporine and ketoconazole for the treatment of perianal fistulas in dogs. *J Am Vet Med Assoc*. 2002;220:1009.

Rinkardt NE, et al. Azathioprine induced bone marrow toxicity in four dogs. *Can Vet J*. 1996;37:612.

Roberts ES, et al. Safety, tolerability, and pharmacokinetic of 6-month daily dosing of an oral formulation of cyclosporine (ATOPIC for cats) in cats. *J Vet Pharmac Therap*. 2014;37:161.

Rodriguez DB, et al. Relationship between red blood cell thiopurine methyltransferase activity and myelotoxicity in dogs receiving azathioprine. *J Vet Intern Med*. 2004;18:339.

Scott-Moncrieff JC, et al. Human intravenous immunoglobulin therapy. *Semin Vet Med Surg (Small Anim)*. 1997;12:178.

Singer LM, et al. Leflunomide pharmacokinetics after single oral administration to dogs. *Vet Pharmacol Ther*. 2011;34:609.

Slovak J. Safety of oral and intravenous mycophenolate mofetil in healthy cats. *J Feline Med Surg*. 2017;20(2):184–188.

Spurlock NK, et al. A review of current indications, adverse effects, and administration recommendations for intravenous immunoglobulin. *J Vet Emerg Crit Care*. 2011;21:471.

Steffan J, et al. Clinical trial evaluating the efficacy and safety of cyclosporine in dogs with atopic dermatitis. *J Am Vet Med Assoc*. 2005;226:1855.

Tsuchiya R, et al. Prothrombotic and inflammatory effects of intravenous administration of human immunoglobulin G in dogs. *J Vet Intern Med*. 2009;23:1164.

Wang A, et al. Treatment of canine idiopathic immune-mediated haemolytic anaemia with mycophenolate mofetil and glucocorticoids: 30 cases (2007 to 2011). *J Small Anim Pract*. 2013;54(8):399.

Whelan MF, et al. Use of human immunoglobulin in addition to glucocorticoids for the initial treatment of dogs with immune-mediated hemolytic anemia. *J Vet Emerg Crit Care*. 2009;19:158.

Whitley NT, et al. Immunomodulatory drugs and their application to the management of canine immune-mediated disease. *J Small Anim Pract*. 2011;52:70.

Woolcock AD, et al. Treatment of canine meningoencephalomyelitis of unknown aetiology with mycophenolate mofetil and corticosteroids: 25 cases (2007-2012). *Vet Med Sci*. 2016;2(2):125.

CHAPTER 73

Common Immune-Mediated Diseases



IMMUNE-MEDIATED HEMOLYTIC ANEMIA

Etiology

Immune-mediated hemolytic anemia (IMHA) is a clinical syndrome in which anemia results from the accelerated destruction of red blood cells (RBCs) by immune-mediated mechanisms (see Chapter 70). IMHA is the most common cause of hemolytic anemia in dogs but is uncommon in cats. In primary IMHA (true autoimmune hemolytic anemia) antibodies are directed against RBC membrane antigens. The target antigens have not been well characterized in the dog or cat, but antibodies directed against spectrin, band 3, and the family of erythrocyte membrane glycoproteins, known as *glycophorins,* have been identified in some dogs. True autoimmune hemolytic anemia may also be a manifestation of systemic lupus erythematosus (SLE). In secondary IMHA, an underlying disease is implicated as a precipitating factor. Causes of secondary IMHA include infection and neoplastic diseases (Box 73.1). Secondary IMHA may also occur after exposure to certain drugs, venoms, and possibly vaccines. Most studies in dogs suggest that primary autoimmune hemolytic anemia is more common than the secondary form, although the frequency of identification of a secondary cause likely depends on the extent of the diagnostic evaluation because a diagnosis of primary IMHA is usually made by ruling out secondary causes.

The common antibody classes identified on the RBC in both dogs and cats with IMHA are, in order from most to least common, immunoglobulin (Ig) G, IgM, and IgA. Complement is usually also present. In secondary IMHA antibodies may be directed against antigens that adsorb to the RBC membrane or against a microbial antigen combined with a self-determinant, with the RBCs destroyed as "innocent bystanders." Alternatively, previously hidden membrane antigens may be exposed by membrane damage due to microbes or toxins, or microbial and drug antigens may be cross-reactive with self-determinants. Lastly, nonspecific activation of lymphocytes can result in formation of self-reacting lymphocytes in any chronic inflammatory process.

Recent vaccination has been implicated in the pathogenesis of IMHA. The occurrence of IMHA within 2 to 4 weeks of vaccination has been a clinical observation of concern for many owners and veterinarians. In one study of 58 dogs with IMHA, 26% of dogs had been vaccinated within 4 weeks of developing IMHA compared with a control group in which only 5% had been vaccinated within the previous 4 weeks. Mortality rates between the recently vaccinated dogs and unvaccinated dogs were not significantly different. In a later study that compared 72 dogs with IMHA with a control group, a temporal association between vaccination and development of IMHA was not identified. The importance of vaccination in the etiology of IMHA thus remains unclear.

IMHA clearly has a genetic predisposition, with the disease recognized more frequently in certain breeds (Box 73.2). The Cocker Spaniel is the breed at greatest risk, accounting for as many as one third of cases. The presence of dog erythrocyte antigen 7 has been investigated for its possible protective effect in Cocker Spaniels, but consistent association has not been identified with this or other cell surface antigens.

In IMHA the presence of antibody and/or complement on the RBC ultimately results in intravascular or extravascular hemolysis (see Chapter 82). Extravascular hemolysis is more common than intravascular hemolysis, is typically a less acute process, and is commonly accompanied by spherocytosis and hyperbilirubinemia (Figs. 73.1 and 73.2). Although hyperbilirubinemia is a common feature of IMHA, it does not occur in all cases, and lack of hyperbilirubinemia does not rule out IMHA. In one study, bilirubin concentrations were significantly higher in nonsurvivors when compared with survivors (Harkin et al., 2012). Factors that determine the presence and severity of hyperbilirubinemia include the rate of hemolysis and hepatic function. Hepatic function may be compromised by hypoxia and hepatic necrosis in dogs with IMHA. In one study of 34 dogs that died of IMHA, 53% had moderate to severe centrilobular hepatic necrosis at necropsy.

BOX 73.1

Infectious Diseases Implicated as Causing IMHA in Dogs and Cats

Dogs

Dirofilariasis
Hemotrophic mycoplasmosis
Ehrlichia canis infection
Anaplasma phagocytophilum infection
Leishmaniasis
Babesiosis
Chronic bacterial infection

Cats

Hemotrophic mycoplasmosis
Feline infectious peritonitis
Feline leukemia virus
Chronic bacterial infection

IMHA, Immune-mediated hemolytic anemia.

BOX 73.2

Dog Breeds at Increased Risk of IMHA

Cocker Spaniel
Bichon Frise
Miniature Pinscher
Miniature Schnauzer
English Springer Spaniel
Rough-coated Collie
Finnish Spitz

IMHA, Immune-mediated hemolytic anemia.

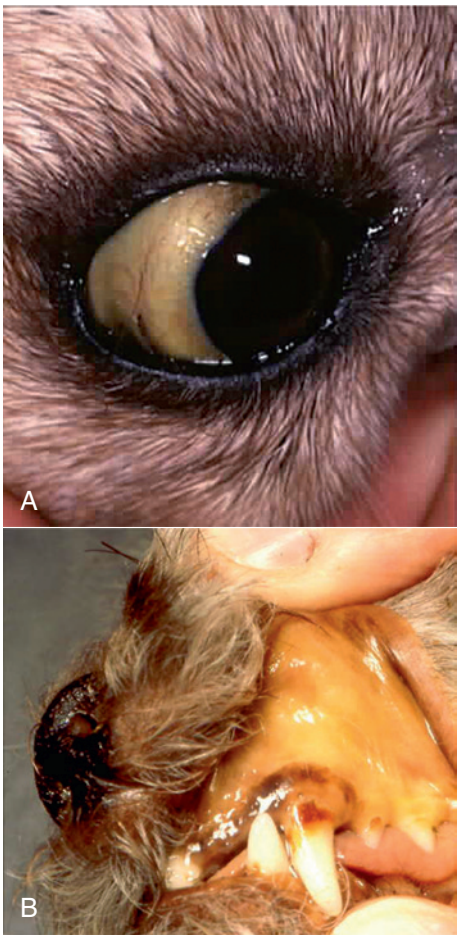


FIG 73.1
Mixed-breed dog with moderate icterus of the sclera **(A)** and the oral mucous membranes **(B).**

Clinical Features

Dogs with primary IMHA are typically young to middle-aged adults, with a reported age range of 1 to 13 years and a median age of 6 years. Females and neutered dogs of both sexes appear predisposed compared with sexually intact male dogs, and several breeds are overrepresented (see Box 73.2). Common clinical signs of IMHA are listed in Box 73.3. The duration of clinical signs before presentation to the veterinary hospital is typically short, with a median of 4 days. Seasonal increases in diagnosis of IMHA have been reported, although the findings are not consistent among studies. The majority of reports suggest an increased frequency of IMHA during the warmer months of the year.

Diagnosis

Diagnosis of IMHA relies on identifying abnormalities consistent with hemolytic anemia on a complete blood count (CBC), serum biochemistry panel, and urinalysis (Box 73.4) followed by identification of antibodies directed against the RBC membrane. Further diagnostic testing is then directed

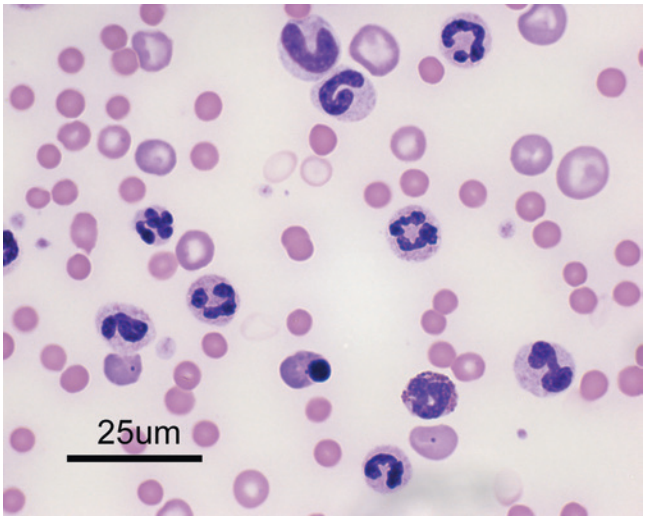


FIG 73.2
Photomicrograph of a blood smear demonstrating presence of spherocytes.

BOX 73.3

History and Physical Examination Findings in Dogs and Cats With IMHA

DOGS	CATS
History	
Lethargy	Lethargy
Anorexia	Anorexia
Pallor	Pallor
Icterus	Icterus
Vomiting	Vomiting
Collapse	Pica
Weakness	
Physical Examination (Additional Findings)	
Systolic heart murmur	Systolic heart murmur
Pyrexia	Pyrexia
Tachycardia	Hypothermia
Tachypnea	Lymphadenomegaly
Pallor	Pallor
Icterus	Icterus
Splenomegaly	
Hepatomegaly	
Abdominal pain	

IMHA, Immune-mediated hemolytic anemia.

BOX 73.4

Abnormalities on the CBC and Serum Chemistry Profile in Dogs With IMHA

CBC

Anemia
Polychromasia
Autoagglutination
Spherocytosis
Ghost cells
Evidence of inflammation (increased neutrophils, bands, metamyelocytes, monocytes)
Thrombocytopenia

Biochemical Profile

Hemoglobinemia
Hemoglobinuria
Hyperbilirubinemia
Hyperbilirubinuria
Increased alanine aminotransferase
Increased alkaline phosphatase

CBC, Complete blood cell count; *IMHA,* immune-mediated hemolytic anemia.

at establishing whether a secondary underlying cause for IMHA can be identified.

The first requirement for making a diagnosis of IMHA is the presence of anemia. The anemia is typically moderate to marked (median hematocrit of 13%) and is usually regenerative, although in approximately 30% of dogs and more than 50% of cats a nonregenerative anemia is present either because of acute onset before the bone marrow has had time to respond (typically takes 3-5 days for maximal regenerative response) or because of antibodies directed against bone marrow precursors. In the latter situation, reticulocytes are destroyed before they enter the peripheral circulation. In the absence of a regenerative response, a rapid fall in the hematocrit with little change in the serum total protein or albumin concentration should be considered suspicious for hemolysis. In anemia caused by decreased RBC production from the bone marrow, the hematocrit should not decrease by more than approximately 1% per day, whereas in blood loss anemia, the drop in the hematocrit is usually accompanied by a concurrent decrease in the total protein or albumin (Table 73.1). Most dogs with IMHA also have an inflammatory leukogram, often with a shift toward immature cells, and mild to severe thrombocytopenia in 60% of cases. Proposed mechanisms for thrombocytopenia include the presence of antibodies directed against platelets and RBCs (Evans syndrome), disseminated intravascular coagulation (DIC), and splenic sequestration.

Identification of autoagglutination or spherocytosis (2+ or more) on a blood smear is considered definitive evidence of antibody-mediated RBC hemolysis (Fig. 73.3). Autoagglutination is detected by macroscopic or microscopic examination of the blood smear and is generally considered diagnostic for IMHA. Autoagglutination has been reported in up to 78% of canine IMHA. Agglutination must be distinguished from rouleaux formation (see Chapter 82).

In dogs with IMHA, spherocytes are formed by partial removal of antibody-coated RBC membranes by macrophages (see Fig. 73.2). This results in loss of the normal discoid shape, decreased size, and loss of central pallor. Spherocytes are more rigid and less deformable than normal RBCs and are removed when they pass through the spleen. Spherocytes are readily identified in the dog but difficult to recognize in cats because of the lack of significant central pallor in their normal RBCs. Spherocytes are considered a hallmark morphologic change in IMHA, and when present in sufficient numbers (2+ or greater) may be regarded as diagnostic for IMHA in dogs. However, because spherocytes are the results of phagocytic activity on the RBCs, they can also be present in other disorders, such as hemophagocytic syndrome, hemophagocytic histiocytosis, and zinc-induced hemolysis, although their numbers tend to be low when compared with dogs with IMHA (i.e., 1+ versus 2+). Techniques for quantification of spherocyte numbers are typically semiquantitative (Table 73.2). In retrospective studies approximately 90% of dogs with IMHA have spherocytes present on the blood smear; however, low numbers may be present in dogs with peracute hemolysis. Ghost cells are remnant membranes of RBCs that have undergone intravascular lysis. Lysis can be induced by immune- or non–immune-mediated mechanisms, so ghost cells are not diagnostic for IMHA.

The direct Coombs test with polyvalent antisera is the most commonly used diagnostic test for IMHA when autoagglutination or spherocytosis is not present; however, this test is neither particularly sensitive nor specific for

TABLE 73.1

Expected Changes on the CBC in Different Causes of Anemia

TYPES	RATE OF DECREASE OF HEMATOCRIT	RETICULOCYTE COUNT	SERUM PROTEINS	EVIDENCE OF INFLAMMATION ON CBC	THROMBOCYTOPENIA
Hemolytic anemia	Fast	High	No change	Yes	Yes (mild to severe)
Nonregenerative anemia	Slow	Low	No change	No	Depends on cause
Blood loss anemia	Fast	High	Decreased	No	Yes (mild only)

CBC, Complete blood cell count.

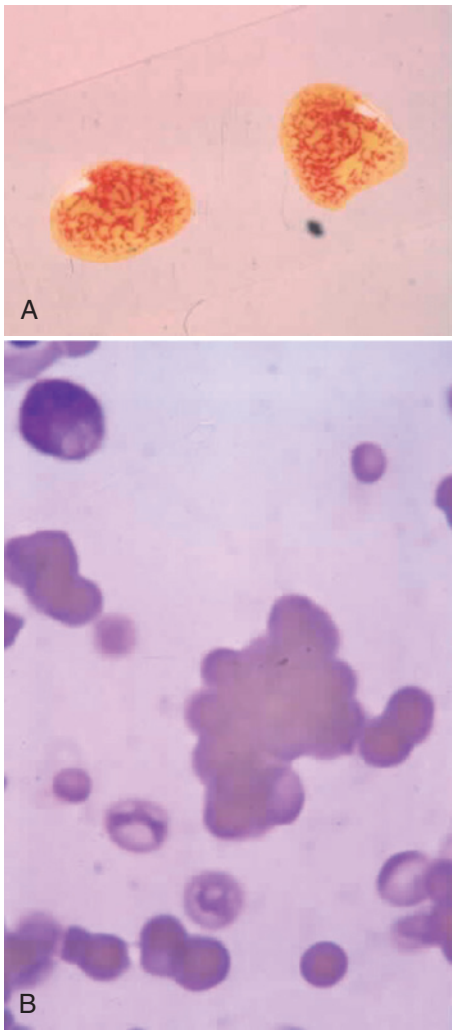


FIG 73.3
Blood smear showing gross **(A)** and microscopic **(B)** agglutination. Note the three-dimensional clustering of red blood cells on the microscopic view.

confirming a diagnosis of IMHA. A positive Coombs test indicates that antibody, complement, or both are on the surface of the RBC but does not mean that the antibody is directed specifically against the RBC membrane or that the antibody is causing hemolysis. Approximately 60% to 80%

TABLE 73.2

Semiquantitative Scoring System for Numbers of Spherocytes on a Slide

APPROXIMATE NUMBER OF SPHEROCYTES PER × 1000 FIELD	ASSIGNED SCORE
1-10	1+
11-50	2+
51-150	3+

of canine patients with IMHA have a positive Coombs test. Conversely, a positive Coombs test can occur in a variety of other inflammatory diseases causing false-positive results. False-negative results can also occur and might reflect a low concentration of antibody present (see Chapters 72 and 82). In people, the Coombs test is performed at two different temperatures, to detetct cold and warm agglutinins, maximizing the possibility of identifying a positive result. There is some evidence in people that cold agglutinin positive/warm agglutinin negative Coombs tests are more likely to indicate IMHA due to a secondary cause. This has not been shown to be true in dogs, but certain laboratories will still report cold and warm agglutinin Coombs test results.

A search for secondary causes of IMHA should always be undertaken in a dog or cat with IMHA because the underlying disease may influence both management strategy and prognosis. Potential secondary causes of IMHA are listed in Table 73.3. The diagnostic approach to ruling out secondary IMHA includes a thorough history of drug, vaccine, and toxin exposure; detailed physical examination, including rectal, ophthalmologic, and neurologic examinations; tests for specific infectious diseases; investigation into causes of chronic antigenic stimulation; and a search for evidence of neoplasia. Diagnostic tests to consider in addition to a CBC, biochemical panel, and urinalysis include urine culture, abdominal and thoracic radiographs, abdominal ultrasound, bone marrow cytology and/or histopathology (if the anemia is nonregenerative), and appropriate titers for infectious diseases.

TABLE 73.3

Secondary Causes of IMHA in Dogs and Cats

	EXAMPLES	DIAGNOSTIC TESTS INDICATED
Neoplasia	Lymphoma Hemangiosarcoma Leukemia Malignant histiocytosis	Abdominal/thoracic radiographs Abdominal ultrasound Bone marrow aspirate Lymph node aspirates
Infection (see Box 73.1)	Feline leukemia virus Hemotrophic mycoplasmosis *Dirofilaria immitis*	Serology IFA/PCR Serology Thoracic radiographs Urinary tract infection
Chronic inflammation	Prostatitis Colitis Diskospondylitis Polyarthritis	Urine culture Ultrasound of urinary tract Colonoscopy Spinal radiographs Synovial fluid collection and radiographs
Exposure to drugs vaccines or toxins	Antibiotics (sulfonamides, β-lactam antibiotics)	Detailed history

IFA, Immunofluorescent antibody; *IMHA,* immune-mediated hemolytic anemia; *PCR,* polymerase chain reaction.

Results of bone marrow evaluation in dogs with nonregenerative primary IMHA typically reveal erythroid hyperplasia with a low myeloid/erythroid (M/E) ratio, although maturation arrest at the rubricyte or metarubricyte stage may also be observed. Some dogs initially suspected to have IMHA on the basis of the presence of spherocytosis or a positive Coombs test have pure red cell aplasia (PRCA). Myelofibrosis is identified on bone marrow core biopsy in many dogs with nonregenerative IMHA. In dogs with myelofibrosis, collection of adequate bone marrow elements by aspiration cytology is difficult. Myelofibrosis is likely a secondary response to bone marrow injury and usually resolves in dogs that respond to treatment.

In dogs without the classic morphologic changes of immune-mediated hemolysis (regenerative anemia, autoagglutination, spherocytes), confirming a diagnosis of IMHA is challenging. A positive direct Coombs test should be interpreted cautiously in such cases because false-positive results may occur. The logical approach is to rule out other causes of anemia (see Chapter 82) and use the Coombs test and other indications of hemolysis as supporting evidence of IMHA if no other cause of anemia is identified.

Treatment

Choosing an appropriate treatment regimen for dogs with IMHA is a frustrating task for the clinician. Lack of prospective studies of treatment efficacy, the poor prognosis associated with the disease, and the high cost of treatment and supportive care are some reasons for this frustration. In addition, serious complications such as pulmonary thromboembolism and DIC are relatively common occurrences but are hard to anticipate in individual patients. Because of the lack of prospective studies of treatment efficacy, recommendations for approach to treatment in dogs with IMHA are based primarily on clinical experience rather than objective data.

When planning the management of a dog with IMHA, the goals of treatment should include prevention of RBC hemolysis, alleviation of tissue hypoxia by blood transfusion, prevention of thromboembolism, and provision of supportive care.

PREVENTION OF HEMOLYSIS

Immunosuppressive drugs are the key for prevention of hemolysis in dogs with IMHA. The mechanism of action and adverse effects associated with the use of various immunosuppressive drugs recommended for use in dogs and cats with autoimmune disorders were discussed in Chapter 72.

High doses of glucocorticoids are the first line of treatment for controlling hemolysis in dogs with IMHA. In dogs that can tolerate oral medication, prednisolone or prednisone at a dose of 2-4 mg/kg/day orally (PO) is the authors' corticosteroid of choice. Prednisolone may have higher bioavailability than prednisone in cats and possibly dogs, so it is the best choice in both species. The higher end of the dose range is recommended as a starting dose except in large-breed dogs (>30 kg). Most dogs that respond to prednisolone show some improvement within the first 7 days of treatment, but the full therapeutic effect may not be evident until 2 to 4 weeks after initiation of treatment. Indications suggesting resolution of hemolysis include stabilization and then an increasing hematocrit, conversion from a positive to negative Coombs test, resolution of autoagglutination, resolution of spherocytosis, normalization of the reticulocyte

count, and resolution of the inflammatory leukogram. Once the hematocrit increases above 30%, a taper of the prednisone dose can be initiated The dose is tapered by a maximal rate of 20% to 30% per month over a 3- to 6-month period depending on the hematocrit and severity of adverse effects. If after 6 months the prednisolone dose is tapered to a low every-other-day dose and the disease is in remission, discontinuation of medication should be attempted. A CBC and reticulocyte count should be performed before and 2 weeks after any change in immunosuppressive therapy.

Some dogs with IMHA do not respond to glucocorticoid treatment alone, or the dose of prednisolone required for disease control results in unacceptable adverse effects. In these cases, an additional immunosuppressive drug should be added to the treatment regimen. One common clinical dilemma is whether all dogs with IMHA should be treated with an additional immunosuppressive drug early in the course of treatment, or whether waiting and identifying which dogs are likely to benefit is more appropriate. The advantage of starting another immunosuppressive drug early is that no time is lost waiting to identify which patients will respond to glucocorticoid treatment alone. Most adjunctive immunosuppressive drugs take 2 to 4 weeks to have an appreciable effect on immune cells, so an argument could be made that starting them earlier will save time. The disadvantages include the risk of adverse effects, the cost of immunosuppressive drugs, the lack of evidence of benefit, and the lack of consensus about which adjunctive agent should be considered "second line" after glucocorticoids. In a retrospective study comparing a cohort of dogs treated with prednisolone and azathioprine with a cohort of dogs treated with prednisolone alone, no benefit of azathioprine therapy could be identified. Despite this finding, other large IMHA retrospective studies report that the majority of IMHA cases are managed with glucocorticoids and adjunctive immunosuppressive agents. Use of more than one adjunctive immunosuppressive drug concurrently is strongly discouraged because of the potential for severe immunosuppression and resultant susceptibility to infection.

The choice for adjunctive immunosuppression varies among clinicians. The most common drugs used are azathioprine, cyclosporine, and mycophenolate. The authors consider any of these to be appropriate adjunctive immunosuppressive medications, especially in dogs that do not respond within 5 to 7 days of initiating glucocorticoid treatment and in dogs that require more than two blood transfusions. Adjunctive immunosuppressive medications should also be used in dogs known to have a poor tolerance of the adverse effects of glucocorticoids (e.g., large-breed dogs) and in those with other poor prognostic indicators (e.g., intravascular hemolysis, serum bilirubin concentration greater than 8 to 10 mg/dL, persistent autoagglutination, Evans syndrome).

The adjunctive immunosuppressive medication should be initiated at a recommended dose to achieve appropriate suppression of immune cells, namely lymphocytes. Once the anemia is controlled, the adjunctive immunosuppressive medication is continued at the same dosage while the dose of prednisolone is tapered. The adjunctive medication can then be tapered once prednisolone has been discontinued. If a relapse occurs during tapering of the drugs, lifelong prednisolone, the adjunctive medication, or both are recommended at the lowest dose that controls hemolysis.

Azathioprine has the most evidence for its use in canine IMHA, though there is no evidence that its use improves response to treatment or survival. Azathioprine requires more regular monitoring of the CBC and hepatic enzymes due to the risk of bone marrow suppression and hepatotoxicity. Current recommendations are to reduce the frequency of administration of azathioprine to every other day after the first 2 weeks of daily administration to reduce the risk of toxicity.

Cyclosporine is being used with greater frequency for the treatment of canine IMHA. The cost of cyclosporine is a major deterrent to its use, and its potent immunosuppressive effects mandate frequent monitoring of the patient for secondary infections (bacterial, fungal, protozoal). The bioavailability of some cyclosporine formulations has been shown to be poor in dogs, making Atopica® the most appropriate formulation to use in veterinary patients. In a prospective study of 38 dogs with IMHA, no difference in survival was found between dogs treated with prednisone alone and those treated with prednisone and cyclosporine; however, most of the deaths occurred early, before the effects of cyclosporine had likely reached maximal effect. In a study to characterize the predominant inflammatory cytokines in canine IMHA, interleukin-2 (IL-2) was consistently increased in dogs with IMHA. This might suggest that cyclosporine has good potential for success, as the calcineurin inhibition leads to a decreased transcription of cytokines, primarily IL-2. Cyclosporine appears to be relatively safe in dogs with IMHA, and clinical experience suggests that it is useful and effective in the treatment of dogs with IMHA that do not respond to prednisolone or azathioprine. (For dosing and monitoring recommendations for cyclosporine, see Chapter 72 and Tables 72.3 and 72.4.)

Mycophenolate mofetil (MMF) has historically been used in refractory cases of IMHA and other immune-mediated diseases. The mechanism of MMF is similar to that of azathioprine. It was originally designed as an alternative to azathioprine in human transplant patients, due to fewer side effects. A retrospective evaluation of dogs with IMHA treated with prednisolone and mycophenolate reported dose-dependent gastrointestinal toxicity including severe hemorrhagic diarrhea. However, when used at recommended doses, mycophenolate is well tolerated in dogs. Mycophenolate is also available for intravenous administration, so it is a good option for patients unable/unwilling to take oral medications in the early stages of the disease.

There are anecdotal reports and a few retrospective case series reporting positive responses to treatment of canine IMHA with human intravenous immunoglobulin (hIVIG). In a controlled, blinded, prospective study of 28 dogs with IMHA, no benefit was evident when three doses of hIVIG

were administered together with glucocorticoids compared with prednisone alone. Cost is often a deterrent to using hIVIG, and there is potential for sensitization to human proteins, so caution is advised when administering more than one dose.

BLOOD TRANSFUSION

Most dogs and cats with acute, severe IMHA need oxygen-carrying support. Oxygen supplementation alone is of limited benefit. The need for blood transfusion depends on the severity, rate of onset and chronicity of the anemia, and the presence and severity of concurrent disease such as pulmonary thromboembolism and gastrointestinal blood loss. No specific hematocrit level should be used as a transfusion trigger; rather, each patient should be considered individually. In general, transfusion should be considered when the dog has problems with tachycardia, tachypnea, anorexia, lethargy, or weakness while at rest. Most dogs with acute IMHA and a hematocrit less than 15% have some degree of tissue hypoxia and will benefit from a blood transfusion regardless of how the dog appears clinically. Severe tissue hypoxia likely exacerbates the complications of IMHA, such as hepatic necrosis, DIC, and thromboembolism.

Transfusion of packed RBCs (pRBCs) is ideal; whole blood is acceptable but less ideal because the plasma component is not necessary and may increase the risk of a transfusion reaction. (See Chapter 82 for more information about blood transfusions.)

PREVENTION OF THROMBOEMBOLISM

The majority of dogs with IMHA are hypercoagulable on presentation as assessed by thromboelastrography (TEG), a viscoelastic assessment of coagulation, and some have evidence of DIC. Abnormalities of the hemostatic system that have been identified include prolongation of activated partial thromboplastin time (aPTT) and prothrombin time, increased D-dimer, increased fibrinogen degradation products (FDPs), decreased antithrombin (AT) concentration, and hyperfibrinogenemia.

Thromboembolic events (TEs) are a common complication and important cause of death in dogs with IMHA. TEs have been documented at necropsy in 29% to 100% of dogs with IMHA. Intravenous catheter placement and identification of certain clinicopathologic abnormalities, such as thrombocytopenia, hyperbilirubinemia, leukocytosis, and hypoalbuminemia, are associated with an increased risk of TE in dogs with IMHA. The pathogenesis of thrombus formation is unknown, and effective regimens for prophylaxis have not been established. Treatment options currently used for prevention of thromboembolic complications include heparin, low-molecular-weight heparin, aspirin, clopidogrel, or a combination of these modalities. The recommended starting dose for heparin in patients with IMHA is 200 to 300 U/kg subcutaneous (SC) q6h, and the dose is adjusted by measuring anti-Xa activity (0.35-0.7 U/mL) or, less ideally, monitoring the aPTT with the aim to prolong aPTT by 25% to 50% of baseline. An individually adjusted heparin dosing regimen for thromboprophylaxis based on measurement of anti-Xa activity is associated with a better outcome in dogs with IMHA rather than a fixed dose of 150 U/kg SC q6-8h heparin (Helmond et al., 2010). (For a discussion of the use of low-molecular-weight heparin, see Chapter 87.) Low-dose aspirin (0.5 mg/kg PO q24h) has also been used to prevent thromboembolic complications in dogs with IMHA. Weinkle et al. (2005) reported that dogs treated with a protocol that included prednisone, azathioprine, and low-dose aspirin had the longest survival times. Low-dose aspirin may not result in appropriate platelet inhibition in all dogs. Aspirin resistance was identified in 30% of dogs in one study, yet another 30% experienced only partial responsiveness to low-dose aspirin. Clopidogrel bisulfate is an inhibitor of the ADP receptor on platelets and is the gold standard for prevention of cardiogenic arterial thromboembolism in cats. Clopidogrel was compared with low-dose aspirin, prospectively, in a group of dogs with IMHA, and survival was similar between the two groups. (See Chapters 12 and 87 for more information on treatment and prevention of thromboembolism.)

SUPPORTIVE CARE

Aggressive supportive care is critical to a good outcome in dogs with IMHA. Identification and treatment of underlying disease, detection of complications associated with immunosuppressive drug therapy, and good nursing care positively influence outcome. In addition to transfusion, fluid therapy should be administered in dogs with evidence of dehydration to improve tissue perfusion. In dehydrated dogs, fluid therapy will decrease the measured hematocrit, but this does not change the total RBC mass. Fluid therapy should not be withheld because of fear of exacerbating anemia. In reality, fluid therapy reveals the true severity of the anemia.

Careful investigation and treatment of underlying disease in dogs with IMHA is important. Immunosuppressive therapy is usually still necessary in dogs with secondary IMHA. However, the duration of immunosuppression may be shorter if an underlying cause can be identified and treated. If an infectious disease is identified, addition of adjunctive immunosuppressive drugs should be avoided.

Complications of immunosuppressive drug therapy include bone marrow suppression, infection, gastrointestinal ulceration, and iatrogenic hyperadrenocorticism. Gastrointestinal hemorrhage can contribute to anemia in dogs with IMHA, either from the gastrointestinal effects of high doses of glucocorticoids or concurrent thrombocytopenia, vasculitis, ischemia, or other concurrent disease. Recognition of occult gastrointestinal hemorrhage is important because the resulting anemia may be confused with a failure to respond to treatment for IMHA (see Chapter 80). Drugs used for treatment of gastrointestinal hemorrhage include gastrointestinal protectants such as sucralfate, H_2 blockers (e.g., famotidine), and proton pump inhibitors (e.g., omeprazole).

Prognosis

In approximately 60% of dogs with IMHA, medications can ultimately be discontinued after a slow tapering of the

immunosuppressive drugs. The remaining dogs require long-term immunosuppressive therapy. Factors that clinically appear to confer a good prognosis in dogs with IMHA include a rapid response to treatment with glucocorticoids, ability to maintain the packed cell volume above 30% with glucocorticoids alone, and identification of a treatable secondary cause.

The prognosis is guarded in dogs that require multiple drugs to control the disease and those with persistent autoagglutination, azotemia, an elevated bilirubin concentration, marked thrombocytopenia, and severe leukocytosis. In a multicenter study, prognostic factors for canine IMHA were investigated, and a model using the presence of SIRS, bilirubin, urea, and creatinine concentrations, and ASA score was predictive of outcome in 80% of cases. In this model, bilirubin concentration and azotemia were independently associated with death. Reported mortality rates of dogs with primary IMHA range from 26% to 70%; thromboembolism is the cause of death in 30% to 60% of cases. Other common causes of death include infection due to immunosuppression, DIC, and failure to control anemia. Interestingly, patients that are hypercoagulable as assessed by TEG have a better prognosis than those that have normal coagulability; it has been proposed that, in these dogs, there is an underlying consumptive coagulopathy. If a major TE does occur in a dog with IMHA, particularly if the blood supply to a major organ is disrupted, the long-term prognosis is poor. Contrary to popular opinion, the prognosis in Cocker Spaniels with IMHA does not differ from that of other breeds.

FELINE IMMUNE-MEDIATED HEMOLYTIC ANEMIA

Cats with primary IMHA tend to be younger than dogs, with a median age of 2 years. Males are slightly overrepresented, with no influence of neuter status. Secondary causes for antierythrocyte antibody formation are identified more frequently in cats, with feline leukemia virus and *Mycoplasma haemofel*is being common infections associated with IMHA. Primary IMHA in cats is more likely to present with a nonregenerative anemia, accounting for about 50% of cases.

Most cats with IMHA respond to prednisolone alone, and the adverse effects of glucocorticoids are less severe. In cats that need an additional immunosuppressive drug to treat IMHA, treatment with chlorambucil, cyclosporine, or mycophenolate should be considered. Not enough published information exists to recommend one drug over another. *Azathioprine is not recommended in cats because of the risk of unacceptable adverse effects* (see Chapter 72). The authors typically use chlorambucil or cyclosporine in cats that need an additional immunosuppressive drug. There is an increased risk of diabetes mellitus in cats treated with glucocorticoids; in these cats a second immunosuppressive drug should be added to allow tapering and ultimately discontinuation of glucocorticoids.

PURE RED CELL APLASIA

PRCA is a rare disorder characterized by severe, nonregenerative anemia with marked depletion or absence of erythroid precursors in the bone marrow. In some cases, evidence of concurrent peripheral hemolysis is present on the basis of the presence of spherocytes and a positive direct Coombs test. Other cell lines are usually normal. The erythroid aplasia in PRCA is in contrast to the nonregenerative form of IMHA, in which there is erythroid hyperplasia or sometimes maturation arrest of the erythroid maturation sequence at the rubricyte or metarubricyte level. PRCA is likely one end of the spectrum of IMHA, with acute peripheral hemolysis at the other end of this spectrum (Table 73.4). The affinity of circulating antibody for different erythroid precursors likely influences the level at which damage occurs in the bone marrow. As with IMHA, both primary and secondary forms of PRCA are recognized. Secondary causes of PRCA include treatment with recombinant human erythropoietin and parvovirus infection in dogs. Infection with feline leukemia virus subtype C is a cause of PRCA in cats.

Dogs with PRCA have a similar signalment and present with similar clinical signs as dogs with IMHA. As is the case with primary IMHA, cats with primary PRCA are typically younger than dogs, with an age range of 8 months to 3 years. Dogs and cats with PRCA have severe, nonregenerative anemia, whereas the platelet count and leukogram are typically normal. In contrast to IMHA, the biochemical panel and urinalysis are also usually unremarkable, with no evidence of peripheral hemolysis or inflammation. Low numbers of spherocytes are sometimes present in dogs with PRCA. The Coombs test is usually negative.

Diagnosis of PRCA is made by evaluation of a bone marrow aspirate and bone marrow core biopsy. In PRCA, erythroid precursors are rare or absent and the M/E ratio is high (>99:1). In contrast to nonregenerative IMHA, severe myelofibrosis is rare.

Treatment of PRCA is similar to IMHA. In the authors' experience, most dogs with PRCA respond to prednisolone alone; however, other drugs are commonly added to the treatment protocol because of the length of time it takes to see a response in some dogs. Adjunctive immunosuppressive medications have been used with success in dogs that have an incomplete response to prednisolone alone. These adjunctive medications include azathioprine, cyclophosphamide, cyclosporine, and mycophenolate. The time taken to achieve complete remission (2-6 months) is longer in dogs with PRCA compared with IMHA, and it is sometimes difficult to judge whether a particular protocol is failing or whether inadequate time has been allowed for the bone marrow to respond to treatment and begin to produce and release RBCs into the circulation. Sequential bone marrow evaluations should ideally be used to determine when to change the treatment protocol. A repeat bone marrow aspirate should be considered after 2 months of treatment if no improvement in the anemia is observed. Repeated transfusion of pRBCs or whole blood is necessary while waiting for a response to

TABLE 73.4

Comparison of Regenerative IMHA, Nonregenerative IMHA, and PRCA in Dogs

	RATE OF DECREASE OF HEMATOCRIT	RETICULOCYTE COUNT	COOMBS TEST (% POSITIVE)	EVIDENCE OF INFLAMMATION ON CBC	THROMBOCYTOPENIA	BONE MARROW EVALUATION
Regenerative hemolytic anemia	Fast	High	60%-80%	Severe inflammatory leukogram in most dogs	Yes (60%)	Erythroid hyperplasia, myelofibrosis in some cases
Nonregenerative anemia	Variable	Low	57%	Mild inflammation in 50% of dogs only	Rare	Erythroid hyperplasia, myelofibrosis common
PRCA	Slow	Low	Rarely positive	No	No	Erythroid hypoplasia, myelofibrosis uncommon

CBC, Complete blood count; *IMHA,* immune-mediated hemolytic anemia; *PRCA,* pure red cell aplasia.

treatment. Dogs with PRCA do not typically have evidence of systemic inflammation and are not at increased risk of TE, so anticoagulant treatment is not indicated. The prognosis for PRCA in dogs is better than for IMHA, with a mortality of less than 20%. The major cause of death is euthanasia because of the high cost of supportive care. Response to treatment and mortality rates in cats with PRCA appears to be similar to dogs, although cats respond to treatment more quickly (1.5-5 weeks) and are more likely to relapse if treatment is discontinued. Cyclophosphamide and cyclosporine have been used in cats that do not respond to glucocorticoids alone. See Chapter 80 for additional information on PRCA.

IDIOPATHIC APLASTIC ANEMIA

Aplastic anemia (aplastic pancytopenia) is characterized by cytopenia of all three marrow-derived cell lines and a hypocellular/acellular bone marrow, with the marrow elements replaced by adipose tissue. Reported causes of aplastic anemia in dogs and cats include infectious agents (*Ehrlichia* spp., parvovirus, sepsis, feline leukemia virus, feline immunodeficiency virus); hormonal (estrogens); drug associated; radiation associated; and idiopathic. By definition, the cause of idiopathic aplastic anemia is unknown; however, evidence in humans suggests that it may be immune mediated. Although an immune-mediated cause has not been established for idiopathic aplastic anemia in dogs and cats, trial therapy with prednisone, cyclosporine, or both may be considered once other causes of aplastic anemia, most notably infectious agents, have been ruled out. An immune-mediated cause for idiopathic anemia is currently difficult to prove but should be suspected in cases that respond to immunosuppressive therapy. The prognosis for idiopathic aplastic anemia is generally guarded to poor. See Chapter 86 for more information on this topic.

IMMUNE-MEDIATED THROMBOCYTOPENIA

Classification/Etiology

Immune-mediated thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) is a clinical syndrome in which thrombocytopenia results from antibody-mediated accelerated destruction of platelets. Immune-mediated thrombocytopenia is diagnosed in approximately 5% of cases of thrombocytopenia and is the most common cause of severe thrombocytopenia in dogs (Table 73.5). In primary thrombocytopenia (true autoimmune thrombocytopenia), antibodies are directed against platelet antigens, presumably because of an underlying defect in immune regulation. Antibodies directed against platelet membrane glycoproteins IIb/IIIa have been identified as target antigens in dogs, although others may be important as well. Primary ITP is a common cause of thrombocytopenia in dogs but is rare in cats. Environmental factors suspected to precipitate ITP in some cases include stress, changes in environmental temperature, hormonal changes, vaccination, and surgery. A recent retrospective study of 48 dogs with immune mediated thrombocytopenia was unable to document a temporal association between vaccination and development of thrombocytopenia.

In secondary ITP, antibody-mediated platelet destruction occurs as a result of an underlying inflammatory or neoplastic disease. Causes of secondary immune-mediated thrombocytopenia in dogs and cats are listed in Table 73.5. Immune-mediated thrombocytopenia may be a component of SLE and may occur in conjunction with IMHA (Evans syndrome).

Clinical Features

Dogs with primary ITP range in age from 8 months to 15 years, with a median age of 6 years. Females are affected twice as often as males; although any breed can be affected, the Cocker Spaniel, Poodle (all varieties), German Shepherd dog, and Old English Sheepdog are overrepresented. Common findings include sudden onset of petechial and ecchymotic hemorrhages in the skin and mucous membranes, epistaxis, hematochezia, hematemesis, easy bruising, lethargy, weakness, and anorexia. Additional findings on physical examination may include evidence of melena or hematochezia, hematuria, hyphema, retinal hemorrhage, and pale mucous membranes (Fig. 73.4). Neurologic signs and blindness may occur from bleeding into the central nervous system (CNS) and eye, respectively. Because rapid-onset, life-threatening hemorrhage is rare in dogs with ITP, anemia is usually initially mild and slowly progressive unless IMHA is concurrent. As affected dogs become moderately to severely anemic, lethargy, exercise intolerance, tachypnea, tachycardia, and a heart murmur may develop. In some dogs with ITP, clinical signs of hemorrhage are not present and thrombocytopenia is an incidental finding on a CBC performed for another reason. The platelets present in dogs with ITP are often larger and may be hemostatically more competent, which may explain why not all dogs with severe ITP bleed spontaneously. Platelet dysfunction (impaired aggregation) has been documented in normal canine platelets after incubation with serum from dogs with ITP, suggesting that antibodies or other factors in the serum impair platelet function in some dogs with ITP. Certain breeds such as the Greyhound are known to have lower platelet counts than other dogs and do not appear to have increased risk of bleeding. Macrothrombocytopenia is a disorder associated with low platelet counts and increased mean platelet volume (MPV) reported to be caused by a β1-tubulin mutation in Cavalier King Charles Spaniels; platelet counts as low as 30,000/μL have been reported in otherwise healthy dogs. Similar conditions have been reported in other breeds such as the Norfolk Terrier. Affected dogs do not have a bleeding diathesis, and treatment is not required.

Diagnosis

Because ITP can occur in association with many other disorders (see Table 73.5 and Chapter 86), a diagnosis of

TABLE 73.5

Causes of Thrombocytopenia in Dogs and Cats

CAUSE	MECHANISM	DOGS	CATS
Immune-mediated disease	Antibody mediated	Primary ITP Secondary ITP	Secondary ITP Primary ITP
Neoplasia	Antibody mediated Bone marrow suppression Myelophthisis	Lymphoma Hemangiosarcoma Leukemia Malignant histiocytosis Histiocytic sarcoma Unclassified carcinoma/sarcoma Many others	Lymphoma Leukemia Hemangiosarcoma Many others
Infection	Antibody mediated Bone marrow suppression Myelophthisis	*Ehrlichia canis* *Anaplasma phagocytophilum* *Anaplasma platys* Rocky Mountain spotted fever Bartonellosis *Dirofilaria immitis* *Angiostrongylus vasorum* Distemper virus infection Bacteremia/sepsis Babesiosis Borrelia Leishmaniasis Leptospirosis	Feline leukemia virus Feline immunodeficiency virus Feline infectious peritonitis virus Feline panleukopenia virus Toxoplasmosis
Exposure to drugs, vaccines, or toxins	Antibody mediated Bone marrow suppression Idiosyncratic	Antibiotics (trimethoprim/sulfadiazine, etc.) Phenobarbital Primidone Gold salts (auranofin)	Griseofulvin Methimazole Propylthiouracil Albendazole Chloramphenicol
Disseminated intravascular coagulation	Platelet utilization	Neoplasia Hepatic disease Infection Pancreatitis	Neoplasia Hepatic disease Infection Pancreatitis
Inherited macrothrombocytopenia (macrothrombocytosis)	β1-tubulin mutation in Cavalier King Charles Spaniel	Cavalier King Charles Spaniel Norfolk Terrier Beagle	Not reported

ITP, Immune-mediated thrombocytopenia.

primary ITP can only be made by ruling out other causes of thrombocytopenia. In primary ITP, thrombocytopenia is usually severe (<50,000 platelets/μL). Dogs with ITP confirmed by the presence of platelet-bound antibody have lower platelet counts than dogs with non–immune-mediated thrombocytopenia, and dogs with primary ITP have lower platelet counts than those with secondary ITP. Platelet fragments (microthrombocytosis) may be identified on blood smears and are caused by immune injury or because larger platelets are preferentially removed from circulation. Platelet fragments are considered to be a specific but insensitive indication of immune platelet destruction. The presence of large platelets on the blood smear has been reported to support the presence of increased bone marrow production of platelets, but this is not specific for a regenerative response because bone marrow injury may also cause enlarged platelets. Paradoxically a recent study reported that MPV in dogs with primary ITP is lower than MPV in other causes of thrombocytopenia. Potential explanations for this finding may be that large platelets with a higher density of bound antibody are more likely to be destroyed; large platelets may also be preferentially removed from circulation because they are more active and adherent. The presence of platelet fragments (microparticles) may falsely decrease the MPV.

Diagnosis of ITP is confirmed by ruling out other causes of severe thrombocytopenia (see Table 73.5 and Chapter 86). Spurious thrombocytopenia from platelet clumping, other technical problems, and breed-related thrombocytopenia should be considered in dogs that do not have clinical signs of bleeding. In dogs with thrombocytopenia,



FIG 73.4
Photographs of three dogs with immune-mediated thrombocytopenia and ecchymotic hemorrhage. **(A)** Note the ecchymotic hemorrhages in the skin of the abdomen. **(B)** Note the hemorrhage into the anterior chamber of the eye. **(C)** Note petechial hemorrhage in the oral mucous membranes.

examination of a bone marrow aspirate is the most reliable method for differentiating lack of platelet production from increased platelet consumption or destruction. A bone marrow evaluation should ideally be performed early in the diagnostic workup of cases with severe thrombocytopenia (<20,000/μL) and evidence of other hematologic abnormalities, especially other cytopenias. In these cases, evaluation of bone marrow is helpful to rule out disorders such as myelophthisis, neoplasia, megakaryocytic aplasia, and aplastic anemia (see Chapter 86). Megakaryocytic aplasia is a rare disorder in which aplasia of the megakaryocytic cell line results in severe thrombocytopenia. This disease may be a primary immune-mediated disease or secondary to infections such as *Ehrlichia canis* and *Borrelia burgdorferi*. Immune-mediated megakaryocytic aplasia will look similar to primary immune-mediated thrombocytopenia on presentation but has a more severe clinical course and a poorer prognosis. Bone marrow aspiration and biopsy can be safely performed even in severely thrombocytopenic dogs because hemorrhage can be controlled with local pressure. In most dogs with ITP, normal to increased numbers of megakaryocytes are present on a bone marrow aspirate. Decreased numbers of megakaryocytes in the bone marrow have been associated with a poorer prognosis in dogs with ITP. In dogs with severe thrombocytopenia (<20,000/μL) and no evidence of other hematologic abnormalities, the results of a bone marrow examination rarely reveal nonmegakaryocytic bone marrow abnormalities or result in a definitive diagnosis, so this procedure has a relatively low diagnostic yield in this subset of patients.

The presence of a positive assay for platelet-bound antibody (see Chapter 71) is highly sensitive but not specific for a diagnosis of ITP. A diagnosis of ITP is unlikely if the test result is negative. Prior immunosuppressive therapy may result in a negative test. A positive test result is not specific for ITP because immune-mediated mechanisms are responsible for many causes of thrombocytopenia in dogs, including thrombocytopenia due to neoplasia, inflammation, drug reactions, and infectious causes. In summary the diagnostic approach to a dog with suspected ITP includes a thorough history and physical examination; a minimum database (CBC, serum biochemical profile, urinalysis); evaluation of coagulation status (platelet count, aPTT, partial thromboplastin time [PTT], FDPs); diagnostic imaging (thoracic radiographs, abdominal ultrasound); infectious disease titers (depending on geographic location); plus or minus bone marrow cytology; and histopathology. Although the majority of cases of ITP will have megakaryocytic hyperplasia, the rare case of megakaryocytic aplasia or hypoplasia can only be diagnosed by examination of the bone marrow; if a bone marrow examination is not performed at the time of diagnosis, it should definitely be performed in any dog with suspected ITP that does not respond to routine immunosuppressive treatment.

IMMUNOSUPPRESSION

Treatment

Immunosuppressive drugs are the key to treating ITP; however, because results of serology for infectious causes of immune-mediated thrombocytopenia may be delayed, concurrent treatment with doxycycline is often initiated with immunosuppressive drugs. High doses of corticosteroids block macrophage-mediated destruction of platelets and are the first line of treatment. Prednisolone or prednisone at a dose of 2-4 mg/kg/day PO is the corticosteroid of choice. Dexamethasone (0.25-0.6 mg/kg intravenous [IV] q24h) is an acceptable alternative in dogs that do not tolerate oral glucocorticoids. Treatment with one dose of vincristine (0.02 mg/kg IV) should be considered early in the course of treatment for dogs with severe ITP (platelet count < 15,000/μL) or those showing evidence of active hemorrhage. Dogs treated with vincristine have a more rapid increase in platelet count and shortened duration of hospitalization compared with untreated dogs (see Chapter 72).

A prospective study in 18 dogs with ITP demonstrated that adjunctive treatment with hIVIG shortens platelet recovery time compared with treatment with glucocorticoids alone. In another prospective study comparing platelet recovery times in dogs treated with hIVIG versus vincristine as adjunctive therapy for ITP, recovery times were similar for dogs treated with hIVIG compared with vincristine. Because hIVIG is much more expensive than vincristine, its use in dogs with ITP should be limited to patients that fail to respond to glucocorticoids and vincristine. The median platelet recovery time in dogs treated with prednisone and either vincristine or hIVIG is 3 days (range 1-10 days). Once the platelet count is in the reference range, the dose of prednisone can be slowly tapered. Because of the risk of relapse, the dose should not be tapered more rapidly than 20% to 30% per month over a 3- to 6-month period. If after 6 months the prednisone dose has been tapered to a low every-other-day dose and the disease is in remission, discontinuation of medication should be attempted.

In dogs that do not respond to glucocorticoids and vincristine, bone marrow aspiration cytology and biopsy should be performed, if not already done, to rule out megakaryocytic hypoplasia, which has a much poorer prognosis. Adjunctive immunosuppressive medications should be considered in dogs that do not have an adequate response to prednisone alone (platelet count <100,000 per μL) or when the dose of prednisone cannot be decreased low enough to manage the adverse effects of glucocorticoids. Azathioprine, cyclosporine, and mycophenolate have all been described as appropriate adjunctive immunosuppressive medications for dogs with ITP. At the authors' institution, azathioprine and mycophenolate are used most commonly as adjunctive immunosuppressive medications for dogs with ITP. In a recent study, survival of dogs on prednisolone and cyclosporine was similar to that of dogs receiving prednisolone and mycophenolate, but the cost of therapy and side effects were fewer in the dogs receiving mycophenolate. If the adjunctive immunosuppressive medication is tolerated, it should be continued at an unchanged dose while the prednisone is being tapered. Once the prednisone has been discontinued, the adjunctive medication is then tapered slowly. If a relapse occurs, lifelong therapy with prednisone and/or the adjunctive immunosuppressive medications should be continued at the lowest dose that maintains the platelet count within the reference range. A platelet count should be performed before and 2 weeks after any change in immunosuppressive therapy. In some dogs with ITP, maintaining the platelet count within the reference range is not possible without incurring severe glucocorticoid side effects. In these dogs, maintaining the platelet count greater than 100,000 per μL is acceptable because this degree of thrombocytopenia does not cause increased risk of bleeding. Splenectomy may be indicated in dogs with ITP that have chronic relapses while tapering prednisone and azathioprine therapy (see Chapter 72).

SUPPORTIVE CARE

Supportive care for dogs with ITP is critical to a positive outcome. Cage rest and exercise restriction to prevent trauma, minimizing venipuncture, and eliminating all except absolutely necessary diagnostic procedures decrease risk of hemorrhage. A balance between appropriate monitoring and minimizing blood collection is important. Patients should be frequently monitored for development of clinical signs that could be the result of new hemorrhage, especially evidence of neurologic or ophthalmologic bleeding. Patients with clinically relevant anemia and those that are actively bleeding require blood transfusion. Blood products that provide clinically significant platelet activity are fresh whole blood, platelet-rich plasma, platelet concentrate, and frozen platelet concentrate (see Chapter 82). Platelet-rich plasma or platelet concentrates are the ideal products for administration to actively bleeding patients before they become anemic; however, availability and cost limit their use in most hospitals. In the authors' experience fresh whole blood often provides enough platelets to stop an episode of clinical bleeding, although a measurable increase in the platelet count is not expected. The authors have found that the beneficial effect of a fresh whole blood transfusion typically lasts approximately 48 hours. Blood typing of the donor and crossmatching of the recipient should be performed as described in Chapter 82. Administration of gastric protectants such as H_2 blockers (e.g., famotidine) or proton pump inhibitors (e.g., omeprazole) and sucralfate may help prevent adverse effects of glucocorticoid treatment on the gastrointestinal tract, especially in dogs with gastrointestinal bleeding. Administration of desmopressin (1 μg/kg SC q24h for 3 doses) was associated with control of spontaneous bleeding and increased platelet counts in three dogs with secondary immune-mediated thrombocytopenia. This approach requires further study.

Evans syndrome (concurrent IMHA and ITP) should be treated aggressively by starting glucocorticoids and an

adjunctive immunosuppressive medication concurrently. One dose of vincristine should be considered if the thrombocytopenia is severe (platelet count < 15,000/μL). Whole blood transfusion rather than pRBCs should be administered in dogs with Evans syndrome that are actively bleeding. Dogs with Evans syndrome should not be treated with heparin because of the risk of exacerbating hemorrhage due to thrombocytopenia.

Prognosis

The prognosis for dogs with ITP is good to guarded, with a short-term survival rate of 74% to 93%. Most dogs respond to medical treatment, although relapse occurs in 9% to 58% of dogs as drug dosages are reduced. Dogs with megakaryocytic hypoplasia have a poor prognosis. The prognosis for dogs with concurrent IMHA and ITP is also poor, with reported mortality rates as high as 80%, although in one study, mortality in dogs with Evans syndrome was similar to that of dogs with IMHA alone. See Chapter 82 for more information on this topic.

FELINE IMMUNE-MEDIATED THROMBOCYTOPENIA

Most cats with thrombocytopenia have an underlying cause identified, and primary feline immune-mediated thrombocytopenia is an extremely rare disorder. The clinical presentation and response to treatment is similar to that of dogs. Spontaneous bleeding due to thrombocytopenia is less common. In the rare cases that do not respond to glucocorticoids alone, chlorambucil is recommended as an adjunctive immunosuppressant. Practitioners should be aware that platelet clumping leading to marked pseudothrombocytopenia (i.e., <30,000/μL) is more common in cats than in dogs, so a blood smear for semiquantitative platelet estimation or a platelet count performed in citrate or heparin tubes should always be evaluated in asymptomatic thrombocytopenic cats.

IMMUNE-MEDIATED NEUTROPENIA

Etiology

Immune-mediated neutropenia (IMN) is rare in dogs and cats, accounting for approximately 0.4% of cases of neutropenia (see Chapter 85). In IMN (also called *idiopathic neutropenia* or *steroid-responsive neutropenia*), serum antineutrophil IgG antibodies can be detected by flow cytometry in the serum. Antibody and complement directed against myeloid cells within the bone marrow have also been identified; however, because these tests are rarely done, the term is primarily used for dogs and cats with "idiopathic" neutropenia that responds to steroids. As with other immune-mediated disorders, IMN may be a primary disorder or may occur secondary to drug therapy, neoplasia, or other immune-mediated disorder (Table 73.6). The majority of canine cases reported in the literature have been primary. Only one case of suspected IMN in a cat has been reported.

TABLE 73.6

Causes of Severe Neutropenia in Dogs and Cats

ETIOLOGY	EXAMPLE
Infection	Parvovirus, ehrlichiosis, bacterial sepsis
Drug associated	Chemotherapeutic agents, cytotoxic drugs, vincristine, estrogens, trimethoprim/sulfadiazine, phenobarbital
Bone marrow suppression	Aplastic anemia, *Ehrlichia canis* infection, myelodysplasia, myeloid hypoplasia, leukemia
Immune mediated	Primary immune-mediated neutropenia

Clinical Features

In the largest retrospective report of 35 dogs with suspected IMN, a variety of breeds were represented and 22/35 cases were female. Affected dogs were typically young, with a median age of 5 years. Clinical signs included fever, lameness, anorexia, and lethargy, and the duration of clinical signs ranged from 3 to 180 days. Common abnormalities detected on CBC, serum biochemistry panel, and urinalysis included severe neutropenia (median 110 cells/μL), thrombocytopenia, mild anemia, hyperglobulinemia, and increased alkaline phosphatase activity. It has been proposed that up to 25% of dogs diagnosed with IMN have concurrent ITP. In the large retrospective study, 25% of dogs had thrombocytopenia, with 14% having platelet counts of <99,000/μL. Further evaluation of affected dogs with bacterial culture, infectious disease serology, and imaging did not reveal a cause for the neutropenia. Bone marrow cytology and histopathology revealed myeloid hyperplasia in two thirds of affected dogs and myeloid hypoplasia in the other one third of dogs, with maturation arrest identified in 20%.

Diagnosis and Treatment

A clinical diagnosis of IMN is made by exclusion of other causes of neutropenia. Additionally, antineutrophil antibodies can be detected by flow cytometry. Blood samples can be submitted to the University of Tennessee Diagnostic Immunology Laboratory (UTCVM Immunology Service, 2407 River Dr, Knoxville, TN 37996; immunology@utk.edu). Presumptive diagnosis may be made by rapid response to treatment with glucocorticoids at an initial dose of 2-4 mg/kg/day of oral prednisone. In dogs who do not initially respond to prednisone or those who relapse during prednisone tapering, addition of an adjunctive immunosuppressive medication is appropriate. Azathioprine and cyclosporine have been described for the treatment of IMN. Gradual withdrawal of corticosteroid therapy is conducted in a similar way as described for IMHA and ITP. Some dogs require long-term immunosuppression. Routine monitoring is important to

detect recurrence of neutropenia and monitor for infection. See Chapter 85 for more information on this topic.

POLYARTHRITIS

Etiology

Immune-mediated polyarthritis is defined as chronic synovial inflammation in two or more joints, failure to isolate an organism from the joint fluid, and a positive response to immunosuppressive therapy. Immune-mediated polyarthritis is primarily a type III immune complex hypersensitivity disorder (see Chapter 70) in which immune complexes are deposited in the synovial membrane, initiating local inflammation and release of proteolytic enzymes and cytokines, with resultant cartilage degeneration. In rheumatoid arthritis, type IV hypersensitivity may also be present with perivascular infiltration of mononuclear cells into the synovial membrane (see Chapter 70). Immune-mediated polyarthritis may be classified as primary or secondary. In secondary polyarthritis, immune complex deposition in the joints is secondary to an underlying inflammatory or neoplastic disease. Infectious agents are an important cause of secondary polyarthritis. Chronic bacterial infections may cause secondary or reactive polyarthritis, and *Anaplasma* spp., *Ehrlichia* spp., and *B. burgdorferi* also cause polyarthritis, although they cannot usually be visualized in or cultured from affected joints. Administration of live calicivirus vaccine also causes transient polyarthritis in cats.

In primary immune-mediated polyarthritis, no underlying cause of polyarthritis can be identified. This form of polyarthritis is believed to be attributable to an underlying immune system dysfunction or imbalance (true autoimmunity).

The most commonly recognized forms of polyarthritis in the dog and cat are idiopathic nonerosive polyarthritis; reactive nonerosive polyarthritis secondary to underlying inflammatory disease (gastrointestinal disease, chronic inflammation, neoplasia, or infection); and rheumatoid arthritis. A number of breed-specific syndromes are also recognized in dogs (Table 73.7). Nonerosive polyarthritis is also one of the most common clinical signs in dogs with SLE. See Chapter 69 for a more detailed discussion of the various forms of polyarthritis.

Clinical Features

The clinical hallmark of immune-mediated polyarthritis is the presence of nonseptic inflammation within the synovial membrane of two or more joints. Consequently, the diagnosis is made by analysis of synovial fluid collected from joints suspected to be affected. Common clinical signs are listed in Box 73.5. In some cases, neurologic disease is initially suspected because the animal is unable to ambulate; however, the neurologic examination in dogs with polyarthritis is normal. Many dogs and cats with polyarthritis have clinical signs of systemic illness, including fever, anorexia, and lethargy. In some cases, joint pain and swelling may be mild or not clinically detected, and fever is the only clinical sign. Polyarthritis is one of the most common causes

TABLE 73.7

Forms of Polyarthritis Recognized in Dogs and Cats

SYNDROME	CLINICAL MANIFESTATIONS	BREED PREDISPOSITION
Idiopathic nonerosive	Small distal joints	Large-breed dogs, rarely cats
Secondary nonerosive	Similar to idiopathic but clinical signs of underlying disease also present	Any breed
Breed-specific idiopathic nonerosive	Similar to idiopathic but more severe and often concurrent meningeal inflammation	Akitas, Weimaraners, Newfoundlands
Familial Shar-Pei fever	Recurrent fever, soft tissue swelling around affected joints, predisposition to systemic amyloidosis	Shar Peis
Lymphoplasmacytic synovitis	No sign of systemic illness, cranial cruciate rupture, lymphocytes and plasma cells in synovial fluid	Rottweilers, Labrador Retrievers, Newfoundlands, Staffordshire Terriers
SLE	Multisystemic immune disease	German Shepherd dogs, rarely cats
Rheumatoid arthritis	Initially similar to nonerosive form but progresses to joint crepitus, laxity, luxation, and deformity of affected joints (carpi, hocks, phalanges)	Small and toy breeds, rarely cats
Erosive polyarthritis of Greyhounds	Erosive changes in phalanges, carpi, hocks, elbow, stifles; lymphoplasmacytic inflammation in synovial fluid	Young Greyhounds

SLE, Systemic lupus erythematosus.

BOX 73.5

Clinical Signs of Polyarthritis in Dogs and Cats

Dogs

Palpable joint swelling
Distention of joint capsule
Shifting leg lameness
Unwillingness to rise
Hesitant or "walking on eggshells" gait
Joint pain
Fever
Anorexia
Lethargy
Cervical pain

Cats

Palpable joint swelling
Distention of joint capsule
Joint pain
Fever
Anorexia
Lethargy
Generalized hyperesthesia
Decreased activity/hiding

of unexplained fever in dogs. Joint pain from polyarthritis may also cause cervical pain, and concurrent meningeal inflammation has been reported in dogs with polyarthritis. Polyarthritis should therefore be considered in any dog or cat presenting with cervical pain without neurologic deficits. Cats with polyarthritis may appear to have generalized hyperesthesia and be resistant to handling. Cats may also present for decreased activity, and the owners often note that the animal has become withdrawn, often hiding in inaccessible locations. In the less-common erosive forms of polyarthritis, affected joints may become distorted or collapsed as the disease progresses, resulting in a severe gait abnormality. These changes are typically irreversible.

Diagnosis

Diagnosis of immune-mediated polyarthritis is made by documentation of inflammation within the synovial fluid, synovial membrane, or both (Fig. 73.5). Synovial fluid for cytologic evaluation and culture should be collected from at least three and preferably four joints. Synovial fluid should be collected from the more distal joints (carpus, tarsus, stifle) because these are the most commonly affected. The approach to joint fluid collection is discussed in Chapter 68. Joint fluid may be grossly turbid, with decreased viscosity and increased volume. Cytologic evaluation reveals neutrophilic and/or lymphocytic inflammation with no evidence of sepsis. Fluid should always be collected for bacterial culture and sensitivity to rule out an occult infection (especially likely if the animal has been previously treated with antibiotics). Once inflammation within multiple joints has been documented, the next step is to identify the type of polyarthritis

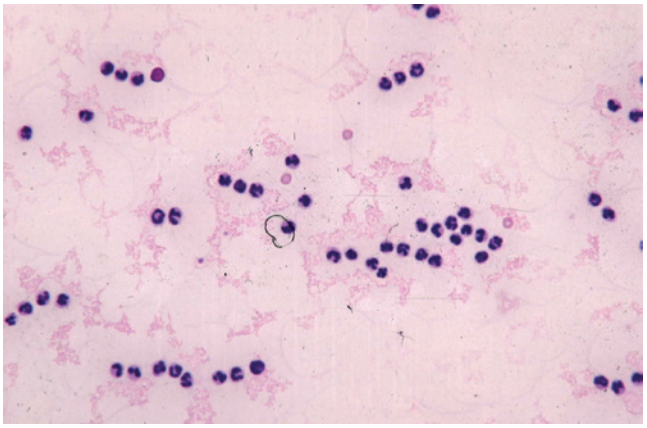


FIG 73.5
Direct smear of synovial fluid from a dog with idiopathic immune-mediated polyarthritis. Note the presence of increased numbers of nondegenerate neutrophils.

(see Table 73.7) and whether it is from a primary autoimmune disease or secondary to underlying inflammation, infection, or neoplasia. Diagnostic tests should include a CBC, biochemistry profile, urinalysis, urine culture, thoracic radiographs, abdominal ultrasound, and infectious disease titers or SNAP test *(E. canis, Anaplasma phagocytophilum, Anaplasma platys, Ehrlichia ewingii, Ehrlichia chaffeensis, B. burgdorferi)* (SNAP 4DX Plus, IDEXX, Westbrook, Maine). Because polyarthritis is usually a component of the acute form of ehrlichiosis or anaplasmosis, affected dogs may have negative SNAP results; convalescing test results (i.e., 10-14 days later) are usually positive in those patients. In some cases, blood cultures may also be indicated. In suspected erosive arthritis, radiographs of the joints are useful to assess severity of joint destruction. In dogs with suspected rheumatoid arthritis, a rheumatoid factor test should be performed (see Chapter 68). In dogs and cats with evidence of multiple organ involvement, an antinuclear antibody (ANA) titer is indicated to investigate for SLE (see Chapter 71). C-reactive protein (CRP), a positive acute phase protein and nonspecific marker of inflammation, has been shown to be increased in dogs with immune-mediated polyarthritis. CRP should not be used to diagnose IMPA but may be useful to monitor response to therapy in lieu of repeat arthrocentesis.

Treatment

Treatment of secondary immune-mediated polyarthritis depends on identification of an underlying cause. Secondary polyarthritis usually resolves with appropriate treatment and use of antiinflammatory doses of glucocorticoids or nonsteroidal antiinflammatory drugs. In areas endemic for infectious causes of polyarthritis (see previous discussion), empirical treatment with doxycycline should be instituted while awaiting the results of preliminary diagnostic testing for infectious agents. Dogs with infectious causes of polyarthritis typically show rapid clinical improvement after treatment with appropriate antibiotics.

In dogs with primary (autoimmune) polyarthritis, immunosuppressive dosages of prednisone/prednisolone are the initial treatment of choice (2-4 mg/kg/day PO). More aggressive immunosuppression is usually necessary in polyarthritis associated with SLE, in the breed-specific polyarthritis of Akitas, and in rheumatoid arthritis. Due to the fact that long-term glucocorticoid therapy can have deleterious effects on the musculoskeletal system (e.g., muscle atrophy, ligamentous laxity), several studies have investigated treating IMHA with nonglucocorticoid immunosuppression. Cyclosporine and leflunomide have both shown success in small studies as monotherapy for canine IMPA. Remission rates were similar when compared with treatment with prednisone, but clinical signs improved more slowly. Nonsteroidal antiinflammatory drugs can be added to address pain and inflammation while waiting for the onset of immune suppression when relying on nonglucocorticoid immunosuppressive medications.

Response to treatment should be monitored by assessment of clinical signs and cytologic changes within the joint fluid. Joint fluid should be cytologically normal before tapering immunosuppressive therapy. Failure to establish cytologic remission in addition to clinical remission may result in disease relapse or progressive injury to the joints that ultimately results in degenerative joint disease. Approximately 80% of dogs with idiopathic nonerosive polyarthritis treated with prednisone alone respond well to initial treatment, and half of these dogs can be weaned off therapy after 3 to 4 months. The prognosis for idiopathic nonerosive polyarthritis is good, with a mortality/euthanasia rate of less than 20%. Relapses are common, however, and some dogs require lifelong therapy. The prognosis for other forms of immune-mediated polyarthritis varies with the different forms of the disease. See Chapters 68 and 69 for more information on this topic.

SYSTEMIC LUPUS ERYTHEMATOSUS

Etiology

SLE is a multisystemic immune disorder in which antibodies to specific tissue proteins (type II hypersensitivity) and immune complex deposition (type III hypersensitivity) result in immune-mediated damage to multiple organs. Type IV mechanisms (delayed hypersensitivity) may also contribute to tissue damage. The underlying cause of SLE is still poorly understood, but an increased CD4/CD8 ratio, increased expression of a T-cell activation marker, and marked lymphopenia have been reported in dogs with active disease. These findings suggest that T-suppressor cells may be defective in dogs with SLE. The disease is heritable, although not by simple autosomal mechanisms. Breeds that are predisposed include the German Shepherd dog, Shetland Sheepdog, Collie, Beagle, and Poodle. Several colonies of dogs with a high predisposition toward SLE have been established, and an association with certain major histocompatibility complex (MHC) (dog leukocyte antigen [DLA]) types exists. Other risk factors likely include environmental factors and exposure to certain infectious agents and drugs.

Clinical Features

The disease is uncommon in dogs and rare in cats. In dogs SLE most commonly occurs in middle-aged dogs (age range, 1-11 years), and there is no sex predisposition. Because any organ system may be affected in SLE, a wide range of clinical signs is possible. The most common signs are fever (100%), lameness or joint swelling due to nonerosive polyarthritis (91%), dermatologic manifestations (60%), and signs of renal failure such as weight loss, vomiting, polyuria, and polydipsia. Proteinuria from glomerulonephritis (GN) is detected in 65% of patients. The dermatologic lesions often involve areas of skin exposed to sunlight; photosensitization is common. The dermatologic manifestations are highly variable and may include alopecia, erythema, ulceration, crusting, and hyperkeratosis. Mucocutaneous lesions may also occur. Other possible clinical manifestations of SLE are hemolytic anemia, PRCA, thrombocytopenia, leukopenia, myositis, pleuropericarditis, laryngeal paralysis, and CNS dysfunction. A similar spectrum of disease manifestations has been reported in cats with SLE, with dermatologic lesions being the most common. SLE typically has a relapsing and remitting course, and different organ systems may be involved with subsequent relapses. For example, a dog initially presenting with clinical signs predominantly relating to the neuromuscular system (polyarthritis or myositis) may later relapse with signs of IMHA or ITP.

Diagnosis

A diagnosis of SLE should be suspected when evidence of involvement of more than one organ system is present in a dog or cat with immune-mediated disease. Because of the large number of organ systems that may be involved, the diagnostic testing required varies widely from patient to patient. Diagnostic tests that should be performed in all dogs and cats with suspected SLE include a CBC, serum biochemical profile, urinalysis, urine protein quantification (provided the urine sediment is inactive), collection of synovial fluid for cytology and culture, and fundic examination. Additional tests that may be indicated include thoracic and abdominal radiographs (investigating fever); abdominal ultrasonography (investigating renal dysfunction); infectious disease titers (investigating fever, thrombocytopenia, hemolytic or nonregenerative anemia, proteinuria, or polyarthritis); Coombs test (in patients with hemolytic anemia); bone marrow aspirate and core (in cases of cytopenia); and skin or kidney biopsy if dermatologic or renal lesions are present. The extent of diagnostic testing for infectious disease will depend on the species and geographic location. For example, testing for feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis should be considered in any cat with suspected SLE. In dogs in Europe, testing for leishmaniasis should be strongly considered because this infection can mimic SLE.

Numerous criteria for the diagnosis of SLE in dogs have been extrapolated from the literature in humans. The most commonly accepted and clinically applicable criteria are shown in Table 73.8. Measurement of serum ANA titer is a relatively sensitive test to confirm the diagnosis of SLE, although the sensitivity reported in the literature ranges from 50% to 100% (see Chapter 71). The variability in diagnostic sensitivity probably arises from variation in the diagnostic criteria for confirming the diagnosis, as well as variations in the populations of dogs tested. When used in dogs that have appropriate clinical criteria for SLE, the ANA test is an excellent test; however, false-positive results can occur in dogs and cats with other inflammatory or infectious disorders or neoplasia. ANAs are detected in 10% to 20% of dogs with seroreactivity to *Bartonella vinsonii*, *E. canis*, and *Leishmania infantum*. Dogs with seroreactivity to multiple pathogens are more likely to be ANA positive. A recent study of 120 dogs in which an ANA titer was measured emphasized the importance of appropriate patient selection for testing. In this study, measurement of an ANA titer was not a useful diagnostic test in dogs without any major clinical or clinicopathologic abnormalities suggestive of SLE. Only 1 of 47 dogs tested that did not have any major signs of SLE had immune-mediated disease, and this dog was seronegative for ANA. Ten (21%) of 47 dogs were seropositive for ANA. Conversely, 13 of 16 dogs with two major signs compatible with SLE had immune-mediated disease, and ANA was positive in 10 of these dogs. These results emphasize that the positive predictive value of a diagnostic test is lower in a population of animals in which the disease prevalence is low.

The LE test is rarely used clinically for diagnosis of SLE because of very low sensitivity. A number of other antibody tests have been investigated in groups of dogs with SLE, including antinative DNA antibodies, antiextractable nuclear antigen antibodies, and antihistone antibodies. None of these tests has been extensively evaluated in dogs, and none is currently commercially available.

Treatment

Immunosuppressive therapy for SLE begins with high doses of prednisone/prednisolone (1-2 mg/kg PO q12h). The dose is then tapered if disease remission is achieved. Addition of

TABLE 73.8

Criteria for Diagnosis of SLE

MAJOR SIGNS	MINIMUM DIAGNOSTIC TESTING NECESSARY TO SUBSTANTIATE MAJOR SIGN	MINOR SIGNS	DIAGNOSTIC TEST NEEDED TO SUBSTANTIATE
Polyarthritis	Synovial fluid analysis and culture	Fever of unknown origin	Abdominal radiographs, urine culture, no response to antibiotics
Dermatologic lesions (consistent with SLE)	Skin scraping, skin biopsy	CNS signs	CT or MRI scan, CSF tap with infectious disease serology
GN	Urine protein/creatinine ratio >2, renal biopsy useful but not required	Oral ulceration	Biopsy of lesions
Polymyositis	Increased creatine kinase or muscle biopsy demonstrating inflammation	Lymphadenopathy	Lymph node aspirate
Hemolytic anemia	Regenerative anemia, positive Coombs test, bone marrow aspirate if anemia not regenerative, negative infectious disease testing	Pericarditis	Echocardiography
Immune-mediated thrombocytopenia	Bone marrow aspirate, negative infectious disease testing	Pleuritis	Thoracic radiographs, thoracocentesis
Immune-mediated leukopenia	Bone marrow aspirate, negative infectious disease testing		

A diagnosis of SLE is considered confirmed if there are two major signs compatible with SLE and the antinuclear antibody (ANA) titer or LE test is positive or if there is one major sign and two minor signs and the ANA test or LE test is positive. A diagnosis is considered probable if there is only one major sign or two minor signs and a positive ANA titer (or LE test) or if there are two major signs and a negative ANA titer. Immune-mediated hemolytic anemia in conjunction with immune-mediated thrombocytopenia (Evans syndrome) is not considered to be a diagnosis of SLE unless there is an additional major or minor sign. Not all testing listed in the table is necessary in all cases. Specific diagnostic tests will depend on the individual case presentation and geographic location.

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *GN,* glomerulonephritis; *LE,* lupus erythematosus; *MRI,* magnetic resonance imaging; *SLE,* systemic lupus erythematosus.

Modified from Marks SL, Henry CJ: CVT update: diagnosis and treatment of systemic lupus erythematosus. In Bonagura JD, ed.: *Kirk's current veterinary therapy XIII: small animal practice,* ed 13, Philadelphia, 2000, WB Saunders, p 514.

other adjunctive immunosuppressive drugs (e.g., azathioprine, cyclosporine, mycophenolate) is usually necessary to induce or maintain remission. Little information is available on the efficacy of drug protocols for treating SLE. The prognosis for dogs with SLE is guarded to poor. Relapse is common regardless of the drug protocol used, and long-term and often lifelong immunosuppressive therapy is necessary to control the disease. Relapses may involve different organ systems and clinical signs than at initial presentation (e.g., hemolytic anemia initially and polyarthritis at relapse).

GLOMERULONEPHRITIS

Etiology

Acquired GN is more common in dogs than cats and results from the presence of immune complexes within the glomerular capillary walls (see Chapter 40). Immune complexes may be circulating antigen-antibody complexes that are deposited or trapped in the glomerulus or may form in situ when circulating antibodies react with either endogenous glomerular antigens or nonglomerular antigens within the glomerular capillary wall. Soluble circulating immune complexes formed in the presence of mild antigen excess, or when both antigen and antibody are present in approximately equal quantities, may be deposited along capillary walls, resulting in a granular pattern observed on immunofluorescent or immunoperoxidase staining. Infectious and inflammatory diseases are common identifiable causes for deposition of immune complexes within the glomerulus (Box 73.6). Unfortunately, in the majority of cases of GN, an underlying cause is not identified. When immune complexes form in situ, a smooth linear pattern is observed with immunofluorescent or immunoperoxidase staining. Causes of in situ deposition of immune complexes may be either true autoimmune disease when antibodies are directed against the basement membrane of the glomerular capillaries or when antigen becomes localized in the glomerular capillary wall. For example, in dogs with heartworm disease, soluble *Dirofilaria immitis* antigens have been shown to adhere to the glomerular capillary wall by a carbohydrate-glycoprotein interaction.

Whatever the cause of immune complex deposition, the consequences are similar (see Chapter 40) and ultimately lead to severe proteinuria, systemic hypertension, renal failure, and predisposition to thromboembolism.

BOX 73.6

Infectious and Inflammatory Diseases Implicated in Pathogenesis of Glomerulonephritis in Dogs

Ehrlichiosis
Dirofilariasis
Leptospirosis
Borreliosis
Brucellosis
Endocarditis
Pyelonephritis
Prostatitis

Clinical Features

The hallmark of GN is proteinuria, which is readily detected on routine urinalysis. In many cases proteinuria is initially identified as an incidental finding, and the animal may have no obvious clinical signs or only subtle abnormalities (e.g., weight loss, lethargy, decreased appetite). In other cases, animals present with clinical signs of renal failure (e.g., anorexia, weight loss, vomiting, polyuria, polydipsia), and proteinuria is identified in the course of the evaluation. In nephrotic syndrome, which is defined as the presence of proteinuria, hypoalbuminemia, hypercholesterolemia, and either peripheral edema or ascites, the clinical signs are more severe and often rapidly progressive. Other clinical signs in dogs with GN may relate to the presence of hypertension or hypercoagulability. Hypertension may result in retinal changes and blindness, whereas TEs may occur as a result of the hypercoagulable state.

Diagnosis

A diagnosis of protein-losing nephropathy (PLN) is made by documentation of persistent proteinuria that cannot be explained by inflammation of the lower urinary tract or blood contamination of the urine. Initial dipstick estimates of urine protein should be evaluated in the light of the urine sediment and specific gravity of the urine. The severity of protein loss should then be quantitated by measurement of a protein-to-creatinine ratio, preferably on a urine sample with no inflammation or hematuria. A protein-to-creatinine ratio greater than 0.5 is abnormal; most dogs and cats with PLN have a ratio greater than 2.0. Once persistent proteinuria has been documented, further testing is necessary to determine whether evidence of tubular dysfunction also exists and to investigate for the presence of underlying infectious or inflammatory diseases implicated as causes of GN. Diagnostic tests that should be performed include a CBC, serum biochemical profile, urinalysis and urine culture, blood pressure, and radiographs of the thorax and abdomen. Ultrasonography of the kidneys is useful to investigate for evidence of pyelonephritis, nephroliths, or other underlying renal disease, but it rarely detects changes associated with GN. An occult heartworm test should be performed and serum titers submitted for the infectious diseases listed in Box 73.6. Testing for hyperadrenocorticism should be considered in dogs if the appropriate signalment and clinical signs are present. Renal biopsy should be considered if an underlying cause for the proteinuria cannot be identified. Tissue samples should be submitted for routine histopathology, electron microscopy, and immunopathology. Goals of renal biopsy should be to confirm the underlying disease process (specific type of GN, hereditary nephritis,

glomerulosclerosis, amyloidosis); determine severity of the disease; and, if possible, determine a prognosis and guide specific therapy.

Treatment

Therapy for immune-mediated GN should be directed at treating the underlying disease (if identified), decreasing protein loss in the urine, decreasing the likelihood of thromboembolism, and initiating appropriate dietary therapy and supportive care. Angiotensin-converting enzyme inhibitors (ACEIs) (e.g., enalapril 0.5-1.0 mg/kg PO q12h-24h) are currently the most effective treatment for proteinuria. Angiotensin receptor blockers (e.g., telmisartan 0.5-1.0 mg/kg PO q24) can be used in cases where proteinuria is refractory to traditional ACEI therapy. Anticoagulation is recommended to decrease the likelihood of thromboembolism in dogs with GN, especially in those with documented antithrombin deficiency (<70%). Low-dose aspirin (0.5 mg/kg PO q24h) or clopidogrel (1.0-2.0 mg/kg PO q24h) may be beneficial for their anticoagulant effects. Other supportive measures include control of hypertension (if not controlled by ACEI alone); dietary sodium restriction; a low-protein, high-quality protein diet with n-3 fatty acid supplementation; and control of ascites and edema if present. Therapy for overt renal failure may also be necessary. See Chapter 41 for further details on general management of renal failure.

In theory, immunosuppression should be useful in idiopathic immune-mediated GN; however, the use of corticosteroids may exacerbate rather than ameliorate proteinuria. Corticosteroid therapy is indicated when GN occurs as part of an immune-mediated disease known to respond to corticosteroids such as SLE. Mycophenolate is recommended as the first choice for treatment of dogs with rapidly progressive glomerular disease of an apparent immune-mediated pathogenesis (10 mg/kg PO q12). GN secondary to *Borrelia burgdorferi* may benefit from immunosuppressive therapy with mycophenolate as well. Other indications for immunosuppressive treatment are currently poorly defined in dogs.

Careful monitoring of response to therapy with monthly measurement of urine protein-to-creatinine ratio; biochemical profile (blood urea nitrogen, creatinine, electrolytes, albumin); and blood pressure is important to assess adequacy of therapy. Prognosis for GN varies depending on the severity of disease, underlying histopathology, and response to treatment. In general, the prognosis is guarded in animals that initially present with concurrent azotemia. The outcome is best in dogs with reversible causes of immune complex deposition and those that respond to diet and medications to control proteinuria. See Chapter 40 for more information on this topic.

ACQUIRED MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a disorder of neuromuscular transmission resulting from deficiency or dysfunction of the nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane. Acquired MG is an autoimmune disease in which antibodies directed against the AChR interfere with the interaction between acetylcholine and its receptor. Antibodies also cross-link AChR and cause receptor internalization. Complement-mediated damage to the postsynaptic membrane also contributes to neuromuscular blockade. As with other immune-mediated diseases, MG may be a primary autoimmune disorder or may occur in association with other disorders, such as thymoma, and other neoplasms. Hypothyroidism and hypoadrenocorticism, which are also immune-mediated disorders, may also occur in association with MG. A breed predisposition exists for MG in dogs, with the Akita, various Terrier breeds, and German Shorthaired Pointer being at increased risk. Abyssinian and Somali cats also have an increased risk of MG compared with other breeds.

The most common clinical presentation of MG is generalized weakness, either with or without concurrent megaesophagus. In focal MG, in which signs of generalized weakness are absent, the most common clinical sign is regurgitation because of megaesophagus, but dysphagia, dysphonia, and cranial nerve dysfunction may also occur. An acute fulminating form of MG is characterized by severe weakness, sometimes with loss of spinal reflexes and usually in conjunction with megaesophagus and aspiration pneumonia. In cats, the two most common clinical presentations are generalized weakness without megaesophagus and generalized weakness associated with a cranial mediastinal mass (i.e., thymoma).

Definitive diagnosis of MG is by measurement of serum autoantibodies against AChR by immunoprecipitation radioimmunoassay. The assay is sensitive and specific, and false-positive results are rare. Seronegative MG occurs in only 2% of dogs with MG. Canine- and feline-specific assay systems should be used. Immunosuppressive doses of corticosteroids lower the antibody concentration and can interfere with testing. Because antibodies are not the cause of congenital MG, results of antibody testing will be negative. Other useful tests in diagnosis of MG include evaluation of the response of clinical signs to a short-acting anticholinesterase drug (edrophonium chloride [Tensilon]) and electrodiagnostic testing. Once a diagnosis of MG has been confirmed, additional testing is necessary to investigate for the presence of other underlying disorders that may lead to secondary MG or occur concurrently.

The first line of treatment for MG is oral or injectable anticholinesterase inhibitors such as neostigmine or pyridostigmine (Table 73.9). These drugs act by prolonging the action of acetylcholine at the neuromuscular junction. Immunosuppression with glucocorticoids should be considered in patients that do not respond well to anticholinesterase inhibitors alone. The advantages of the immunosuppressive effects of glucocorticoids in MG are often outweighed by adverse effects such as worsening of muscle weakness and muscle atrophy. Corticosteroids may also be problematic in animals with aspiration pneumonia, diabetes mellitus, and

TABLE 73.9

Drug Regimens and Doses Used for Routine Management of MG in Dogs and Cats

DRUG	DOGS	CATS
Pyridostigmine	0.5-3 mg/kg PO q8-12h	0.25-3 mg/kg PO q8-12h (start at low end of dose)
Neostigmine (use to bypass gastrointestinal tract in presence of severe regurgitation)	0.04 mg/kg IM q6h	0.04 mg/kg IM q6h
Prednisone	0.5 mg/kg PO q48h to 2 mg/kg/day PO	0.5 mg/kg PO q48h to 2 mg/kg/day PO
Azathioprine	2 mg/kg PO q24h Dose can be decreased to every other day to reduce risk of toxicity	Do not use in cats
Cyclosporine	5-10 mg/kg q12-24h	3-5 mg/kg PO q12h
Mycophenolate mofetil	10 mg/kg PO q12h	

MG, Myasthenia gravis.

gastrointestinal ulceration; if corticosteroids are necessary for MG, care should be used to avoid excessive doses. Therapeutic approaches include starting glucocorticoids at the low end of the immunosuppressive range (prednisone 2 mg/kg/day PO) or starting glucocorticoids at an even lower dose (prednisone 0.5 mg/kg PO every other day) and slowly increasing the dose after 2 weeks if a satisfactory response is not seen. Other immunosuppressive drugs that have been used for adjunctive management of MG include azathioprine, cyclosporine, leflunomide, and MMF. Drug regimens and doses used in the routine management of MG are given in Table 73.9. Thymectomy should be considered in dogs and cats with MG associated with thymoma; good long-term outcomes have been reported in the majority of dogs and cats following resection of thymoma. However, MG does not consistently resolve after surgery, and some cats may develop MG postoperatively.

Spontaneous remission of acquired MG is common in dogs. Clinical remission is accompanied by a decrease of the AChR antibody titer into the reference range. Repeated measurement of the AChR titer is a useful guide for identifying when clinical remission is occurring and when adjustments to therapy may be indicated. The majority of dogs that do not go into remission have underlying neoplasia. See Chapter 66 for more information on this topic.

PERIANAL FISTULA

Etiology

Perianal fistula, also called anal furunculosis, is a chronic inflammatory disease described in dogs. It is characterized by the formation of one or more ulcerations around the circumference of the anus. These ulcerations cause significant pain and can lead to hematochezia, tenesmus, fecal incontinence, and rectal stricture.

The etiology is not fully understood, but the majority of evidence supports an immune-mediated mechanism. Histologically, affected tissues are infiltrated by lymphocytes and plasma cells (primarily secreting IgA and IgG), as well as eosinophils and macrophages. The lymphocytes in these tissues are predominantly T cells, with high concentrations of IL-2 and tumor necrosis factor-α present, indicating a cell-mediated immune response. German Shepherds are the most common breed to be diagnosed with perianal fistulas, and this breed is known to have an impairment in cell-mediated immunity, further supporting an immune-mediated etiology.

Clinical Features

Middle-aged to older German Shepherds are most commonly affected by this disease, although it has been reported in other large-breed dogs (e.g., Labrador Retrievers). Clinical signs usually involve excessive grooming of the perianal region or self-mutilation. Tenesmus, hematochezia, dyschezia, and fecal incontinence can occur as well. The pain associated with this disease tends to be severe and can lead to systemic signs like lethargy, inappetance, and weight loss.

The most important part of the physical examination is the rectal examination, which may require sedation because of the painful lesions. One or more ulcerated draining tracts are typically identified in the perianal region and often a malodorous, mucopurulent discharge is noted. These draining tracts should be cleaned and probed to evaluate how far they extend, as some can extend into the rectal lumen.

Signalment, history, and physical examination typically provide enough evidence to make a diagnosis of perianal fistula. If clinical signs include diarrhea or significant constipation or change in fecal consistency, proctoscopy and/or colonoscopy should be used to evaluate for colitis or rectal abnormalities.

Treatment

Perianal fistula was previously thought to be a surgical disease, but medical management has been shown to be more successful, especially with the evidence of an underlying immune-mediated mechanism.

Cyclosporine treatment has shown the most success for treatment of perianal fistula (5.0-7.5 mg/kg PO q12), with remission rates of 60% to 100%. Cyclosporine treatment should be continued until the fistula(s) have resolved and, at this point, a taper of this medication can be considered. Perianal fistulas do commonly recur, and, even with cyclosporine, recurrence rates have been reported from 30% to 60%. In the literature, up to 30% of cases require some degree of long-term immunosuppression. Prednisone and azathioprine have also been described for treatment of perianal fistula, though their success rates were less than those of cyclosporine, but they are both less costly.

Tacrolimus, a topical immunosuppressant, has also shown success in treating perianal fistula. Caution should be taken when using tacrolimus topically as it is a potent immunosuppressant and should not be ingested. Additionally, use of tacrolimus may be cost prohibitive.

Supportive care and daily cleaning of the perianal region is very important for the treatment of perianal fistula. Stool softeners (e.g., lactulose) and pain relief are helpful for alleviating some of the most severe clinical signs, if present. Perianal fistulas have a guarded prognosis due to the fact that the disease is rarely cured, and recurrence is common. Treatment has improved with the advent of immunosuppressive therapies but still requires long-term, and costly, therapy.

IMMUNE-MEDIATED MYOSITIS

MASTICATORY MYOSITIS

Masticatory myositis is a focal myositis affecting the muscles of mastication (temporalis, masseter, digastricus). Masticatory muscles contain a unique muscle fiber type (type 2M) that differs histopathologically, immunologically, and biochemically from fiber types in limb musculature. Antibodies directed against this unique muscle fiber type are present in more than 80% of dogs with masticatory myositis. The major antigen recognized by the antibodies is masticatory myosin binding protein C, which is localized near the cell surface in masticatory muscle fibers, perhaps making it accessible as an immunogen.

Masticatory myositis is the most common form of myositis in dogs; it has not been reported in cats. Young large-breed dogs are overrepresented, and there is no breed or gender predisposition; although a syndrome of juvenile-onset masticatory myositis has been reported in Cavalier King Charles Spaniels. Clinical signs include inability to open the mouth (trismus), swelling and/or pain of the masticatory muscles, and severe muscle atrophy. In some dogs, an acute phase is recognized in which muscle swelling and pain predominate. If untreated this acute phase progresses to a chronic phase characterized by severe muscle atrophy and trismus. In many affected dogs, the acute phase is not recognized, and the first recognized clinical signs are severe muscle atrophy and inability to open the jaws. In severe cases the jaws can only be separated by a few centimeters, and the affected animal is unable to eat or drink. Less severely affected dogs may be able to use the tongue to lick up fluids or liquidized food. Other clinical signs include fever, depression, weight loss, dysphagia, dysphonia, and exophthalmos from swelling of the pterygoid muscles.

Diagnosis of masticatory myositis is made on the basis of characteristic clinical signs and presence of antibodies against type 2M fibers. This test is positive in greater than 80% of cases and has a specificity approaching 100%. Muscle biopsy is useful to determine the degree of fibrosis and likelihood of return to normal function with treatment, as well as to confirm the diagnosis in dogs in which the antibody test is negative. Multifocal infiltration with lymphocytes, histiocytes, and macrophages, with or without eosinophils, is found on histopathology. Moderate to severe muscle fiber atrophy, fibrosis, and sometimes complete loss of muscle fibers with replacement by connective tissue may be present. Other adjunctive tests that may be useful include measurement of creatine kinase, which is increased in some but not all dogs with masticatory myositis, and electrodiagnostic testing, which allows identification of the most severely affected muscles. Typical electrodiagnostic findings include presence of fibrillation potentials and positive sharp waves.

Treatment of masticatory myositis relies on the use of immunosuppressive doses of corticosteroids (prednisone 2-4 mg/kg PO q24h). Under no circumstances should force be used to open the jaws because fracture or luxation of the temporomandibular joint may result. Once resolution of clinical signs is achieved with corticosteroids, the dose should then be slowly tapered over several months. Disease activity and progression should be monitored by clinical signs (especially range of motion) and measurement of creatine kinase (if elevated at presentation). Long-term treatment with prednisone or an additional immunosuppressive drug such as azathioprine is required in dogs that relapse when prednisone is tapered. Tapering of prednisone too quickly increases the chance of relapse. The goal of therapy is a return to normal muscle function and a normal quality of life. In many cases, especially in the presence of severe fibrotic changes, muscle atrophy persists and is exacerbated by glucocorticoid therapy. Prognosis for return to function is good in most cases. See Chapter 67 for more information on this topic.

POLYMYOSITIS

Polymyositis is characterized by multifocal or diffuse infiltration of skeletal muscle by lymphocytes and negative serology for infectious disease. Although most cases are primary autoimmune, paraneoplastic immune-mediated myositis may be associated with malignancies such as lymphoma (particularly in Boxers), bronchogenic carcinoma, myeloid leukemia, tonsillar carcinomas in dogs, and thymoma in cats. The specific inciting antigen is not known, although the

mechanism of injury is believed to be mediated by cytotoxic T cells (type IV delayed-type hypersensitivity).

Polymyositis is uncommon in dogs and rare in cats. The disease is most common in young large-breed dogs, and Boxers, Newfoundlands, and Vizslas are overrepresented. Clinical signs include generalized weakness that worsens with exercise and a characteristic stiff gait. Cervical ventriflexion may occur, especially in cats. Most animals show pain on palpation of affected muscles, particularly the proximal muscle groups. Dysphagia, generalized muscle atrophy, dysphonia, tongue atrophy, and fever may also be present. Megaesophagus has been reported in 15% of cases. Some dogs with polymyositis also have signs of masticatory myositis, and these dogs are positive for antibodies against type 2M fibers. Polymyositis may also occur in SLE and in canine polyarthritis/myositis syndrome.

Diagnosis of polymyositis is based on characteristic clinical signs, presence of an elevated creatine kinase level (more commonly increased in polymyositis than in masticatory myositis), electrophysiologic testing abnormalities consistent with myositis, serology for infectious causes of myositis (Box 73.7), and muscle biopsy. It is important to rule out infectious causes of myositis in dogs with polymyositis (see Box 73.7). Muscle biopsies in dogs with polymyositis have similar changes to those described for dogs with masticatory myositis; however, the presence of eosinophils in dogs with polymyositis increases the index of suspicion for an infectious cause. A diagnosis of polymyositis has been made in dogs, particularly Boxers, that months later are diagnosed with lymphoma. Potential reasons for this association include paraneoplastic syndrome, malignant transformation of lymphocytes, or misdiagnosis of polymyositis. A complete evaluation for neoplasia should be part of the diagnostic evaluation of dogs with polymyositis, especially if there is lymphadenopathy.

Treatment of polymyositis is similar to treatment of masticatory myositis. Prognosis for return to function is good in most cases. See Chapter 67 for more information on this topic.

DERMATOMYOSITIS

Dermatomyositis is an uncommon immune-mediated disorder affecting the skin, skeletal muscle, and vasculature of Collies and Shetland Sheepdogs. The disorder has an autosomal-dominant pattern of inheritance, and the pathogenesis is suspected to be immune complex deposition, although the target antigen is not known.

In dermatomyositis, cutaneous lesions develop between 2 and 4 months of age, with signs of myositis developing later. The temporalis muscle is most commonly affected, and clinical signs include dysphagia and muscle atrophy. More severe signs may include megaesophagus and generalized polymyositis with diffuse muscle atrophy, especially of the distal appendicular muscles. Diagnosis of dermatomyositis is based on the classic signalment (age, breed, presence of cutaneous signs). The creatine kinase activity is usually only minimally increased. Definitive diagnosis is based on skin and muscle biopsy.

Treatment of dermatomyositis relies on symptomatic care of cutaneous lesions and immunosuppression. The protocol for corticosteroid therapy is similar to that used for polymyositis, but prolonged therapy is necessary and relapses are common. Additional recommendations include avoidance of exposure to sunlight, neutering of sexually intact dogs, and vitamin E supplementation. Pentoxifylline has also been shown to be of some benefit in affected dogs (see Chapter 72). The prognosis depends on severity, being good for mild cases and poor for severely affected dogs. See Chapter 67 for more information on dermatomyositis.

BOX 73.7

Infectious Causes of Polymyositis in Dogs

Toxoplasma gondii
Neospora caninum
Borrelia burgdorferi
Clostridial myositis
Ehrlichia canis
Rickettsia rickettsii
Hepatozoon americanum
Leishmania infantum
Leptospirosis (icterohaemorrhagiae)

Suggested Readings

Balog K, et al. Comparison of the effect of human intravenous immunoglobulin versus vincristine on platelet recovery time in dogs with severe idiopathic immune-mediated thrombocytopenia. *J Vet Intern Med*. 2011;25:1503.

Bexfield NH, et al. Management of myasthenia gravis using cyclosporine in two dogs. *J Vet Intern Med*. 2006;20:1487.

Bianco D, et al. A prospective randomized double blinded placebo-controlled study of human intravenous immunoglobulin for the acute management of presumptive primary immune-mediated thrombocytopenia in dogs. *J Vet Int Med*. 2009;23:1071.

Brown CD, et al. Evaluation of clinicopathologic features, response to treatment, and risk factors associated with idiopathic neutropenia in dogs: 11 cases (1990-2002). *J Am Vet Med Assoc*. 2006;229:87.

Carr AP, et al. Prognostic factors for mortality and thromboembolism in canine immune-mediated hemolytic anemia: a retrospective study of 72 dogs. *J Vet Intern Med*. 2002;16:504.

Chabanne L, et al. Canine systemic lupus erythematosus: part I, clinical and biologic aspects. *Compendium (small animal/exotics)*. 1999a;21:135.

Chabanne L, et al. Canine systemic lupus erythematosus: part II, diagnosis and treatment. *Compendium (small animal/exotics)*. 1999b;21:402.

Clements DN, et al. Type I immune-mediated polyarthritis in dogs: 39 cases (1997-2002). *J Am Vet Med Assoc*. 2004;224:1323.

Colopy SA, et al. Efficacy of leflunomide for treatment of immune-mediated polyarthritis in dogs: 14 cases (2006-2008). *J Am Vet Med Assoc*. 2010;236(3):312.

Cooper SA, et al. Clinical data, clinicopathologic findings and outcome in dogs with amegakaryocytic thrombocytopenia and

primary immune-mediated thrombocytopenia. *J Small Anim Pract*. 2016;57(3):142.
Cummings FO, et al. Treatment of presumptive primary immune-mediated thrombocytopenia with mycophenolate mofetil versus cyclosporine in dogs. *J Small Anim Pract*. 2017;58(2):96.
Davis B, et al. Mutation in beta-tubulin correlates with macrothrombocytopenia in cavalier king charles spaniels. *J Vet Intern Med*. 2008;22:540.
Devine L, et al. Presumed primary immune-mediated neutropenia in 35 dogs: a retrospective study. *J Small Anim Pract*. 2017;58(6):307–313.
Dewey CW, et al. Mycophenolate mofetil treatment in dogs with serologically diagnosed acquired myasthenia gravis: 27 cases (1999-2008). *J Am Vet Med Assoc*. 2010;236:664.
Dircks BH, et al. Underlying diseases and clinicopathologic variables of thrombocytopenic dogs with and without platelet-bound antibodies detected by use of a flow cytometric assay: 83 cases (2004-2006). *J Am Vet Med Assoc*. 2009;235:960.
Dudley A, et al. Cyclooxygenase expression and platelet function in healthy dogs receiving low-dose aspirin. *J Vet Intern Med*. 2013;27(1):141–149.
Duval DJ, et al. Vaccine associated immune-mediated hemolytic anemia in the dog. *J Vet Intern Med*. 1996;10:290.
Evans J, et al. Canine inflammatory myopathies: a clinicopathologic review of 200 cases. *J Vet Intern Med*. 2004;18:679.
Gilmour MA, et al. Masticatory myopathy in the dog: a retrospective study of 18 cases. *J Am Anim Hosp Assoc*. 1992;28:300.
Giudice E, et al. Effect of desmopressin on immune-mediated haemorrhagic disorders due to canine monocytic ehrlichiosis: a preliminary study. *J Vet Pharmacol Therap*. 2010;33:610.
Goggs R, et al. Concurrent immune-mediated haemolytic anaemia and severe thrombocytopenia in 21 dogs. *Vet Rec*. 2008;163:323.
Goggs R, et al. Predicting outcome in dogs with primary immune-mediated hemolytic anemia: results of a multicenter case registry. *J Vet Intern Med*. 2015;29(6):1603.
Grauer GF. Canine glomerulonephritis: new thoughts on proteinuria and treatment. *J Small Anim Pract*. 2005;46:469.
Harkin KR, et al. Erythrocyte-bound immunoglobulin isotypes in dogs with immune-mediated hemolytic anemia: 54 cases (2001-2010). *J Am Vet Med Assoc*. 2012;241(2):227.
Helmond SE, et al. Treatment of immune-mediated haemolytic anemia with individually adjusted heparin dosing in dogs. *J Vet Intern Med*. 2010;24:597.
Huang AA, et al. Idiopathic immune-mediated thrombocytopenia and recent vaccination in dogs. *J Vet Intern Med*. 2012;26:142.
Husbands B, et al. Prednisone and cyclosporine versus prednisone alone for treatment of canine immune mediated hemolytic anemia (IMHA). *J Vet Intern Med*. 2004;18:389.
Kennedy LJ, et al. Association of a common dog leucocyte antigen class II haplotype with canine primary immune-mediated haemolytic anemia. *Tissue Antigens*. 2006;68(6):502.
King LG, et al. Acute fulminating myasthenia in five dogs. *J Am Vet Med Assoc*. 1998;212:830.
Kohn B, et al. Primary immune-mediated hemolytic anemia in 19 cats: diagnosis, therapy, and outcome (1998-2004). *J Vet Intern Med*. 2006;20:159.
Lachowicz JL, et al. Acquired amegakaryocytic thrombocytopenia—four cases and a literature review. *J Small Anim Pract*. 2004;45:507.
Marks SL, Henry CJ. CVT update: diagnosis and treatment of systemic lupus erythematosus. In: Bonagura JD, ed. *Kirk's current veterinary therapy XIII: small animal practice*. 13th ed. Philadelphia: WB Saunders; 2000:514.
McManus PM, et al. Correlation between leukocytosis and necropsy findings in dogs with immune-mediated hemolytic anemia: 34 cases (1994-1999). *J Am Vet Med Assoc*. 2001;218:1308.
Mellett AM, et al. A prospective study of clopidogrel therapy in dogs with primary immune-mediated hemolytic anemia. *J Vet Intern Med*. 2011;25(1):71.
Miller MD, et al. Diagnostic use of cytologic examination of bone marrow from dogs with thrombocytopenia: 58 cases (1994-2004). *J Am Vet Med Assoc*. 2007;231:1540.
Miller SA, et al. Case control study of blood type, breed, sex, and bacteremia in dogs with immune-mediated hemolytic anemia. *J Am Vet Med Assoc*. 2004;224:232.
Neravanda D, et al. Lymphoma associated polymyositis in dogs. *J Vet Intern Med*. 2009;23:1293.
Ohno K, et al. C-reactive protein concentration in canine idiopathic polyarthritis. *J Vet Med Sci*. 2006;68(12):1275.
O'Marra SK, et al. Treatment and predictors of outcome in dogs with immune mediated thrombocytopenia. *J Am Vet Med Assoc*. 2011;238:346.
Orcutt ES, et al. Immune-mediated haemolytic anemia and severe thrombocytopenia in dogs: 12 cases (2001-2008). *Vet Emerg Crit Care*. 2010;20:338.
Piek CJ, et al. Lack of evidence of a beneficial effect of azathioprine in dogs treated with prednisolone for idiopathic immune-mediated haemolytic anemia (a retrospective cohort study). *Vet Res*. 2011;7:15.
Podell M. Inflammatory myopathies. *Vet Clin North Am Small Anim Pract*. 2002;32:147.
Putsche JC, et al. Primary immune-mediated thrombocytopenia in 30 dogs (1997-2003). *J Am Anim Hosp Assoc*. 2008;44:250.
Rhoades AC, et al. Comparison of the efficacy of prednisone and cyclosporine for treatment of dogs with primary immune-mediated polyarthritis. *J Am Vet Med Assoc*. 2016;248(4):395.
Rondeau MP, et al. Suppurative non-septic polyarthropathy in dogs. *J Vet Intern Med*. 2005;19:654.
Rozanski EA, et al. Comparison of platelet count recovery with use of vincristine and prednisone or prednisone alone for treatment for severe immune-mediated thrombocytopenia in dogs. *J Am Vet Med Assoc*. 2002;220:477.
Scott-Moncrieff JC, et al. Hemostatic abnormalities in dogs with primary immune-mediated hemolytic anemia. *J Am Anim Hosp Assoc*. 2001;37:220.
Shelton DG, et al. Risk factors for acquired myasthenia gravis in dogs: 1,154 cases (1991-1995). *J Am Vet Med Assoc*. 1997;211:11428.
Shelton GD. Myasthenia gravis and disorders of neuromuscular transmission. *Vet Clin North Am Small Anim Pract*. 2002;32:189.
Shelton GD, et al. Risk factors for acquired myasthenia gravis in cats: 105 cases (1986-1998). *J Am Vet Med Assoc*. 2000;216:55.
Smee NM, et al. Measurement of serum antinuclear antibody titer in dogs with and without systemic lupus erythematosus: 120 cases (1997-2005). *J Am Vet Med Assoc*. 2007;230:1180.
Smith BE, et al. Antinuclear antibodies can be detected in dog sera reactive to *Bartonella vinsonii* subsp. *Berkhoffii, Ehrlichia canis,* or *Leishmania infantum* antigens. *J Vet Intern Med*. 2004;18:47.
Stokol T, et al. Pure red cell aplasia in cats: 9 cases (1989-1997). *J Am Vet Med Assoc*. 1999;214:75.
Stokol T, et al. Idiopathic pure red cell aplasia and non-regenerative immune-mediated anemia in dogs: 43 cases (1998-1999). *J Am Vet Med Assoc*. 2000;216:1429.
Swann JW, et al. Characterisation of the immunophenotype of dogs with primary immune-mediated hemolytic anemia. *PLoS ONE*. 2016;11(12).

Wang A, et al. Treatment of canine idiopathic immune-mediated haemolytic anaemia with mycophenolate mofetil and glucocorticoids: 30 cases (2007-2011). *J Small Anim Pract*. 2013;54(8):399.
Webb AA, et al. Steroid responsive meningitis-arteritis in dogs with noninfectious nonerosive idiopathic immune-mediated polyarthritis. *J Vet Intern Med*. 2002;16:269.
Weinkle TK, et al. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *J Am Vet Med Assoc*. 2005;226:1869.
Weiss DJ. Primary pure red cell aplasia in dogs: 13 cases (1996-2000). *J Am Vet Med Assoc*. 2002;221:93.
Weiss DJ. Evaluation of antineutrophil IgG antibodies in persistently neutropenic dogs. *J Vet Intern Med*. 2007;21:440.
Whelan M, et al. Use of human immunoglobulin in addition to glucocorticoids for the initial treatment of dogs with immune mediated hemolytic anemia. *J Vet Emerg Crit Care*. 2009;19:158.
Wondratschek C, et al. Primary immune-mediated thrombocytopenia in cats. *J Am Anim Hosp Assoc*. 2010;46:12.
Wu X, et al. Autoantibodies in canine masticatory muscle myositis recognize a novel myosin binding protein C family member. *J Immunol*. 2007;179:4939.

Drugs Used to Treat Immune-Mediated Diseases of Dogs and Cats and General Dosing Guidelines

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Aspirin	Prevent thromboembolic complications of IMHA or PLN	0.5 mg/kg PO q24h	NA
Azathioprine (Imuran)	Immunosuppression	2 mg/kg/day initially. Dose can be decreased to every other day to reduce risk of toxicity	Not recommended
Chlorambucil (Leukeran)	Immunosuppression	0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen	0.1-0.2 mg/kg PO q24h initially, then q24-72h
Clopidogrel (Plavix)	Prevent thromboembolic complications of IMHA or PLN	1-2 mg/kg PO q24h	1-2 mg/kg PO q24h, or 18.75 mg/cat PO q24h
Cyclosporine (Atopica, Neoral)	Immunosuppression	5-10 mg/kg PO q12-24h Recommend using only Atopica® due to concerns for bioavailability of other products Lower doses of 1-2.5 mg/kg q12h if in conjunction with ketoconazole	3-5 mg/kg PO q12h Recommend using only Atopica® due to concerns for bioavailability of other products
Dexamethasone	Immunosuppression	0.25-0.5 mg/kg PO q24h	0.25-1 mg/kg PO q24h
Enalapril (Enacard)	Treatment of proteinuria	0.5-1.0 mg/kg q12-24h	NA
Famotidine (Pepcid)	Treatment and prevention of gastric ulceration	0.5-mg/kg PO/IM/SC q12-24h	0.5 mg/kg PO/IM/SC q12-24h
Heparin (unfractionated)	Anticoagulation	200-300 U q6h as initial dose. Adjust on basis of measurement of aPTT or anti-Xa activity	NA
hIVIG	Immunosuppression	0.25-1.5 g/kg as an IV infusion over 6-12 hours (one dose only)	NA
Leflunomide (Arava)	Immunosuppression	2-4 mg/kg PO q24h	NA
Mycophenolate mofetil (CellCept)	Immunosuppression	10 mg/kg q12h	10 mg/kg q12h
Neostigmine (Prostigmin)	Anticholinesterase inhibitor	0.04 mg/kg IM q6h	0.04 mg/kg IM q6h

Continued

Drugs Used to Treat Immune-Mediated Diseases of Dogs and Cats and General Dosing Guidelines—cont'd

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Omeprazole (Prilosec)	Treatment and prevention of gastric ulceration	0.5-1.0 mg/kg PO q12-24h	0.5-1.0 mg/kg PO q12-24h
Pentoxifylline	Immunomodulation	10-15 mg/kg PO q8h	NA
Prednisone/ prednisolone	Immunosuppression	2-4 mg/kg/day PO	2-8 mg/kg/day PO
Pyridostigmine (Mestinon)	Anticholinesterase inhibitor	0.5-3 mg/kg PO q8-12h	0.25-3 mg/kg PO q8-12h (start at low end of dose)
Sucralfate (Carafate)	To prevent drug-induced gastritis	0.5-1 g PO q6-12h	0.25-0.5 g PO q8-12h
Vincristine (Oncovin)	Increase platelet count in ITP	0.02 mg/kg IV as a single dose for treatment of ITP	NA

aPTT, Activated partial thromboplastin time; *hIVIG,* human intravenous immunoglobulin; *IMHA,* immune-mediated hemolytic anemia; *ITP,* immune-mediated thrombocytopenia; *NA,* not applicable.

PART TWELVE ▪ Oncology

C. Guillermo Couto

CHAPTER 74

Cytology



GENERAL CONSIDERATIONS

Evaluation of a cytologic specimen obtained by fine-needle aspiration (FNA) in small animals with suspected neoplastic lesions often yields information that can be used to make a definitive diagnosis, thereby circumventing the immediate need to perform a surgical biopsy. At the authors' hospitals, almost every mass or enlarged organ is evaluated cytologically before a surgical biopsy is performed because the risks and costs associated with FNA are considerably lower than those associated with surgical biopsy. Frequently, a definitive cytologic diagnosis allows the clinician to institute a specific treatment (i.e., multicentric lymphoma treated with chemotherapy) and spares the patient the need for a surgical biopsy.

In a study of 269 cytologic specimens from dogs, cats, horses, and other animal species, the cytologic diagnosis completely agreed with the histopathologic diagnosis in approximately 40% of cases and partially agreed in 18% of the cases; complete agreement ranged from 33% to 66%, depending on the lesion and location, and was highest for skin/subcutaneous lesions and for neoplastic lesions (Cohen et al., 2003). Interestingly, in the author's experience, the cytologic and histopathologic diagnoses agree in more than 70% of the cases. When a clinician with experience on cytology evaluates a cytologic specimen, the bias experienced after obtaining a history and performing a physical examination is beneficial in the cognitive processing of information. For example, being fairly certain that a dog has multicentric lymphoma (on the basis of the history and physical examination) makes specimen interpretation easier.

Clinically applicable diagnostic cytologic techniques are summarized in this chapter, with emphasis on sample collection and the cursory interpretation of the specimens. Although some clinicians can obtain sufficient diagnostic information, a board-certified veterinary clinical pathologist should always evaluate a cytologic specimen before any prognostic or therapeutic decisions are made.

FINE-NEEDLE ASPIRATION

In FNA, a single cell suspension is obtained using a small-gauge needle (i.e., 23-25 gauge) of the appropriate length for the desired target organ or mass; this needle can be coupled to a 6-, 12-, or 20-mL sterile, dry plastic syringe, but frequently this is not necessary; the size of the syringe is based on how comfortable it is for the operator. Although the technique is still referred to as "FNA," in most cases no aspiration is performed with the syringe (see later). Tissues easily accessible using this technique include the skin and subcutis, deep and superficial lymph nodes, spleen, liver, kidneys, lungs, thyroid, prostate, and intracavitary masses (e.g., mediastinal mass).

If the clinician is sampling superficial masses, sterile preparation of the site is not necessary. However, clipping and sterile surgical preparation should always be done when aspirating organs or masses within body cavities. Once the mass or organ has been identified by palpation or radiography, it should be manually isolated, if feasible; manual isolation is not necessary when performing ultrasonography-, computed tomography (CT)–, or fluoroscopy-guided FNAs. A needle, either by itself or coupled to a syringe, is then introduced into the mass or organ; if the "needle-alone" technique is used, the needle is reinserted into the tissue/mass several times; this can be referred to as the "woodpecker technique" due to the repeated puncturing motion that mimics a woodpecker at work. This allows the clinician to core out small samples, which will be completely contained within the hub of the needle. Once a sample has been obtained, a clean disposable syringe is loaded with air and coupled to the needle. The specimen is then gently expelled onto slides, as described later in this chapter. If the needle-syringe technique is used, suction is applied to the syringe three or four times. If the size of the mass or lesion allows it, the needle is then redirected two or three times and the procedure is repeated. Before withdrawing the needle and

syringe, the clinician should release the suction to avoid aspirating blood that would contaminate the sample or air that would make the sample irretrievable from the barrel of the syringe. The needle is then detached, air is aspirated into the syringe, the needle is recoupled, and the sample is expelled onto a glass slide. It is important to do this in a gentle fashion; loading the whole syringe with air and expelling the sample abruptly will result in "aerosolization" of the sample. In that case, each droplet will dry instantly upon touching the glass slide; because the cells will not spread out, they will be difficult to identify. Instead, the clinician should apply gentle pressure in the plunger of the syringe until a minuscule droplet appears in the tip of the syringe, and then touch the glass slide with it and make the smears immediately. In most cases, no material is seen in the syringe, but the amount of cells present within the hub of the needle is usually adequate to obtain four to eight good-quality smears.

Rarely, tumor cells can be transplanted along the needle tract. This occurs more frequently in dogs with transitional cell carcinomas of the urinary bladder or prostate but has also been documented in dogs with primary pulmonary, intestinal, and prostatic adenocarcinomas. Hence, if a dog has a potentially resectable apical bladder mass, we do not do percutaneous FNAs but rather transurethral, ultrasonography-guided catheter aspirates.

Superficial ulcerated masses can easily be sampled by scraping their surface with a sterile scalpel blade, wooden tongue depressor, or gauze. Smears are then made by either touching a glass slide onto the ulcerated lesion (see the following section, Impression Smears) or further scraping the surface with a tongue depressor and transferring the material thus obtained onto the slide. "Pull" smears made using two glass slides are preferable over "push" smears. Once the smears have been made, they are air-dried and stained using any of the techniques described in the next section.

IMPRESSION SMEARS

Impression smears of surgical specimens or open lesions are commonly used in practice. When making impression smears from surgical specimens, the clinician first gently blots the tissue onto a gauze pad or paper towel to remove any blood or debris and then gently grasps it with forceps from one end. When making impression smears of endoscopic gastrointestinal or urinary bladder lesions, it is important, if possible, to orient the sample in such fashion that the deep aspect of the lesion is used for the smears; this avoids nondiagnostic samples obtained by applying the surface (i.e., epithelium) onto the glass slides. Touch imprints are made on a glass slide by gently touching the slide with the tissue specimen. We make two or three rows of impressions along the slide and then stain them. It is advisable to submit a different tissue specimen for histopathologic evaluation. IMPORTANT: Do not make the smears next to the formalin vial or the fumes will irreversibly damage the cells!

STAINING OF CYTOLOGIC SPECIMENS

Several staining techniques are practical for in-office use, including rapid Romanowsky (e.g., Diff-Quik; various manufacturers) and new methylene blue (NMB) stains. Most commercial laboratories use Romanowsky stains, such as Wright or Giemsa.

These staining techniques have some differences. Romanowsky stains are slightly more time consuming, but they produce better cellular detail and offer worse contrast between nucleus and cytoplasm; moreover, the smears can be permanently archived. NMB, on the other hand, is a quick stain (it takes literally seconds to stain a smear), but it is not permanent, which means that slides cannot be saved for consultation; moreover, cellular details are not as sharp as they are on Romanowsky-stained smears. In addition, because nuclear DNA and RNA stain extremely well with this technique, most cells appear to be malignant. We routinely use Diff-Quik stain on the clinic floor. The main difference between rapid hematologic stains (e.g., Diff-Quik) and Giemsa or Wright-Giemsa stains is that, in a small proportion of canine mast cell tumors (MCTs), the former do not stain the granules. It was suggested that the lack of staining of MCT granules with Diff-Quik was due to the relatively short fixation recommended by the manufacturer and that more prolonged fixation (e.g., minutes) would result in the granules staining. A study revealed that longer fixation does not improve the staining of mast cell granules (Jackson et al., 2013). In addition, rapid hematologic stains do not stain granules in some large granular lymphocytes (LGLs) or in eosinophils from Greyhounds, other sighthounds, and some Golden Retrievers.

INTERPRETATION OF CYTOLOGIC SPECIMENS

Although the clinician should strive to evaluate cytologic specimens proficiently, a board-certified veterinary clinical pathologist should always make the ultimate cytologic diagnosis. The following are guidelines for cytologic interpretation. As a general rule, cytologic specimens are classified into one of the following six categories: normal tissue, hyperplasia/dysplasia (difficult to diagnose), inflammation, neoplasia, cystic lesions (contains fluid of various types), or mixed cellular infiltrate. The latter is usually either a malignant tumor with ongoing inflammation (e.g., squamous cell carcinoma with neutrophilic inflammation) or a hyperplastic tissue secondary to chronic inflammation (e.g., chronic cystitis with epithelial hyperplasia/dysplasia). Cytology of cystic lesions is not discussed in this chapter.

NORMAL TISSUES

Epithelial Tissues

Most epithelial cells, particularly those of the glandular or secretory epithelium, tend to cling together (i.e., they have

desmosomes), forming clusters or sheets. Individual cells are easily identifiable and are round or polygonal; both nucleus and cytoplasm are well differentiated (i.e., the nucleus is small and has heavily clumped chromatin). Most cells in Romanowsky-stained smears have blue cytoplasm and round to oval nuclei.

Mesenchymal Tissues

Cells from mesenchymal tissues (e.g., fibroblasts, fibrocytes, chondroblasts) are difficult to obtain in routine FNA material or tissue scrapings because they are usually surrounded by intercellular matrix. Mesenchymal cells are typically spindle-shaped, polygonal, or oval and have irregular nuclei; cytoplasmic boundaries are usually indistinct, and cell clumps are seen rarely.

Hematopoietic Tissues

A detailed morphologic description of circulating blood cells is beyond the scope of this chapter. Briefly, however, most cells from hemolymphatic organs are round, individual cells (with no tendency to clump); they have a blue cytoplasm on Romanowsky-stained smears and a variable nuclear size. Most nuclei are round or kidney-shaped. Tissue such as bone marrow has cells in different stages of development (i.e., from blasts to well-differentiated circulating cells).

HYPERPLASTIC PROCESSES

Hyperplasia commonly results in enlargement of glandular organs and lymphoid structures. The cytologic features of epithelial and lymphoid hyperplasia differ; lymphoid hyperplasia is discussed later in this chapter. Cytologically, epithelial hyperplastic changes may be difficult to recognize because they can mimic either normal or neoplastic tissues (i.e., the morphologic features are in between those of normal and neoplastic tissues). Care should be taken when evaluating specimens from organs such as enlarged prostates or thickened urinary bladders because the high degree of hyperplasia and dysplasia frequently suggests malignancy; abundance of inflammatory cells suggests that the changes are due to chronic irritation (i.e., hyperplasia).

INFLAMMATORY PROCESSES

Most inflammatory reactions are characterized cytologically by the presence of inflammatory cells and debris in the smear. The type of cell present depends on the etiologic agent (e.g., neutrophils in pyogenic infections, eosinophils in parasitic or allergic reactions) and the duration of the inflammatory process (i.e., acute processes are usually characterized by a predominance of granulocytes, whereas macrophages and lymphocytes predominate in chronic processes). BEWARE: Chronic inflammation frequently results in hyperplasia of fibroblasts and angioblasts, which can mimic a malignant mesenchymal tumor (sarcoma) (Fig. 74.1). The following pathogens are frequently identified in cytologic specimens: *Histoplasma, Blastomyces, Sporothrix, Cryptococcus, Coccidioides, Aspergillus/Penicillium, Toxoplasma, Leishmania,*

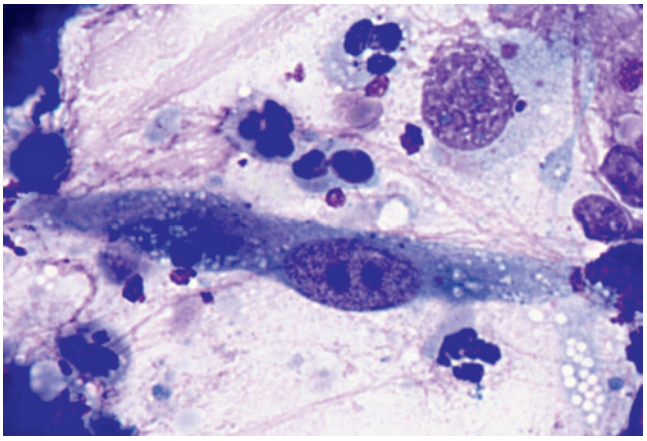


FIG 74.1
Photomicrograph of a fine-needle aspirate of a vaccine reaction in a 2-year-old, castrated, mixed-breed dog; note spindle cell with cytologic features of malignancy (likely a fibroblast) (×1000).

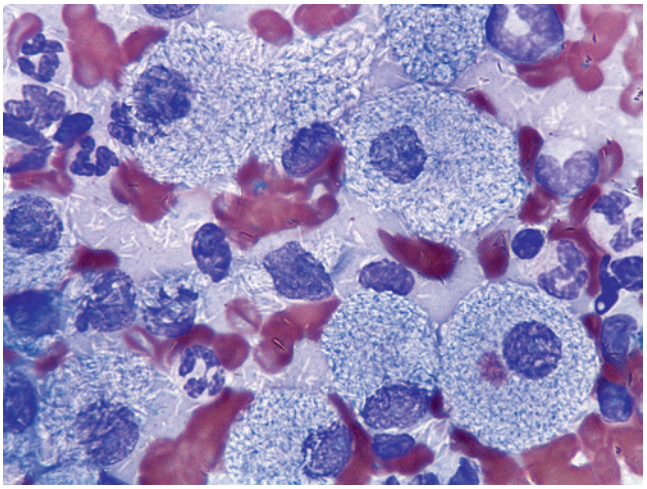


FIG 74.2
Photomicrograph of a splenic fine-needle aspirate of a 2-year-old Schnauzer with tuberculosis. The rod-shaped nonstaining inclusions in the macrophages are *Mycobacterium avium* (×1000).

Mycobacterium, other rickettsial agents, bacteria, and *Demodex* (Fig. 74.2).

MALIGNANT CELLS

The cells that make up most normal organs and tissues (with the exception of bone marrow precursors) are well differentiated, in that most of them are similar in size and shape, they have a normal nuclear-to-cytoplasmic (N:C) ratio, the nuclei usually have condensed chromatin and no nucleoli, and the cytoplasm may exhibit features of differentiation (e.g., keratin formation in squamous epithelium).

Malignant cells have one or more of the following features (Box 74.1): a high N:C ratio (i.e., larger nucleus and smaller cytoplasm); a delicate chromatin pattern; nucleoli (usually multiple); anisokaryosis (i.e., cells have nuclei of different

sizes); nuclear molding (i.e., a nucleus in a multinucleated cell is compressed by a neighboring one); morphologic homogeneity (i.e., all cells look alike); pleomorphism (i.e., cells in different stages of development); vacuolization (primarily in malignant epithelial tumors); anisocytosis (i.e., cells are of different sizes); multinucleated giant cells; and, occasionally, phagocytic activity. Another feature of malignancy is heterotopia (i.e., the presence of a given cell type where it is not found anatomically); for example, relevant numbers of epithelial cells can appear in a lymph node only as a consequence of metastasis from a carcinoma. In addition, malignant cells tend to be morphologically different from the progenitor cell population (see Box 74.1). On the basis of the predominant cytologic features, malignancies can be classified as carcinomas (epithelial), sarcomas (mesenchymal), or round (or discrete) cell tumors (Fig. 74.3).

BOX 74.1

Cytologic Characteristics of Malignant Neoplasms

Large nuclei
Fine chromatin pattern
One or more nucleoli
Anisokaryosis
Nuclear molding
Monomorphism
Pleomorphism
Anisocytosis
Cytoplasmic vacuolization
Cytoplasmic basophilia
Multinucleated giant cells
Phagocytosis
Heterotopia

Carcinomas

Most carcinomas are composed of round or polygonal cells that tend to cling together, forming clusters or large sheets. Their cytoplasms are usually deep blue, and in most adenocarcinomas vacuolization is evident. Cytoplasmic boundaries are difficult to recognize, and the cells resemble a mass of protoplasm rather than a sheet of individual cells. In squamous cell carcinomas, cells usually appear individualized, can be irregular or polygonal, have a deep blue cytoplasm (with an occasional eosinophilic fringe), and have large vacuoles; neoplastic cells in squamous cell carcinomas frequently exhibit leukophagia. Nuclei in both adenocarcinomas and squamous cell carcinomas are large, with a fine chromatin pattern and evident nucleoli (Fig. 74.4).

Sarcomas

The cytologic features of sarcomas vary according to the histologic type. As a general rule, sarcomas do not exfoliate well; however, hemangiopericytomas and other spindle cell sarcomas exfoliate so well that the clinician's first impression on evaluating a smear may be that of a carcinoma (i.e., the cells appear to be in groups) (Fig. 74.5). Most mesenchymal tumors have spindle-shaped, polygonal, polyhedral, or oval cells, with a reddish-blue to dark blue cytoplasm and irregularly shaped nuclei. Most cells are individualized, although clumping may occur (particularly in impression smears or when a large-bore needle is used for sample collection). The

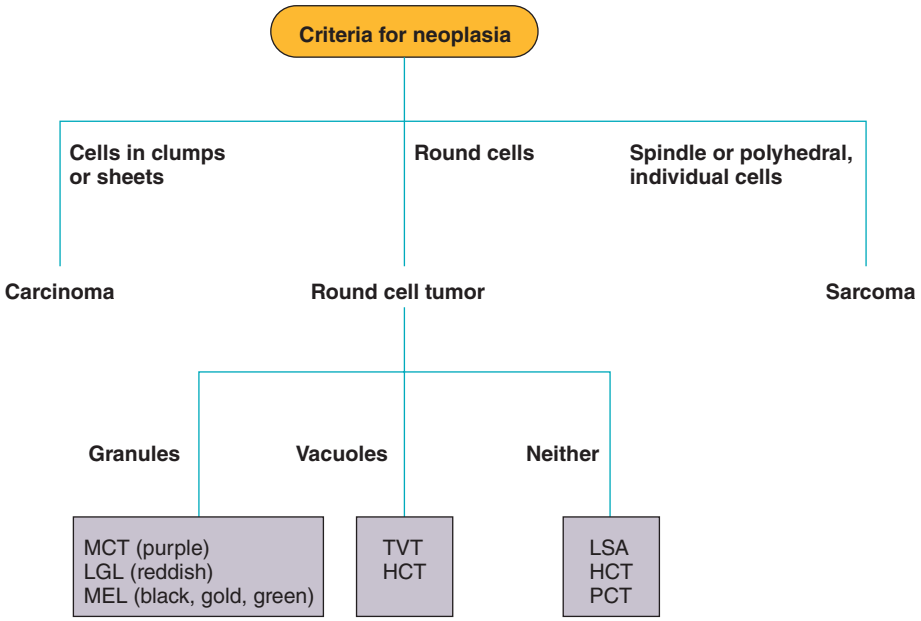


FIG 74.3
Flow chart for the cytologic diagnosis of tumors in dogs and cats. *HCT,* Histiocytoma; *LGL,* large granular lymphoma; *LSA,* lymphoma; *MCT,* mast cell tumor; *MEL,* melanoma; *PCT,* plasma cell tumor; *TVT,* transmissible venereal tumor.

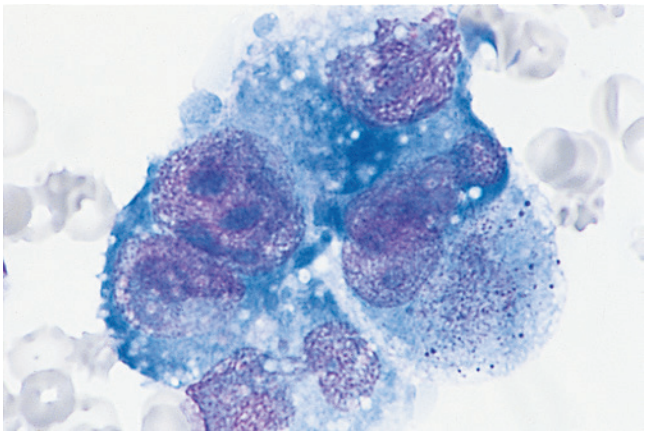


FIG 74.4
Photomicrograph of pleural fluid from an older female Irish Setter showing a cluster of deeply basophilic cells, with vacuolated cytoplasm, anisocytosis, anisokaryosis, and prominent nucleoli. The cytologic diagnosis was carcinomatosis (i.e., metastatic adenocarcinoma of unknown origin) (×1000).

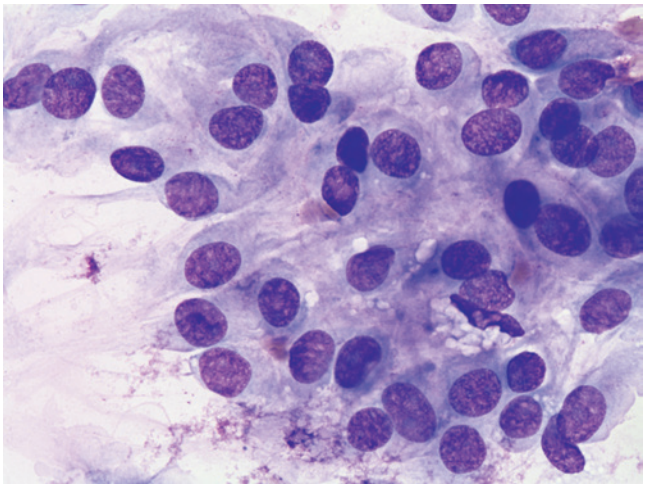


FIG 74.5
Photomicrograph of a fine-needle aspirate of a firm, lobulated, subcutaneous mass in an older dog. The cells appear to be in clusters, but closer inspection reveals that it is an aggregate of spindle cells consistent with spindle cell sarcoma. The clinical diagnosis was hemangiopericytoma (×500).

cells in most sarcomas tend to form "tails," and the nuclei protrude from the cytoplasm (Fig. 74.6). The presence of spindle-shaped or polygonal cells with a vacuolated blue-gray cytoplasm is highly suggestive of hemangiosarcoma (Fig. 74.7). Intercellular matrix (e.g., osteoid, chondroid) is found occasionally in osteosarcomas (OSAs) and chondrosarcomas (CSAs), respectively; in these two tumor types the cells are usually round or ovoid. The preferred approach to lytic bone lesions in our clinics is to perform an FNA (see Chapter 81); the probability of obtaining a definitive diagnosis is higher than when doing a bone biopsy, with significantly lower cost,

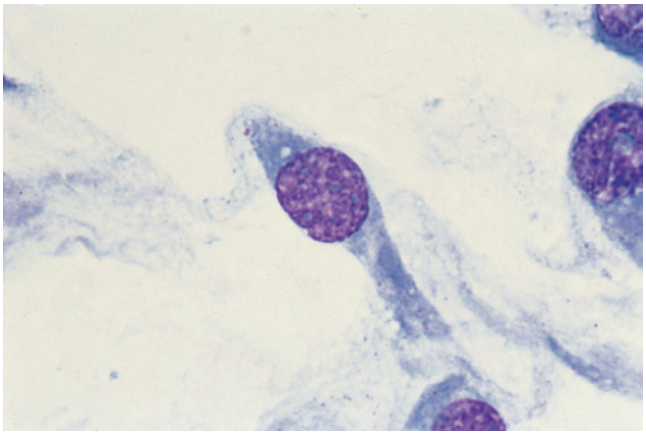


FIG 74.6
Photomicrograph of a fine-needle aspirate of a firm, lobulated, subcutaneous mass in an older dog. The cells are spindle-shaped, have "tails," and do not associate with other cells. The nuclei appear to be protruding from the cytoplasm (×1000). The cytologic diagnosis is spindle cell sarcoma. Histopathologic findings were diagnostic for fibrosarcoma.

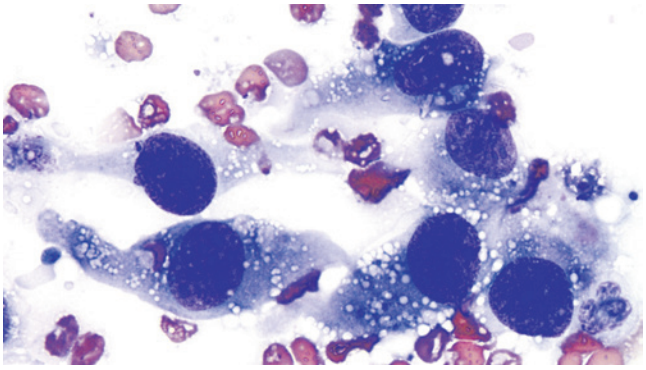


FIG 74.7
Photomicrograph of one of several purple cutaneous nodules in a dog with a primary splenic hemangiosarcoma. The polygonal to spindle-shaped cells with blue-gray cytoplasm and vacuoles are characteristic of hemangiosarcoma (the lesions were metastases from the primary tumor) (×1000). (Courtesy Dr. S. M. Nguyen.)

and minimal discomfort to the patient. Multinucleated giant cells are common in some sarcomas in cats.

As discussed earlier, because sarcoma cells usually do not exfoliate well, aspirates may yield false-negative results. Therefore, if a mass is clinically suspected to be a sarcoma and FNA findings are negative, a core biopsy specimen of the mass should be obtained because it is likely to be a sarcoma.

Round (Discrete) Cell Tumors

Tumors composed of a homogeneous population of round (or discrete) cells are referred to as *round* (or *discrete*) *cell tumors* (RCTs). These tumors are common in dogs and cats and include lymphoma (LSA), histiocytoma (HCT), MCT, transmissible venereal tumor (TVT), plasma cell tumor

(PCT), and malignant melanoma (MM); as discussed earlier, OSAs and CSAs can be composed of round cells, so they are included within this category. RCTs are easily diagnosed on the basis of cytology; the presence or absence of cytoplasmic granules or vacuoles and the location of the nucleus aid in the classification of RCTs (see Fig. 74.3).

Cells in MCTs (Fig. 74.8), LGL LSAs (Fig. 74.9), and MMs (Fig. 74.10) usually have cytoplasmic granules; cells in neuroendocrine tumors (i.e., thyroid carcinomas) can also have granules. When hematologic stains are used, the granules are purple in MCTs; red in LGL LSAs; and black, green, brown, or yellow in MMs. Lymphomas (Fig. 74.11), HCTs (Fig. 74.12), PCTs, and TVTs do not have cytoplasmic granules. Cells in OSA occasionally have small to large pink cytoplasmic granules (osteoid) (see Fig. 81.6 in Chapter 81). Cytoplasmic vacuoles are common in TVTs and HCTs.

Briefly, large cell LSAs are characterized by a monomorphic population of individual poorly differentiated round cells with large nuclei, a coarse chromatin pattern, and one or two nucleoli; occasional cells may be vacuolated (see Fig. 74.11). Small and intermediate cell lymphomas may be difficult to recognize cytologically because the neoplastic population may resemble normal lymphocytes. Cells in HCTs are similar to those in lymphomas except that the chromatin pattern is fine rather than coarse, they have more abundant cytoplasm, and they are frequently vacuolated (see Fig.

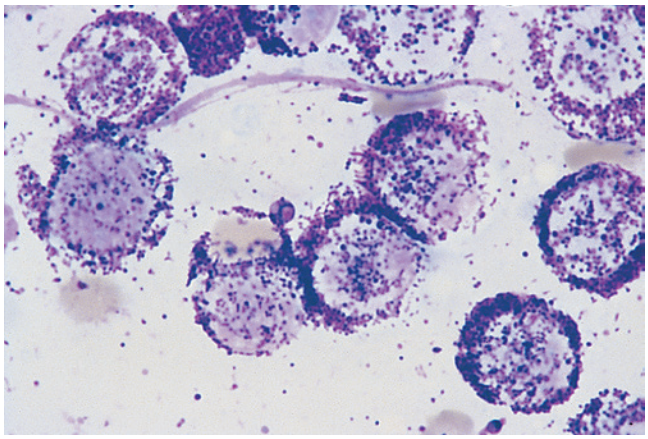


FIG 74.8
Photomicrograph of a fine-needle aspirate from a subcutaneous mass in an older Boxer with multiple dermoepidermal and subcutaneous masses and marked multifocal lymphadenopathy. Note the monomorphic population of round cells containing purple granules. The cytologic diagnosis was mast cell tumor (×1000).

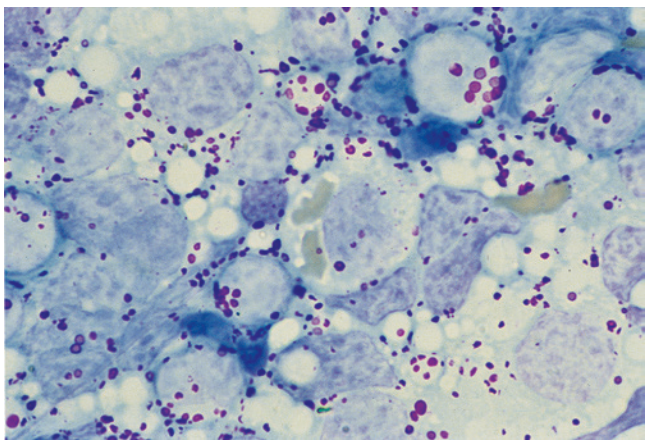


FIG 74.9
Photomicrograph of an impression smear from a mesenteric lymph node in an old cat evaluated because of vomiting and diarrhea. Note the large round cells with red, large cytoplasmic granules. The diagnosis was lymphoma of large granular lymphocytes (×1000).

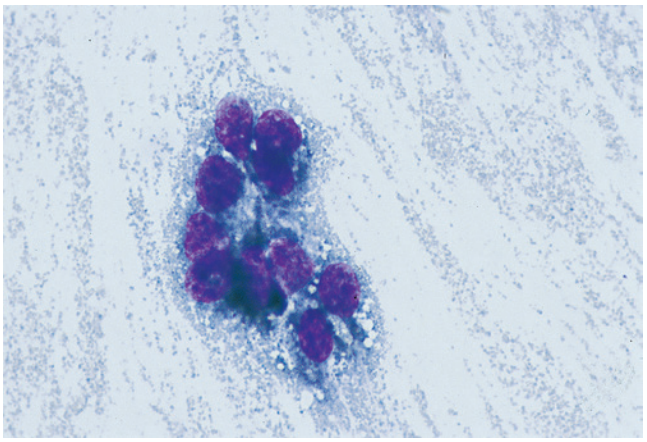


FIG 74.10
Photomicrograph of a fine-needle aspirate from a mass in the oral cavity of a 10-year-old Schnauzer. Note the dark, fine granules in the cytoplasm. The diagnosis was melanoma (×400).

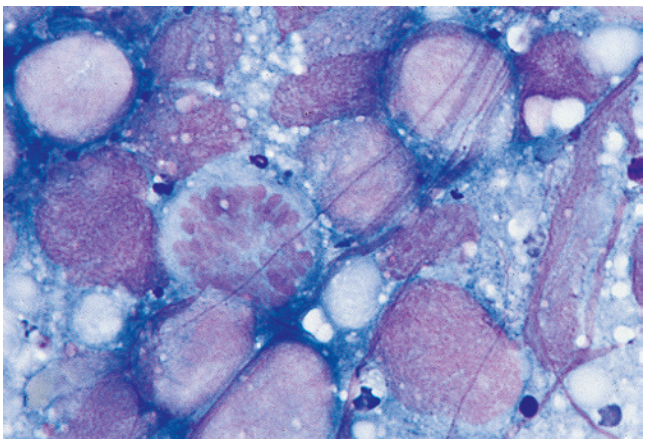


FIG 74.11
Photomicrograph of a fine-needle aspirate from the kidney of a middle-aged Boxer with bilateral renomegaly. Note the monomorphic population of round cells, with large nuclei, prominent nucleoli, and no cytoplasmic granules or vacuoles. A mitotic figure is seen in the center. The cytologic diagnosis was lymphoma (×1000).

74.12). Because inflammation is an important component of HCTs, inflammatory cells (i.e., neutrophils, lymphocytes) are commonly found in these tumors. MCTs are distinctive in that the cytoplasm of the neoplastic cells contains purple (metachromatic) granules, which can be so numerous as to obscure the nuclear features; eosinophils are also a common feature in these tumors. Mast cell granules may be absent in poorly differentiated tumors or in tumors stained with Diff-Quik (Fig. 74.13).

LYMPH NODES

Cytologic evaluation of lymph node aspirates is commonly done in practice. In our clinics, a cytologic diagnosis is obtained in approximately 90% of dogs and 60% to 70% of cats with lymphadenopathy. If the cytologic findings of an enlarged lymph node are inconclusive, the node should be surgically excised and submitted for histopathologic evaluation.

When evaluating cytologic specimens prepared from lymph node aspirates or impression smears, the clinician should keep in mind that these organs react to a variety of stimuli following a distinct pattern. In general, four cytologic patterns are recognized: normal lymph node, reactive or hyperplastic lymphadenopathy, lymphadenitis, and neoplasia.

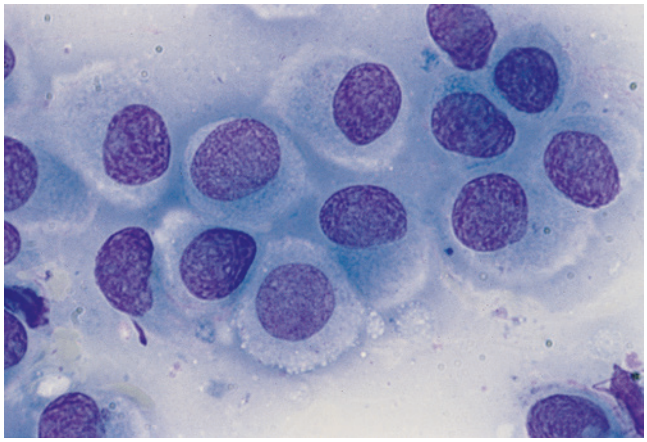


FIG 74.12
Photomicrograph of a fine-needle aspirate from a small, round, dermoepidermal mass in the head of a 1-year-old dog. Note the large round cells with abundant clear cytoplasm and fine chromatin pattern. The diagnosis was histiocytoma (×1000).

Normal Lymph Node

Cytologic specimens from normal nodes are composed predominantly (≈70% to 90%) of small lymphocytes; thus they are monomorphic. These cells are approximately 7 to 10 µm in diameter (1-1.5 times the diameter of a red blood cell and smaller than a neutrophil) and have a dense chromatin pattern and no nucleoli. The remaining cells are macrophages, lymphoblasts, plasma cells, and other immune cells.

Reactive or Hyperplastic Lymphadenopathy

Lymphoid tissues reacting to different antigenic stimuli (e.g., bacterial, fungal, neoplastic) are cytologically similar in that the cell population is composed of a mixture of small, intermediate, and large lymphocytes; lymphoblasts; plasma cells; and macrophages (Fig. 74.14). In addition, other cell types may be present, depending on the specific agent (e.g., eosinophils in parasitic or allergic reactions). The first impression when evaluating a reactive or hyperplastic node cytologically is that of a heterogeneous population of cells. The presence of cells in different stages of development indicates that the lymphoid tissue is undergoing polyclonal expansion (i.e.,

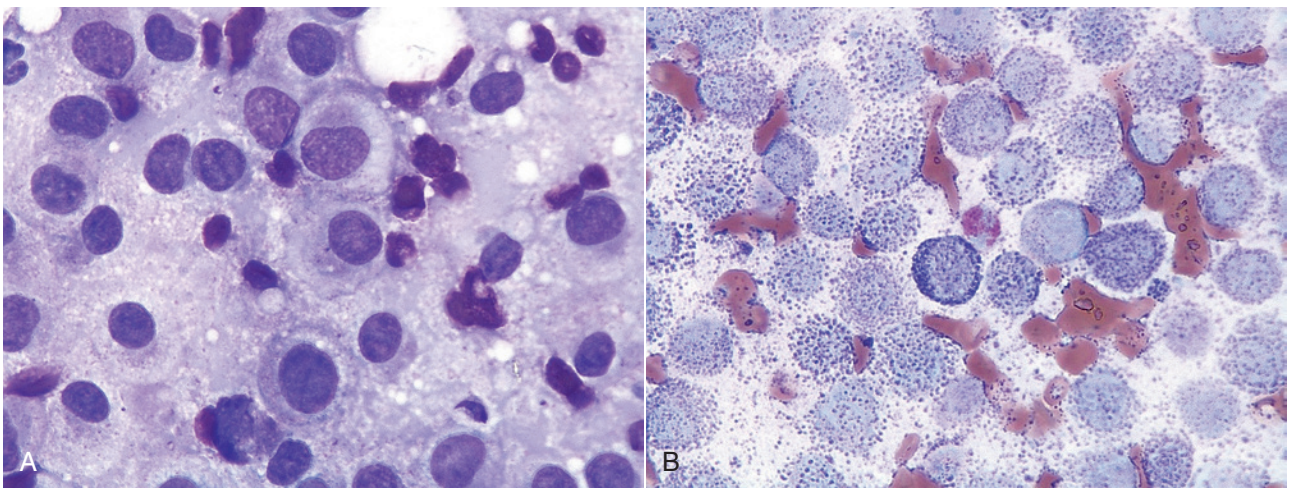


FIG 74.13
Photomicrograph of a fine-needle aspirate of a dermoepidermal mass in a Shar-Pei. Diff-Quik stain **(A)** does not reveal cytoplasmic granules; counterstaining the same slide with Wright-Giemsa **(B)** reveals typical cytoplasmic granules of mast cells. Final diagnosis: mast cell tumor (×1000).

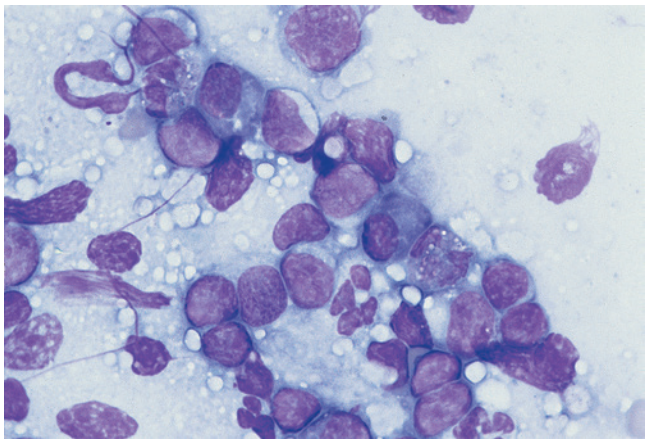


FIG 74.14
Photomicrograph of a fine-needle aspirate from a reactive lymph node in a dog. Note the heterogeneous population of lymphoid cells (small, medium, and large), plasma cells, and macrophages (×1000).

response to multiple antigens). Reactive lymph nodes in cats frequently lack plasma cells but contain large numbers of lymphoblasts, so they may be difficult to distinguish from lymphoma.

Lymphadenitis

Inflammatory processes affecting the lymph nodes produce cytologic changes similar to the ones seen in reactive lymphadenopathy, although there is a profusion of bloodborne inflammatory cells (e.g., neutrophils in suppurative infections) and degenerative changes (e.g., pyknosis, karyorrhexis) in most cell lines. The etiologic agents may be visualized.

Neoplasia

Neoplastic cells can appear in a lymph node either as a result of lymphatic or vascular dissemination (i.e., metastasis from a primary tumor draining into the lymph node) or as a primary process affecting these structures (i.e., lymphomas). Cytologic features of metastatic lymph node lesions consist of a reactive pattern and the presence of neoplastic cells; in advanced metastatic lesions it is frequently difficult to identify normal lymphoid cells because the node architecture is effaced by the tumor. The morphology of the metastatic cells depends on the primary tumor type. As discussed in the preceding section, lymphomas are characterized by a monomorphous population of large, immature lymphoid cells; these cells are usually large and have an abnormally low N:C ratio, coarse chromatin, and evident nucleoli. As discussed previously, small cell lymphomas are difficult to diagnose cytologically.

Decision Making in Lymph Node Cytologic Evaluation

From our perspective, the easiest approach to classifying a lymph node cytologically is to first determine whether the cell population is homogeneous (i.e., >70% of the cells resemble one another) or heterogeneous. If the population is homogeneous, it is either a normal node (i.e., the cells are normal lymphocytes) or it is neoplastic (lymphoma or metastasis); if it is heterogeneous, it is either reactive, inflammatory, or early neoplastic.

Suggested Readings

Baker R, et al. *Color atlas of cytology of the dog and cat*. St Louis: Mosby; 2000.

Ballegeer EA, et al. Correlation of ultrasonographic appearance of lesions and cytologic and histologic diagnoses in splenic aspirates from dogs and cats: 32 cases (2002-2005). *J Am Vet Med Assoc*. 2007;230:690.

Barton CL. Cytologic diagnosis of cutaneous neoplasia: an algorithmic approach. *Compend Contin Educ*. 1987;9:20.

Bertazzolo W, et al. Canine angiosarcoma: cytologic, histologic, and immunohistochemical correlations. *Vet Clin Pathol*. 2005;34:28.

Bonfanti U, et al. Diagnostic value of cytologic examination of gastrointestinal tract tumors in dogs and cats: 83 cases (2001-2004). *J Am Vet Med Assoc*. 2006;229:1130.

Cohen M, et al. Evaluation of sensitivity and specificity of cytologic examination: 269 cases (1999-2000). *J Am Vet Med Assoc*. 2003;222:964.

Cowell RL, et al. *Diagnostic cytology and hematology of the dog and cat*. 3rd ed. St Louis: Elsevier; 2007.

Ghisleni G, et al. Correlation between fine-needle aspiration cytology and histopathology in the evaluation of cutaneous and subcutaneous masses from dogs and cats. *Vet Clin Pathol*. 2006;35:24.

Grimes JA, et al. Agreement between cytology and histopathology for regional lymph node metastasis in dogs with melanocytic neoplasms. *Vet Pathol*. 2017;54:579.

Jackson D, et al. Evaluation of fixation time using Diff-Quik for staining of canine mast cell tumor aspirates. *Vet Clin Pathol*. 2013;42:99.

Mills JN. Lymph node cytology. *Vet Clin North Am*. 1989;19:697.

Millward L. Cytology from Fine- Needle Aspirates. Veterinary Team Brief. October:27; 2017.

Morrison WB, et al. Advantages and disadvantages of cytology and histopathology for the diagnosis of cancer. *Semin Vet Med Surg*. 1993;8:222.

Powe JR, et al. Evaluation of the cytologic diagnosis of canine prostatic disorders. *Vet Clin Pathol*. 2004;33:150.

Radin MJ, et al. *Interpretation of canine and feline cytology*. Wilmington, Del: Gloyd Group; 2001.

Raskin RE, et al. *Atlas of canine and feline cytology*. Philadelphia: WB Saunders; 2001.

Sharkey LC, et al. Maximizing the diagnostic value of cytology in small animal practice. *Vet Clin N Am Small Anim Pract*. 2007;37:351.

Stockhaus C, et al. A multistep approach in the cytologic evaluation of liver biopsy samples of dogs with hepatic diseases. *Vet Pathol*. 2004;41:461.

Vignoli M, et al. Computed tomography-guided fine-needle aspiration and tissue-core biopsy of bone lesions in small animals. *Vet Radiol Ultrasound*. 2004;45:125.

Wang KY, et al. Accuracy of ultrasound-guided fine-needle aspiration of the liver and cytologic findings in dogs and cats: 97 cases (1990-2000). *J Am Vet Med Assoc*. 2004;224:71.

Wellman ML. The cytologic diagnosis of neoplasia. *Vet Clin N Am*. 1990;20:919.

CHAPTER 75

Principles of Cancer Treatment



GENERAL CONSIDERATIONS

Cancer remains the main cause of death in dogs and possibly cats as well. In some dog breeds, including Golden Retrievers and retired racing Greyhounds, 60% of the deaths are due to cancer. For years, a variety of therapeutic modalities have been used in dogs and cats with cancer (Box 75.1). However, until 2 or 3 decades ago, surgery remained the mainstay of cancer treatment for pets. Today, nonresectable or metastatic malignancies can be treated with varied degrees of success, using some of the modalities listed in Box 75.1.

When evaluating a pet with cancer, the clinician should bear in mind that, in most cases, if given the option, owners will elect to treat their pets. Although euthanasia still remains a reasonable choice in some small animals with cancer, every effort should be made to investigate treatment options. More than 60% of human cancer patients have a life expectancy of at least 5 years, and a sizable portion of cancer patients, including those with high-grade lymphoma, some acute leukemias, and some carcinomas and sarcomas, are cured. Although such numbers are not available for dogs and cats with cancer, in the author's clinic, the proportion of cancer patients evaluated for 2- to 5-year follow-up is increasing.

A major philosophical difference when treating cancer in humans versus pets is the concept of cure. Although cure is a laudable goal in people, the price paid in terms of toxicity (and the expenses) makes it difficult to justify such an approach in pets. In the author's clinic, quality of life (QOL) drives the treatments of choice (see later).

Depending on the tumor type, biologic behavior, and clinical stage, a clinician may recommend one or more of the treatments listed in Box 75.1. However, in addition to tumor-related factors, many other factors influence the selection of the optimal treatment for a pet with cancer. These include patient-related, family-related, and treatment-related factors.

PATIENT-RELATED FACTORS

It is important to remember that the best treatment for a particular tumor does not necessarily constitute the best treatment for a particular patient or the best treatment from the family's perspective. The most important patient-related factor to be considered is the animal's general health and activity or performance status (Table 75.1). For example, a cat or dog with markedly diminished activity and severe constitutional signs (i.e., poor performance status) may not be a good candidate for aggressive chemotherapy or the repeated anesthetic episodes required for external beam radiotherapy. Age by itself is not a factor that should be considered when discussing cancer therapy with the owner; the author believes that "age is not a disease." For example, a 14-year-old dog in excellent health is a better candidate for chemotherapy or radiotherapy than a 9-year-old dog with chronic kidney disease or decompensated congestive heart failure. Patient-related factors should be addressed before instituting specific cancer treatment (e.g., correct the azotemia, improve the nutritional status with enteral feeding).

FAMILY-RELATED FACTORS

Family-related factors play an important role in determining the treatment to be implemented in pets with cancer. Every clinician is aware of the impact of the owner-pet bond; this bond is so important that it often dictates the treatment approach used in a given patient. For example, owners may be so apprehensive about having their dog with lymphoma receive chemotherapy that they refuse such treatment; thus the optimal treatment is denied to this patient.

In the author's experience, pet owners should be made a part of the medical team. If they are assigned tasks to perform at home such as measuring the tumor to monitor the response to treatment, taking their pet's temperature daily, and monitoring their pet's performance status, they

BOX 75.1

Treatment Options for Animals With Cancer

Surgery
Radiotherapy
Traditional chemotherapy
Metronomic chemotherapy
Targeted molecular therapy
Immunotherapy (biologic response modifiers)
Hyperthermia
Cryotherapy
Phototherapy
Photochemotherapy
Electrochemotherapy
Thermochemotherapy
Unconventional (alternative)

TABLE 75.1

Modified Karnovsky's Performance Score for Dogs and Cats

GRADE	ACTIVITY/PERFORMANCE
0—Normal	Fully active, able to perform at predisease level
1—Restricted	Restricted activity from predisease level but able to function as an acceptable pet
2—Compromised	Severely restricted activity level; ambulatory only to the point of eating but consistently defecating and urinating in acceptable areas
3—Disabled	Completely disabled; must be force-fed; unable to confine urinations and defecations to acceptable areas
4—Dead	

Modified from Beveridge IB, Sobin LH: International histological classification of tumors of domestic animals, *Bull World Health Organ* 53:145, 1976.

assume responsibility for the fate of their pet and are therefore quite cooperative. The clinician should always be available to answer concerned pet owners' questions and guide them through difficult times. We always discuss all potential treatment options with the owner, emphasizing the pros and cons of each (e.g., beneficial effects and potential for adverse effects of treatment A versus B versus C versus no treatment). The authors also clearly explain what will (or should) happen during the pet's treatment, including a thorough description of the potential adverse effects by presenting different case scenarios (i.e., best-case scenario versus worst-case scenario). By observing these easy steps, the clinician usually cultivates realistic expectations on the part of the owner and ensures that the interaction with the owner is smooth and uneventful. As discussed in later paragraphs, the option of euthanasia may also be addressed at this time, either as an immediate option or eventual option if treatments fail.

Another important owner-related factor is finances. In general, the treatment of a cat or dog with disseminated or metastatic malignancy is relatively expensive, as judged by the average clinician. However, it is the owner who should determine whether this treatment is indeed too costly. It is relatively common for an owner to spend $5000 to $10,000 to treat a dog or cat with surgery, radiotherapy, or chemotherapy. In contrast, a common orthopedic surgical procedure (e.g., tibial plateau leveling osteotomy) costs $2500 to $4000. Therefore all treatment options should be described and offered to the pet family, regardless of their cost. Occasionally, families spend what most people consider to be exorbitant amounts of money to treat their pet with cancer or other diseases. As numerous owners explain, this is their family member, and it is their money!

TREATMENT-RELATED FACTORS

Several important treatment-related factors must be considered when planning cancer therapy. First, the specific indication should be considered. Surgery and radiotherapy are treatments aimed at eradicating a locally invasive tumor with a low metastatic potential (and potentially curing the patient), although they can be used palliatively in dogs or cats with extensive (bulky) disease or in those with metastatic disease. On the other hand, chemotherapy usually does not constitute a curative treatment, although palliation of advanced disease can easily be accomplished for several tumor types. Immunotherapy (the use of biologic response modifiers) also constitutes an adjuvant or palliative approach (i.e., tumors are rarely cured by immunotherapy alone). Recently, targeted molecular therapy has been aimed at blocking specific pathways present in neoplastic but not normal cells. In general, it is best to use an aggressive treatment when the tumor is first detected (because this is when the chances of eradicating every single tumor cell are the highest) rather than to wait until the tumor is in an advanced stage (i.e., to "treat big when the disease is small"). Removing "only" 99% of the tumor cells will not lead to a cure.

In some cases, the highest success rates are obtained by combining two or more treatment modalities. For example, the combination of surgery and chemotherapy has resulted in a significant prolongation of disease-free survival in dogs with osteosarcoma of the appendicular skeleton (4 months with surgery alone versus 12-18 months with surgery and chemotherapy).

The complications and adverse effects of different treatments also constitute treatment-related factors to be considered when planning therapy. Complications of chemotherapy are addressed in Chapter 77. As discussed later, the patient's QOL should be maintained (or improved) during cancer treatment. At the authors' clinic, this is the priority in a cat

or dog with cancer receiving treatment. Our motto is "The patient should feel better with the treatment than with the disease."

Cancer treatment can be either palliative or curative. Given the current paucity of information regarding specific tumor types and treatments, these two approaches sometimes overlap (i.e., a treatment initially thought to be palliative may result in cure, or vice versa). As discussed earlier, every effort should be made to eradicate every single cancer cell in the body (i.e., obtain a cure) shortly after diagnosis, if "the price is right" (i.e., the cost and toxicity are not excessive and the patient's QOL will be good). This means taking immediate action rather than adopting a wait-and-see attitude. With few exceptions, malignant tumors do not regress spontaneously. In other words, by delaying treatment in a patient with confirmed malignancy, the clinician is only increasing the probability that the tumor will disseminate locally or systemically, thereby decreasing the likelihood of a cure. As discussed earlier, surgery and radiotherapy are potentially curative treatments, whereas chemotherapy and immunotherapy are usually palliative.

If a cure cannot be obtained, the two main goals of treatment used to be to induce remission while achieving a good QOL. The term *remission* refers to shrinkage of the tumor. When objectively evaluating the effects of therapy, the clinician should measure the tumor or tumors and assess the response using the criteria given in Box 75.2. Recently, veterinary oncologists adopted RECIST (response evaluation criteria in solid tumors), commonly used in people (Eisenhauer et al., 2009), and have adapted them to lymphomas (Vail et al., 2010).

A newer approach that may become more and more common as data are generated is the use of novel, low-dose treatment (metronomic chemotherapy) to "keep the tumor at bay" while preserving the patient's QOL. Most cancer patients are not symptomatic when they first present; hence keeping the tumor as-is while preserving the QOL is a viable (and attractive) option for an elder patient. Metronomic chemotherapy is discussed in detail in Chapter 76.

The QOL issue is important in small animal oncology (see preceding paragraphs). In a QOL survey of owners whose pets had undergone chemotherapy for nonresectable or metastatic malignancy conducted in the author's clinic, more than 80% responded that the QOL of their pets was maintained or improved during treatment. If a good QOL cannot be maintained (i.e., the patient's performance status deteriorates), the treatment should be modified or discontinued. Several useful QOL evaluation tools have been developed for use in pets with cancer (Lynch et al., 2011).

Palliative treatments are acceptable for small animals with cancer and to their owners. For example, even though chemotherapy rarely achieves a cure for most tumors, veterinarians can provide a cat or dog (and its family) with a prolonged, good-quality survival. Although these patients ultimately die of tumor-related causes, the owners are usually pleased to have a pet that is asymptomatic for a longer period of time. Another common example that is frequently forgotten is palliative surgery (e.g., in dogs or cats with ulcerated mammary carcinomas and small pulmonary metastases, euthanasia is frequently recommended because the primary lesion is draining and thus does not allow for the patient to be a "pet," as in sitting on the owners' lap or on the furniture). Clinicians now know that performing a mastectomy or lumpectomy (even if the owners decline chemotherapy) is likely to result in several months of good-quality survival, until the metastatic lesions finally cause respiratory compromise. In another example, dogs with apocrine gland

BOX 75.2

Criteria Used to Assess Tumor Response to Treatment in Pets With Lymphoma

Complete Response (CR):

Target lesions: Disappearance of all evidence of disease. All lymph nodes must be nonpathologic in size in the judgment of the evaluator(s).

Nontarget lesions: Any pathologic lymph nodes must be considered to have returned to normal size in the judgment of the evaluator(s), and no new sites of disease should be observed. Spleen and liver should be considered within normal limits by the evaluator(s).

Partial Response (PR):

Target lesions: At least a 30% decrease in the mean sum LD of target lesions taking as reference the baseline mean sum LD. Nontarget lesions: Not applicable.*

Progressive Disease (PD):

Target lesions: At least a 20% increase in the mean sum LD taking as reference the smallest mean sum LD at baseline or during follow-up (this includes the baseline mean sum LD if that is the smallest on study). The LD of at least one of the target lesions must demonstrate an absolute increase of at least 5 mm compared with its nadir for PD to be defined. For target lesions less than 10 mm at nadir, an increase in LD of any single previously identified target lesion to 15 mm or greater.

Nontarget lesions: unequivocal progression of existing nontarget lesions, in the judgment of the evaluator. (*Note:* The appearance of one or more new lesions is also considered progression.)

Stable Disease (SD):

Target lesions: Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD. Nontarget lesions: Not applicable.*

LD, Longest diameter.
This is a modification of the RECIST criteria (Eisenhauer et al., 2009) and can be applied to pets with solid tumors.
Modified from Vail DM, et al.: Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)—a Veterinary Cooperative Oncology Group (VCOG) consensus document, *Vet Comp Oncol* 8:28, 2010.
*Nontarget lesions will be assessed as "CR," "PD," "non-CR/non-PD," or, if there are no nontarget lesions, "None."

TABLE 75.2

Analgesics Commonly Used in Dogs With Cancer

DRUG	BRAND	DOSAGE
Nonsteroidal Antiinflammatories		
Carprofen	Rimadyl	1-2 mg/kg PO q12h
Deracoxib	Deramaxx	1 mg/kg PO q24h
Meloxicam	Metacam	0.1-0.2 mg/kg PO q24h
Firocoxib	Previcox	5 mg/kg PO q24h
Piroxicam	Feldene	0.3 mg/kg PO q24-48h
Opioids		
Tramadol	Ultram	1-4 mg/kg PO q8-12h
Buprenorphine	Buprenex	0.01-0.03 mg/kg PO or SC q8-12h

adenocarcinoma of the anal sac and metastatic sublumbar lymphadenopathy benefit from surgical resection of the primary tumor and/or metastatic nodes, even if adjuvant chemotherapy is not being considered. Removal of the primary mass improves clinical signs of straining in these patients; because the colon and rectum are compressed ventrally by the enlarged lymph nodes and laterally or dorsally by the primary mass, the removal of one of the lesions easily alleviates clinical signs. Sublumbar (or iliac) lymphadenectomy and chemotherapy in dogs with metastatic apocrine gland adenocarcinoma of the anal sacs in the author's clinic result in survival times of 1 to 3 years.

Needless to say, the clinician should also address the presence of paraneoplastic syndromes even if specific antineoplastic therapy is not contemplated. For example, treatment of hypercalcemia of malignancy with bisphosphonates causes remarkable improvement in the QOL of affected dogs. The authors' clinics have used pamidronate (at a dosage of 1-2 mg/kg, administered intravenously q6-8 weeks) or zoledronate (at a dosage of 0.1 mg/kg administered intravenously q3-8 weeks) in dogs with tumor-associated hypercalcemia in which the neoplastic disease could not be surgically removed or that had failed chemotherapy. In most dogs, serum calcium concentrations were maintained within normal limits, and no appreciable toxicity was detected. In addition, pain control has recently contributed markedly to improving the QOL in small animal cancer patients. Opioids, nonsteroidal antiinflammatories, and other drugs have resulted in excellent clinical results (Table 75.2).

Finally, most cats and dogs with cancer are treated using a team approach. This team includes the pet, family, medical oncologist, oncologic nurse, surgical oncologist, radiotherapist, clinical pathologist, and anatomic pathologist. A smooth interaction among the members of the team results in marked benefits for the pet and its owner.

Suggested Readings

Aiken SW. Principles of surgery for the cancer patient. *Clin Tech Small Anim Pract*. 2003;18:75.

Couto CG. Principles of cancer treatment. In: Nelson R, Couto CG, eds. *Small animal internal medicine*. 4th ed. St Louis: Elsevier; 2009:1150.

Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228.

Lagoni L, et al. *The human-animal bond and grief*. Philadelphia: WB Saunders; 1994.

Lynch S, et al. Development of a questionnaire assessing health-related quality-of-life in dogs and cats with cancer. *Vet Comp Oncol*. 2011;9:172.

McEntee MC. Veterinary radiation therapy: review and current state of the art. *J Am Anim Hosp Assoc*. 2006;42:94.

Page RL, et al. Clinical indications and applications of radiotherapy and hyperthermia in veterinary oncology. *Vet Clin North Am Small Anim Pract*. 1990;20:1075.

Vail DM, et al. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)—a veterinary cooperative oncology group (VCOG) consensus document. *Vet Comp Oncol*. 2010;8:28.

Withrow SJ. The three rules of good oncology: biopsy! biopsy! biopsy! *J Am Anim Hosp Assoc*. 1991;27:311.

CHAPTER 76

Practical Chemotherapy



CELL AND TUMOR KINETICS

To better understand the effects of chemotherapy on both neoplastic and normal tissues, it is necessary to have a basic understanding of cell biology and tumor kinetics. As a general rule, the biologic characteristics of neoplastic cells are similar to those of their normal counterparts; however, neoplastic cells usually do not undergo terminal differentiation or apoptosis (programmed cell death). Therefore the cell cycles of normal and neoplastic cells are similar.

Recently, Hanahan and Weinberg reviewed the original hallmarks of cancer (Hanahan and Weinberg, 2011); these hallmarks provide a framework to better understand cancer cell biology. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks is genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Research in the past few years added two emerging hallmarks—reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.

The mammalian cell cycle has two apparent phases: mitosis and the resting phase. The resting phase is actually composed of four phases (Fig. 76.1):

1. Synthesis phase (S): DNA is synthesized.
2. Gap 1 phase (G1): RNA and the enzymes needed for DNA production are synthesized.
3. Gap 2 phase (G2): The mitotic spindle apparatus forms.
4. Gap 0 phase (G0): This is the true resting phase.

The mitosis phase is termed the *M phase.*

Oncogenes serve as checkpoints between different phases of the cell cycle.

Several terms must be defined before chemotherapy is discussed. The *mitotic index* (MI) refers to the proportion of cells in the process of mitosis within a tumor; the pathologist often provides information about the mitotic activity in a given tumor sample, reported as the MI or as the number of mitoses per high-power field (or per 10 high-power fields). The *growth fraction* (GF) refers to the proportion of proliferating cells within a tumor and cannot be quantified in a patient. The *doubling time* (DT) refers to the time it takes for a tumor to double in size; it can be calculated by using sequential measurements of the tumor volume [$V = p/6' (\text{mean diameter})^3$] seen on imaging or determined by direct palpation. In dogs the DT ranges from 2 days (for metastatic osteosarcoma) to 24 days (for metastatic melanoma), whereas in humans it ranges from 29 days (for malignant lymphomas) to 83 days (for metastases from breast cancer). The DT depends on the time spent in mitosis, the cell cycle duration, the GF, and the cell loss resulting from death or metastasis; as a general rule, the shorter the DT, the more aggressive the tumor (and the more likely to respond to conventional chemotherapy). Given our knowledge of tumor kinetics, by the time a pulmonary metastatic nodule is visualized on radiographs, it consists of more than 200 million cells, weighs less than 150 mg, and the cells have already divided 25 to 35 times. A 1-cm palpable nodule has 10^9 tumor cells (1 trillion) and weighs 1 g (Fig. 76.2). As a general rule, most nonneoplastic tissues (with the exception of bone marrow stem cells and intestinal crypt epithelium) have a low GF, low MI, and prolonged DT, whereas most neoplastic tissues have a high MI, high GF, and short DT (at least initially; see Fig. 76.2).

Surgical cytoreduction (debulking) of a tumor that has reached a plateau of growth decreases the total number of cells, thus increasing the MI and GF and shortening the DT through yet unknown mechanisms (Fig. 76.3). In theory, this renders the neoplasm more susceptible to chemotherapy or radiotherapy.

BASIC PRINCIPLES OF CHEMOTHERAPY

Chemotherapeutic agents predominantly kill cells in rapidly dividing tissues. To exploit the tumoricidal effect of different chemotherapeutic drugs, it is common practice to combine three or more drugs to treat a given malignancy. These drugs are selected on the basis of the following principles: Each should be active against the given tumor type, act by a different mechanism of action, and not have superimposed toxicities. It is customary to name the protocol after the first letters of each drug in the combination (e.g., *VAC* for *v*incristine, doxorubicin [or *A*driamycin], and *c*yclophosphamide). As a general rule, combination chemotherapy results in more sustained remissions and prolonged survival times than single-agent chemotherapy; this is thought to result from the fact that multiagent chemotherapy delays (or even prevents) the development of drug-resistant clones. In some cases, single-agent chemotherapy is as effective as

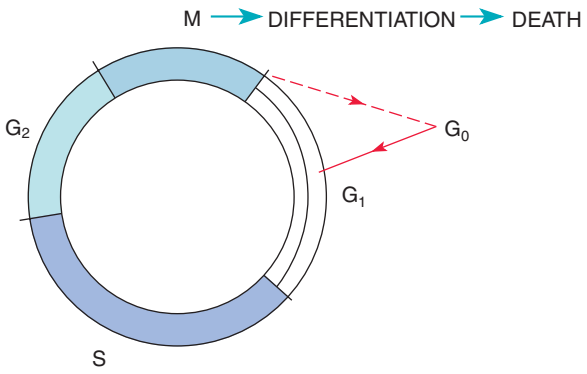


FIG 76.1
Mammalian cell cycle. Cells in mitosis *(M)* can differentiate and subsequently die (the rule in normal tissues); they can also progress to G_0 (true resting phase), from which they can be recruited by a variety of stimuli (see text). G_1, Gap 1; *S,* DNA synthesis; G_2, gap 2.

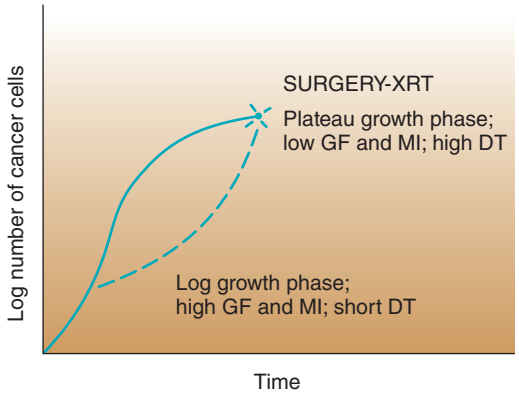


FIG 76.3
The effect of surgical or radiotherapeutic intervention on tumor kinetics. After cytoreduction, cells are recruited from the G_0 phase and the tumor returns to the exponential phase. *DT,* Doubling time; *GF,* growth factor; *MI,* mitotic index; *XRT,* radiation therapy. (From Couto CG: Principles of chemotherapy. In *Proceedings of the tenth annual Kal Kan symposium for the treatment of small animal diseases: oncology,* Kalkan Foods, Inc, 1986, Vernon, Calif, p 37.)

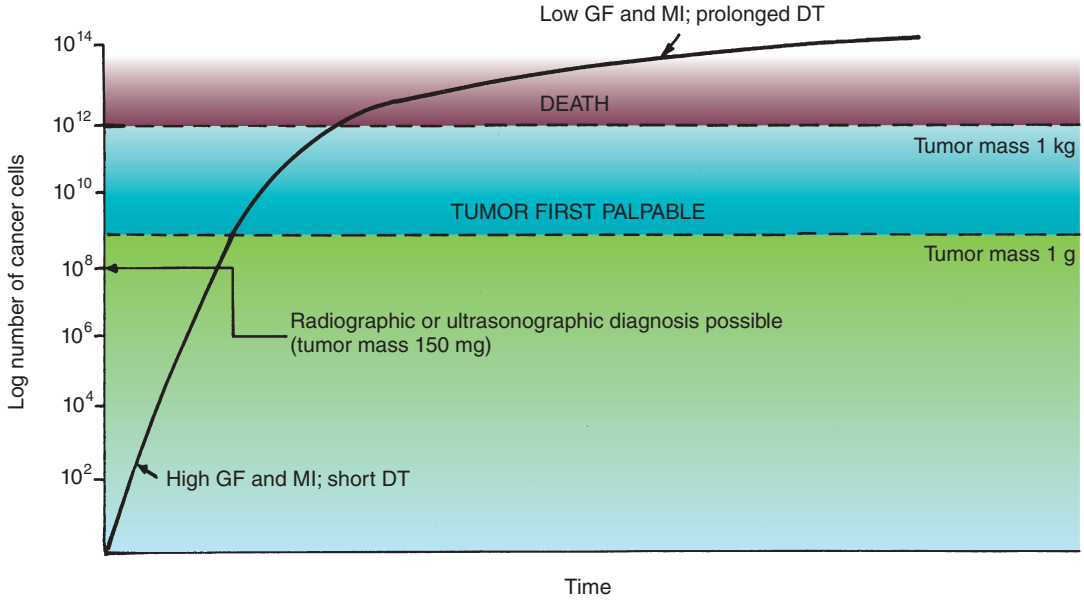


FIG 76.2
Tumor (cell) kinetics. Additional information on tumor kinetics can be found in the text. *GF,* Growth fraction; *MI,* mitotic index; *DT,* doubling time. (From Couto CG: Principles of chemotherapy. In *Proceedings of the tenth annual Kal Kan symposium for the treatment of small animal diseases: oncology,* Kalkan Foods, Inc, 1986, Vernon, Calif, p 37.)

multiagent chemotherapy and is associated with significantly less toxicity. Examples include using carboplatin or doxorubicin as single agents in dogs with osteosarcoma; chlorambucil alone for dogs with chronic lymphocytic leukemia; and vincristine alone in dogs with transmissible venereal tumors.

Another general concept of chemotherapy from the standpoint of cell kinetics is that it is more effective in a relatively small tumor than in a large one, even though the inherent sensitivity to the drug or drugs may be the same. As can be seen in Fig. 76.3, a small tumor (e.g., 10^6 cells) is more likely (e.g., 10^{11} cells) to be completely eradicated by the drugs than a larger one because the smaller mass has a higher MI, a higher GF, and consequently a shorter DT than the larger mass (i.e., more cells are actively dividing at a given time).

Despite continued controversy, the doses of most chemotherapeutic agents are still determined on a body surface area (BSA) basis; exceptions are listed later. This appears to provide a more constant metabolic parameter for comparing doses across species. It can be calculated using the following formula:

$$\frac{\text{Weight (g)}^{2/3} \times \text{K (constant)}}{10^4} = \text{m}^2 \text{ BSA}$$

The constant is 10.1 for the dog and 10 for the cat. Table 76.1 is a conversion table of weight (in kilograms) to BSA (in squared meters) for dogs. Table 76.2 is a conversion table for cats. When using drugs such as doxorubicin or carboplatin, doses determined on the basis of BSA usually lead to adverse effects in very small dogs (i.e., those <10 kg) and in cats. A dose determined on the basis of weight (e.g., 1 mg/kg for doxorubicin, 10 mg/kg for carboplatin) is more appropriate in such small patients, resulting in a relatively lower adverse effect profile.

TABLE 76.1

Conversion of Body Weight to Body Surface Area in Dogs

BODY WEIGHT (kg)	BODY SURFACE AREA (m^2)	BODY WEIGHT (kg)	BODY SURFACE AREA (m^2)
0.5	0.06	26	0.88
01	0.10	27	0.90
02	0.15	28	0.92
03	0.20	29	0.94
04	0.25	30	0.96
05	0.29	31	0.99
06	0.33	32	1.01
07	0.36	33	1.03
08	0.40	34	1.05
09	0.43	35	1.07
10	0.46	36	1.09
11	0.49	37	1.11
12	0.52	38	1.13
13	0.55	39	1.15
14	0.58	40	1.17
15	0.60	41	1.19
16	0.63	42	1.21
17	0.66	43	1.23
18	0.69	44	1.25
19	0.71	45	1.26
20	0.74	46	1.28
21	0.76	47	1.30
22	0.78	48	1.32
23	0.81	49	1.34
24	0.83	50	1.36
25	0.85		

TABLE 76.2

Conversion of Body Weight to Body Surface Area in Cats

BODY WEIGHT (lb)	BODY WEIGHT (kg)	BODY SURFACE AREA (m^2)
5	2.3	0.165
6	2.8	0.187
7	3.2	0.207
8	3.6	0.222
9	4.1	0.244
10	4.6	0.261
11	5.1	0.278
12	5.5	0.294
13	6.0	0.311
14	6.4	0.326
15	6.9	0.342
16	7.4	0.356
17	7.8	0.371
18	8.2	0.385
19	8.7	0.399
20	9.2	0.413

INDICATIONS AND CONTRAINDICATIONS OF CHEMOTHERAPY

Chemotherapy is primarily indicated for animals with systemic (e.g., lymphoma, leukemias) or metastatic neoplasms, although it can also be used for the management of nonresectable, chemoresponsive neoplasms that have historically proved refractory to radiotherapy (primary chemotherapy). It can also be used as an adjuvant treatment after partial surgical debulking of a neoplasm (e.g., partial excision of an undifferentiated sarcoma) and is indicated for the control of micrometastatic disease after the surgical excision of some primary neoplasms (e.g., carboplatin or doxorubicin therapy after limb amputation in dogs with osteosarcoma; VAC or doxorubicin after splenectomy for dogs with hemangiosarcoma). Chemotherapy can also be administered intracavitarily in dogs and cats with malignant effusions or neoplastic involvement of the cavity/area in question (e.g., intrapleurally administered cisplatin or 5-fluorouracil in dogs with pleural carcinomatosis). Finally, neoadjuvant or primary chemotherapy is the approach used in animals with bulky tumors not amenable to surgical excision or radiotherapy. After the drugs cause the tumor to shrink, the tumor can be surgically excised; chemotherapy is then continued to eliminate any residual neoplastic cells (e.g., VAC chemotherapy for dogs with subcutaneous hemangiosarcomas, multiple chemotherapy protocols for dogs with mast cell tumors).

As a general rule, chemotherapy is considered to be palliative in pets with cancer. Although the cure rate of some human cancers treated with chemotherapy is high (e.g., >75% in high-grade lymphomas and pediatric acute lymphoid leukemias), the cost and toxicity associated with the high doses of chemotherapy is unacceptable in pets. For example, a dose of cyclophosphamide for a dog is rarely higher than 300 mg/m^2, whereas in humans doses of 2 to 3 g/m^2 are occasionally used. Similarly, we have used doses of 300 to 600 mg/m^2 of cytarabine once every 1 to 2 weeks in dogs, whereas in humans, some protocols call for 3 g/m^2 q12h for 6 or 7 days. Finally, conventional dosages of doxorubicin in dogs are 30 mg/m^2 q2 or 3 weeks, whereas some human protocols use 75 mg/m^2 q3 weeks.

Chemotherapy should not be used as a substitute for surgery or radiotherapy nor should it be used in animals with severe underlying multiple-organ dysfunction (or it should be used cautiously, with a dose modification) because this increases the risk of systemic toxicity.

MECHANISM OF ACTION OF ANTICANCER DRUGS

The effects of anticancer drugs on a neoplastic cell population follow first-order kinetic principles (i.e., the number of cells killed by a drug or drug combination is directly proportional to the dose used). These drugs kill a constant proportion of cells rather than a constant number of cells. Therefore the efficacy of a drug or drug combination depends on the number of cells in a given tumor (e.g., a drug combination that kills 99% of the cells in a tumor containing 100 million [10^9] cells leaves 1 million [10^6] viable cells).

As discussed in the following paragraphs, different types of anticancer drugs kill tumor cells by different mechanisms. Drugs that kill only dividing tumor cells (i.e., that do not kill cells in the G_0 phase) by acting on several phases of the cycle are termed *cell cycle phase-nonspecific drugs.* Alkylating agents belong to this group. Drugs that selectively kill tumor cells during a given phase of the cell cycle are termed *cell cycle phase-specific drugs.* Most antimetabolites and plant alkaloids are phase-specific drugs. Finally, drugs that kill neoplastic cells regardless of their cycle status (i.e., they kill both dividing and resting cells) are termed *cell cycle-nonspecific drugs.* These latter drugs are extremely myelosuppressive (e.g., nitrosoureas).

TYPES OF ANTICANCER DRUGS

Anticancer drugs are commonly classified into six categories (Box 76.1). Most of these drugs are currently available as generic products at a reasonable cost.

Alkylating agents cross-link DNA, thus preventing its duplication. Because they mimic the effects of radiotherapy, they are also referred to as *radiomimetics.* These drugs are active during several phases of the cell cycle (i.e., they are

BOX 76.1

Types of Anticancer Drugs

Alkylating Agents

Cyclophosphamide
Chlorambucil
Melphalan
CCNU (lomustine)
Carboplatin

Antimetabolites

Cytosine arabinoside
Methotrexate
Gemcitabine
5-Fluorouracil; *SHOULD NOT BE USED IN CATS!*
Azathioprine
Rabacfosadine

Antitumor Antibiotics

Doxorubicin
Bleomycin
Actinomycin D
Mitoxantrone

Plant Alkaloids

Vincristine
Vinblastine
Vinorelbine
Etoposide or VP-16
Paclitaxel

Hormones

Prednisone

Miscellaneous Agents

L-Asparaginase
Rabacfosadine

cell cycle phase-nonspecific) and are more active if given intermittently at high doses. The major toxicities of these drugs are myelosuppression and gastrointestinal. Alkylating agents commonly used in pets with cancer are listed in Box 76.1.

Antimetabolites exert their activity during the S phase of the cell cycle (cell cycle phase-specific) and are more active if given repeatedly at low doses or as continuous intravenous infusions. These drugs are structural analogs of naturally occurring metabolites (fake metabolites) that substitute for normal purines or pyrimidines. The major toxicities of these drugs are myelosuppression and gastrointestinal. Box 76.1 lists the antimetabolites commonly used in small animals with cancer.

Antitumor antibiotics act by several mechanisms (i.e., cell cycle phase-nonspecific), the most important of which appears to be DNA damage produced by free radicals or by a topoisomerase-II–dependent mechanism. There are now several synthetic or semisynthetic antibiotics, such as mitoxantrone. The major toxicities of these drugs are myelosuppression and gastrointestinal; doxorubicin and actinomycin D are extremely caustic if given perivascularly, resulting in severe extravasation injuries. Additionally, doxorubicin has cumulative cardiotoxic effects in dogs and may cause renal tubular damage with repeated dosing in cats. Antitumor antibiotics are listed in Box 76.1.

Plant alkaloids are derived from the periwinkle plant *(Vinca rosea)* and the May apple plant *(Podophyllum peltatum)*. Vinca derivatives disrupt the mitotic spindle and are therefore cell cycle phase-specific (active during M phase), whereas *Podophyllum* derivatives cross-link DNA. The major toxicity is perivascular sloughing if the agent extravasates. Although traditionally etoposide was not given intravenously because the vehicle (Tween 80) causes anaphylaxis, a recent study in 27 dogs with lymphoma using etoposide phosphate, a water-soluble derivative, reported no cases of anaphylaxis. Paclitaxel has also been recently used in dogs with neoplasia, primarily carcinomas; however, after conditional USDA approval for dogs, the drug was taken off the market. Box 76.1 lists selected plant alkaloids.

Hormones (corticosteroids) are commonly used for the treatment of hemolymphatic malignancies, mast cell tumors, and brain tumors (where they result in clinical improvement due to decrease in tumor-associated edema). Box 76.1 lists the most commonly used hormone.

Miscellaneous agents consist of drugs with a mechanism of action that is either unknown or differs from those of agents already described. Box 76.1 lists miscellaneous agents commonly used in small animals with cancer.

A novel approach to anticancer chemotherapy is to exploit the use of inhibitors of molecular targets such as the tyrosine kinase (TK) family receptors. These include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and Tie1/2, among others. Kit is a receptor found on mast cells, and Kit signaling is required for the differentiation, survival, and function of mast cells. Kit mutations are commonly identified in human chronic myelogenous leukemia; imatinib (Gleevec, Novartis, East Hanover, NJ) selectively blocks this TK pathway and induces apoptosis of neoplastic (but not normal) cells. Mutations of Kit are also common in canine mast cell tumors, where other small molecule TK inhibitors have been effective. Toceranib (Palladia, Zoetis, Madison, NJ), masitinib, and imatinib have been used extra-label in small animal patients for a variety of tumors (despite Palladia being approved for use in mast cell tumors); Palladia was the first FDA-approved drug for canine cancer.

METRONOMIC CHEMOTHERAPY

After Judah Folkman discovered tumor angiogenesis, several groups proposed that anticancer drugs may be able to target tumor vasculature because many of the endothelial cells that compose the wall of tumor blood vessels are immature

and constantly proliferating. Antiangiogenic drugs showed promise in mouse studies but not in human or spontaneous animal tumor patients.

Metronomic (from the Greek "metros," in small constant installments) chemotherapy is defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses and with no prolonged drug-free breaks. It is proposed to inhibit tumor growth primarily through antiangiogenic mechanisms, while significantly reducing undesirable toxic adverse effects. Targeted molecular drugs such as toceranib (Palladia, Zoetis, Madison, NJ) and nonsteroidal antiinflammatory drugs (NSAIDs) appear to have antiangiogenic effects by targeting specific receptors.

Metronomic chemotherapy is thought to exert its anticancer activity mainly by inhibiting tumor angiogenesis. However, immunomodulation appears to play a role in tumor response. T-regulatory lymphocytes (T_{REG}) have been shown to be increased in several human, canine, and feline cancers, and appear to correlate with tumor progression and lack of treatment response. Several studies performed in tumor-bearing animals have shown that low-dose cyclophosphamide can increase antitumor immune response by decreasing numbers and inhibiting the suppressive functions of T_{REG} cells but also by increasing both lymphocyte proliferation and memory T cells. Low-dose cyclophosphamide also decreases numbers of circulating T_{REG} in dogs. A third mechanism that appears to contribute to the effectiveness of metronomic chemotherapy is the induction of tumor dormancy or tumor cell apoptosis.

The authors previously evaluated several metronomic chemotherapy protocols that combine an NSAID, low-dose alkylators, and toceranib (Palladia) in dogs with spontaneous neoplasms, which showed objective responses in patients with carcinomas and sarcomas. For metronomic chemotherapy protocols, please see the Cancer Chemotherapy Protocols table (p. 1337).

SAFE HANDLING OF ANTICANCER DRUGS

Cytotoxic drugs have narrow therapeutic indices, with toxic effects occasionally noted at the standard therapeutic dosages. Occupational exposure, as might occur in personnel who commonly administer these drugs, has been documented in the literature; adverse effects, including headache, nausea, liver disease, and reproductive abnormalities, have been reportedly associated with this exposure. As such, no safe exposure level has been identified, and all possible measures to limit personnel exposure to cytotoxic drugs must be taken during their preparation and administration.

Reconstitution of cytotoxic drugs for administration must be performed in a biosafety level II vertical laminar airflow hood. Although the cost for this equipment is not prohibitively expensive for a large veterinary hospital (≈$6000-$10,000), this cost is currently not justified by the frequency of use. Closed system transfer devices (CSTDs) are practical and relatively inexpensive (PhaSeal, Carmel Pharma, Columbus, OH, and EquaShield, Port Washington, NY), which limit operator and environmental drug exposure to almost zero. If containment devices are not available, cytotoxic drugs can be reconstituted at a human hospital or pharmacy, or at a nearby small animal clinic with a sufficiently large oncology caseload. Care should be taken to respect the storage half-life of reconstituted drugs, and they should be administered to the patient as soon as possible after reconstitution. A recent literature review (Chan et al., 2017) described storage recommendations for various chemotherapy agents and can be used as a resource for chemotherapeutic drug storage in practice. Drugs should be delivered in a clearly labeled, sealed plastic bag, and any handling of the drugs should be performed while wearing the appropriate personal protective gear.

Personal protective gear has been shown to all but eliminate detectable occupational exposure to cytotoxic drugs in human oncology nurses when combined with safe, conservative handling practices. All personnel present during chemotherapy administration to animal patients, including veterinarians, technicians, and ward staff, must wear thick latex chemotherapy gloves or two pairs of regular latex examination gloves. The thickness of the gloves is more important than the composition for barrier protection. Ideally, personnel should also wear impermeable disposable gowns, eye protection, and particle-filtering face masks. All fluid lines should be primed before addition of cytotoxic drugs to reduce environmental contamination, and all potentially contaminated supplies, including gowns, gloves, fluid bags, lines, and so forth, should be disposed of in properly labeled biohazard bags or plastic sharps containers. Disposal of material potentially contaminated with cytotoxic drugs may be arranged through a local human hospital; alternatively, an Environmental Protection Agency–approved disposal facility should be located. Materials used in the preparation and administration of chemotherapy should not be reused. Patient waste, including urine and feces, should be disposed of similarly 24 to 48 hours after chemotherapy administration, and personnel involved in the husbandry of these patients should wear the previously recommended personal protective gear when attending patients.

Protocols for handling spills should be prepared in advance and posted in areas where patients may be receiving chemotherapy. This area should be a designated area of the hospital with low traffic and minimal drafts; a stall may be selected for this purpose in equine hospitals. Isolation stalls will minimize exposure of personnel to chemotherapeutic agents. Once the patient has received chemotherapy, its cage should be clearly identified with a notice that contains information about precautions to be taken during handling of the animal and its wastes.

Suggested Readings

Biller B. Metronomic chemotherapy in veterinary patients with cancer: rethinking the targets and strategies of chemotherapy. *Vet Clin North Am Small Anim Pract*. 2014;44(5):817.

Burton JH, et al. Low-dose cyclophosphamide selectively decreases regulatory T cells and inhibits angiogenesis in dogs with soft tissue sarcoma. *J Vet Intern Med*. 2011;25:920.

Chan CM, et al. A literature review of reports of stability and storage of common injectable chemotherapy agents used in veterinary patients. *Vet Comp Oncol*. 2017;15(4):1124.

Gaspar TB, et al. The use of low-dose metronomic chemotherapy in dogs-insight into a modern cancer field. *Vet Comp Oncol*. 2018;16(1):2.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646.

Klahn S. Chemotherapy safety in clinical veterinary oncology. *Vet Clin North Am Small Anim Pract*. 2014;44(5):941.

London CA. Small molecule inhibitors in veterinary oncology practice. *Vet Clin North Am Small Anim Pract*. 2014;44(5):893.

Pasquier E, et al. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol*. 2010;7:455.

CHAPTER 77

Complications of Cancer Chemotherapy



GENERAL CONSIDERATIONS

Because most anticancer agents are relatively nonselective, they kill not only rapidly dividing neoplastic cells but also some of the rapidly dividing normal cells in the host (e.g., villus epithelium, bone marrow cells). In addition, similar to other commonly used agents (e.g., digitalis glycosides), most anticancer agents have low therapeutic indices (i.e., narrow therapeutic-to-toxic ratios).

Because anticancer agents follow first-order kinetic principles (i.e., the fraction of cells killed is directly proportional to the dose used), increasing the dose of a particular drug increases the proportion of the neoplastic cells killed, but it also enhances its toxicity. This is commonly seen when a tumor relapses and higher doses of a previously prescribed chemotherapeutic agent are administered.

Because toxicity generally tends to affect rapidly dividing cells, given the short doubling times of the bone marrow and villal epithelial cells, myelosuppression and gastrointestinal signs are the most common toxicities encountered in practice. Other rare complications of chemotherapy include anaphylactoid (or anaphylactic) reactions, dermatologic toxicity, pancreatitis, cardiotoxicity, pulmonary toxicity, neurotoxicity, hepatopathies, and urotoxicity. Table 77.1 lists anticancer drugs commonly used in small animals and their toxicities.

Several factors can potentiate the effects of anticancer agents and thereby enhance their toxicity. For example, drugs that are excreted primarily through the kidneys (e.g., platinum compounds, methotrexate) are more toxic to animals with renal disease; thus a dose reduction or the use of an alternative drug is usually recommended in such patients.

In addition to the direct effects of some drugs on different organ systems, rapid killing of certain neoplastic cells (i.e., lymphoma cells) can lead to sudden metabolic derangements that result in acute clinical signs mimicking those of drug toxicity (i.e., depression, vomiting, diarrhea). This syndrome is referred to as *acute tumor lysis syndrome* (ATLS) (see p. 1286) and is extremely rare.

In general, cats appear to be more susceptible than dogs to some of the adverse effects of chemotherapy (e.g., anorexia, vomiting) but not to others (e.g., myelosuppression). Certain breeds of dogs, including Collies and Collie crosses, Old English Sheepdogs, Cocker Spaniels, and West Highland White Terriers, also appear to be more prone to some of the acute adverse reactions to chemotherapy (i.e., gastrointestinal signs, myelosuppression) than the general dog population. Interestingly, only some of these breeds (e.g., Collie, Sheltie) have mutations of the *ABCB1* (formerly *MDR1*) gene that encodes for P-glycoprotein, an efflux pump that rapidly eliminates chemotherapeutic agents from the cytoplasm of the cells, so alternative mechanisms of toxicity must be sought.

The overall prevalence of toxicity of different chemotherapy protocols is considerably lower in dogs and cats (≈5%-40%) than in humans (75%-100%) treated with similar drugs or combinations. A survey of owners whose pets had been treated with a variety of chemotherapy protocols at The Ohio State University Veterinary Medical Center revealed that more than 80% considered their pets' quality of life to be as good as or better than that before the institution of chemotherapy. Additionally, a similar study performed at North Carolina State University revealed that 77% of dogs and 66% of cats experienced no negative impact on their quality of life while undergoing chemotherapy, and 65% of dogs and 44% of cats handled chemotherapy better than the owners were expecting.

Recently, the Veterinary Cooperative Oncology Group updated the terminology for adverse events after chemotherapy in dogs and cats (Table 77.2).

HEMATOLOGIC TOXICITY

The high mitotic rate and growth fraction (i.e., 40%-60%) of the bone marrow cells predispose this organ to relevant toxicity from anticancer drugs. Hematologic toxicity constitutes the most common complication of chemotherapy, and often the severe and potentially life-threatening cytopenias that

TABLE 77.1

Toxicity of Anticancer Agents in Cats and Dogs

TOXICITY	DOX	BLEO	ACT	CTX	LEUK	CARBO	CISP	MTX	ARAC	5-FU	L-ASP	VCR	VBL	DTIC	CCNU	TAN
Myelosuppression	S	N	M	M/S	N/M	N/M	M	M/S	M/S	M	N/M	N/M	M/S	M/S	M/S	M
Vomiting/diarrhea	M/S	N	M	M	N/M	N/M	M/S	M/S	N/M	N/M	N	N/M	N/M	M/S	M	M
Cardiotoxicity	M/S	N	N	N/?	N	N	N	N	N	N	N	N	N	N	N	?
Neurotoxicity	N	N	N	N	N	N	N/M	N	N	M	N	N/M	N	N	N	N
Hypersensitivity	M/S	N	N	N	N	N	N	N	N	N	M/S	N	N	N	N	N
Pancreatitis	M	N	N	N/M	N	N	N	N	N/M	N	M/S	N	N	N/M	N	N
Perivascular sloughing	S	N	M/S	N	NA	N	N/M	N	N	N/M	N	M/S	M/S	M/S	N	M/S
Urotoxicity	M/S	N	N	M/S	N	N/M	M/S	M	N	N	N	N	N	N	M	N/M
Hepatotoxicity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M/S	N
Pulmonary toxicity	N	Y	N	N	N	N	S	N	N	N	N	N	N	N	M/S	M/S

ACT, Actinomycin D; *araC,* cytosine arabinoside; *BLEO,* bleomycin; *CARBO,* carboplatin; *CCNU,* lomustine; *CISP,* cisplatin; *CTX,* cyclophosphamide; *DOX,* doxorubicin; *DTIC,* dacarbazine; *5-FU,* 5-fluorouracil; *LEUK,* chlorambucil; *L-asp,* L-asparaginase; *M,* mild to moderate; *MTX,* methotrexate; *N,* none; *NA,* not applicable; *S,* severe; *TAN,* Tanovea; *VCR,* vincristine; *VBL,* vinblastine; *?,* questionable.

TABLE 77.2

Modified Veterinary Cooperative Oncology Group – Common Terminology Criteria for Blood Adverse Events (VCOG-CTCAE) Associated With Chemotherapy (see Supplemental Reading)

	GRADE				
ADVERSE EVENT	**1**	**2**	**3**	**4**	**5**
HGB	Dog: 10 G/dL to <LLRI Cat: 8 G/dL to <LLRI	Dog: 8 G/dL -10 G/dL Cat: 6.5 G/dL-8 G/dL	Dog: 6.5 G/dL-8 G/dL Cat: 5 G/dL-6.5 G/dL	Dog: <6.5 G/dL Cat: <5 G/dL	Death Death
HCT or PCV	Dog: 30% to <LLRI Cat: 25% to <LLRI	Dog: 20%-30% Cat: 20%-25%	Dog:15%-20% Cat: 15%-20%	Dog: <15% Cat: <15%	Death Death
Neutrophils	1500/μL to >LLRI	1000-1499/μL	500-999/μL	<500/μL	Death
Platelets	100,000/μL to LLRI	50,000-99,999/μL	25,000-49,999/μL	<25,000/μL	Death

HCT, Hematocrit; *HGB,* hemoglobin concentration; *LLRI,* lower limit of the reference interval; *PCV,* packed cell volume.
(Courtesy Veterinary Cooperative Oncology Group, 2011.)

occur necessitate the temporary or permanent discontinuation of the offending agent or agents. Table 77.1 lists agents commonly implicated in this type of toxicity.

It is easy to anticipate the cell line that will be affected on the basis of the bone marrow transit times and circulating half-lives of blood-formed elements. For example, the bone marrow transit time and circulating half-life of red blood cells in the dog are approximately 7 and 70 to 120 days, those of the platelets are 3 to 5 days and 4 to 6 days, and those of neutrophils are 5 to 6 days and 4 to 8 hours, respectively. On the basis of this, neutropenia usually occurs first, followed by thrombocytopenia. Chemotherapy-induced anemia is rare in dogs and cats and, if it occurs, is of late onset (3-4 months after initiation of therapy); in some dogs on chemotherapy, iron deficiency anemia is due to chronic gastrointestinal bleeding from gastroduodenal ulcers or erosions (see Chapters 30 and 82). Other patient-related factors (e.g., malnutrition, old age, concurrent organ dysfunction, prior extensive chemotherapy) and tumor-related factors (e.g., bone marrow infiltration, widespread parenchymal organ metastases) can also affect the degree of myelosuppression.

Although thrombocytopenia is probably as common as neutropenia, it is rarely severe enough to cause spontaneous bleeding, and therefore it is not discussed at length here. In general, in most dogs with chemotherapy-induced thrombocytopenia, the platelet counts remain above 50,000 cells/μL; spontaneous bleeding usually does not occur until platelet counts are below 30,000/μL. Some drugs and protocols are associated with predictable thrombocytopenia, including doxorubicin and dacarbazine (ADIC), D-MAC (see the table on cancer chemotherapy protocols in page 1337), lomustine, and melphalan in dogs; platelet counts associated with these protocols can be lower than 50,000/μL. Chemotherapy-induced thrombocytopenia is extremely rare in cats; however, because platelet clumping is common in cats, pseudothrombocytopenia (i.e., low platelet "count" but platelet aggregates on the analyzer graphics or blood smear) is seen frequently. Thrombocytosis is common in cats and dogs receiving vincristine or corticosteroids.

Neutropenia usually constitutes the dose-limiting cytopenia and occasionally leads to life-threatening sepsis in dogs; although neutropenia does occur in cats receiving chemotherapy, it rarely leads to the development of clinically recognizable sepsis. The nadir (i.e., lowest point in the curve) of neutropenia for most drugs usually occurs 5 to 7 days after treatment, and the neutrophil counts return to normal within 36 to 72 hours of the nadir. With certain drugs, the nadir of neutropenia is delayed (i.e., ≈3 weeks for carboplatin in dogs and cats). Dogs with neutrophil counts less than 2000 cells/μL should be closely monitored for the development of sepsis, although overwhelming sepsis rarely occurs in animals with neutrophil counts of more than 1000 cells/μL. As reported in a recent study, the development of sepsis in neutropenic cats is extremely rare or may go unrecognized. In this collaborative study from 8 institutions where patients were selected based on the authors' recall, only 20 cats with febrile neutropenia while undergoing chemotherapy were identified. Most cats had lymphoma and were receiving either lomustine and/or vinca alkaloids (Pierro et al., 2016). We have also observed severe, long-lasting myelosuppression associated with administration of lomustine in a limited number of cats (Fig. 77.1).

The pathogenesis of sepsis in neutropenic animals is as follows: First, the chemotherapy-induced death and desquamation of gastrointestinal crypt epithelial cells occur simultaneously with myelosuppression; next, enteric bacteria are translocated through the damaged mucosal barrier into the systemic circulation; and, finally, because the number of neutrophils in the circulation is not sufficient to phagocytose and kill the invading organisms, multiple organs become colonized with the bacteria and death ensues, unless the animal is treated appropriately.

It is important to identify the septic neutropenic patient using laboratory means due to the fact that the cardinal signs of inflammation (i.e., redness, swelling, increased temperature, pain, abnormal function) may be absent because there are not enough neutrophils to participate in the inflammatory process. The same holds true for radiographic changes

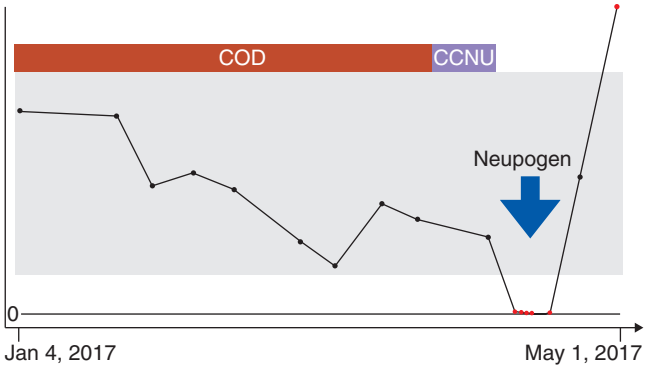


FIG 77.1
Leukocyte count in a Siamese cat with multicentric lymphoma who had a severe, long-lasting myelosuppressive event associated with lomustine administration. *COD,* Cyclophosphamide, vincristine, dexamethasone; *CCNU,* lomustine; *NEUPOGEN,* granulocyte colony-stimulating factor. The grey zone represents the reference interval for the white blood cell count.

compatible with inflammation; for example, dogs with neutropenia and bacterial pneumonia diagnosed on the basis of cytologic and microbiologic findings in transtracheal wash material often have normal thoracic radiographic findings (Fig. 77.2). As a general rule, if a severely neutropenic animal (neutrophil count <500/µL) is evaluated because of pyrexia (>104° F [>40° C]), the fever should be attributed to bacterial pyrogens until proved otherwise, and the patient should be treated aggressively with antimicrobial therapy (see following paragraphs). Neutropenic septic patients can also be hypothermic.

All dogs and cats undergoing chemotherapy should be up to date on their vaccines; it is controversial whether the use of modified-live vaccines should be avoided because of the potential for inducing illness in immunosuppressed animals. Recent evidence suggests that vaccinated dogs with cancer undergoing chemotherapy have protective serum antibody titers for commonly used vaccines.

Hematologic monitoring of the patient receiving chemotherapy constitutes the most effective way to prevent (or anticipate) severe, life-threatening sepsis or bleeding secondary to myelosuppression. Complete blood counts (CBCs) should be obtained weekly or every other week (depending on the treatment protocol), and the myelosuppressive agent or agents should be temporarily discontinued (or the dose decreased) if the neutrophil count decreases to fewer than 1000 cells/µL or if the platelet count decreases to fewer than 50,000 cells/µL. Discontinuing the offending agent or agents for two or three administrations usually allows sufficient time for the cell counts to return to normal. When therapy is reinstituted, it is recommended that only 75% of the initial dose be given and the doses increased during the next 2 to 3 weeks until the initially recommended dose (or a dose that does not produce marked cytopenias) is reached. Obviously, the drawback of discontinuing chemotherapy is the potential for tumor relapse, so the clinician

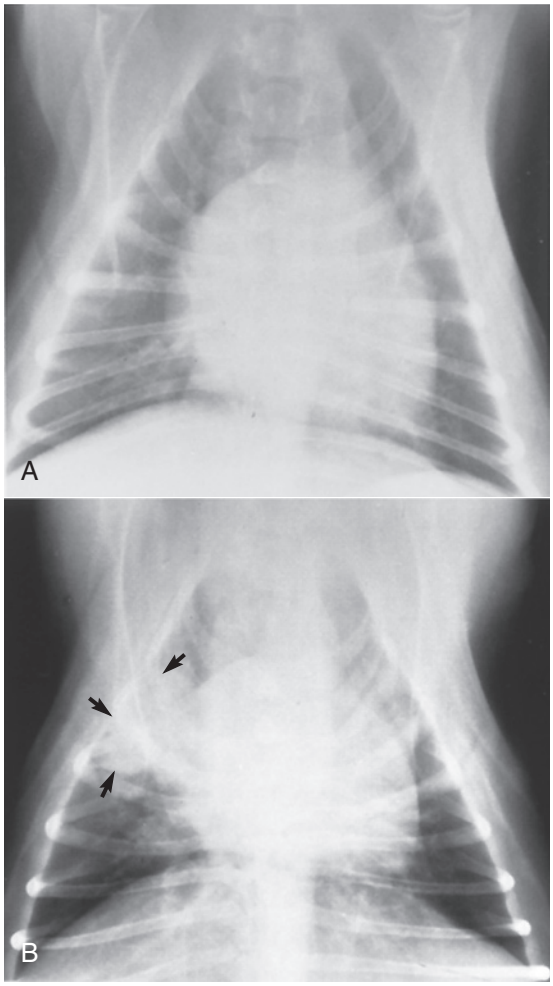


FIG 77.2
Thoracic radiographs from a 5-year-old male, castrated Boston Terrier with multicentric lymphoma treated with doxorubicin and dacarbazine (ADIC) chemotherapy. This dog presented as an emergency because of depression, fever, and mild bilateral nasal discharge. The neutrophil count on admission was 1500/µL. **(A)** Thoracic radiograph findings were considered normal at the time, but a transtracheal wash specimen contained bacteria. **(B)** Two days later, when the neutrophil count increased to 16,300/µL, focal areas of pneumonia became evident. (From Couto CG: Management of complications of cancer chemotherapy, *Vet Clin North Am* 20:1037, 1990.)

and owner must weigh the pros and cons of temporarily discontinuing treatment.

Clinically, neutropenic patients are classified as febrile or afebrile. Neutropenic, febrile patients should be managed aggressively because they are usually septic; thus fever in a neutropenic patient constitutes a medical emergency. The following protocol is the one currently used in such patients at our clinic. First, a thorough physical examination is performed to search for a septic focus, an indwelling intravenous (IV) catheter is placed aseptically, and IV fluids are administered as required. All anticancer agents are discontinued immediately, with the exception of corticosteroids,

which should be discontinued gradually, if at all, because acute hypoadrenocorticism can develop in animals receiving steroid therapy if the drug is abruptly discontinued. Blood samples for a CBC and serum biochemical profile are obtained immediately. A urine sample for urinalysis and bacterial culture may also be obtained, unless the patient is thrombocytopenic, in which case cystocentesis should be avoided to prevent intravesical bleeding. Two or three sets of aseptically collected blood samples can be obtained at 30-minute intervals for aerobic and anaerobic bacterial cultures and antibiotic susceptibility tests, although this is usually not necessary because the bacterial isolates are quite predictable (see following paragraph) and because the results of these tests will not be available for several days. After the second set of samples for blood cultures is collected (if doing so), therapy with an empirical bactericidal antibiotic combination is instituted. The authors use a combination of enrofloxacin (5-10 mg/kg IV q24h) and ampicillin (22 mg/kg IV q8h) or ampicillin/sulbactam (30 mg/kg IV q8h) because most bacterial isolates in such animals are Enterobacteriaceae and staphylococci, organisms commonly susceptible to these agents. Once the neutrophil count returns to normal and the patient's condition is clinically normal (usually within 72-96 hours), the antibiotic combination is discontinued and the animal is allowed to go home, with instructions to the owner to administer sulfadiazine-trimethoprim (ST) at a dosage of 13 to 15 mg/kg by mouth (PO) q12h, amoxicillin-clavulanic acid (CLAV) at a dosage of 13.75 to 20 mg/kg PO q12h, or enrofloxacin at a dosage of 5 to 10 mg/kg PO q24h for 5 to 7 days. When the patient returns for additional chemotherapy, the dose of the offending agent or agents should be decreased by 15% to 20% to prevent an additional occurrence.

In an unpublished study by one of the authors (GC), the yield for three sets of blood cultures in dogs with cancer, fever, and normal-to-high neutrophil counts is approximately 40%, whereas it is approximately 20% in dogs with cancer, fever, and neutropenia. Isolates in the former group usually include *Streptococcus* spp., *Staphylococcus* spp., *Enterobacter* spp., *Klebsiella* spp., and *Escherichia coli,* in decreasing order of frequency. In neutropenic febrile dogs, the isolates include mainly *Klebsiella* spp. and *E. coli; Staphylococcus* spp. is isolated in less than 20% of the dogs.

In a recent study (Shaffer et al., 2016) of 57 neutropenic episodes in 55 dogs undergoing chemotherapy, the prevalence of bacteremia when using 2 sets of blood cultures was 12.3% (7/57) and that of bacteriuria was 7.5%. The prevalence of bacteremia was similar between febrile and afebrile dogs, and most isolates were gram-positive organisms.

Neutropenic, afebrile, asymptomatic patients can be treated as outpatients by discontinuing the drug or drugs as described earlier and administering ST (13-15 mg/kg PO q12h), CLAV (13.75-20 mg/kg PO q12h), or enrofloxacin (5-10 mg/kg PO q24h). The patient that is afebrile but has constitutional signs should be considered to be septic and treated as described in previous paragraphs. If the neutropenia is not severe (i.e., >1000 cells/μL), no therapy is required and the patient should only be observed by the owner. Owners should be instructed to take their pet's rectal temperature twice daily and to call the veterinarian if pyrexia develops, in which case the patient is treated as neutropenic and febrile. ST and fluoroquinolones eliminate the aerobic intestinal flora but preserve the anaerobic bacteria, which are an important component of the local defense system because of their ability to produce local antibiotic factors and for this reason may be considered over CLAV. In addition, ST and fluoroquinolones are active against many pathogens isolated from animals with cancer, and they achieve therapeutic blood and tissue concentrations and also high intragranulocytic concentrations. Recent studies suggest that the use of antibiotics against gram-positive bacteria may shorten survival time in humans with lymphoma or chronic lymphocytic leukemia (Pflug et al., 2016), and that the microbiome composition predicts risk of sepsis in children with acute leukemia (Hakim et al., 2018), thus highlighting the role of the intestinal microbiome on tumor immunomodulation. Moreover, recent studies suggest that chemotherapy modifies the intestinal microbiome in some species and may decrease immunologic response against tumor antigens (Viaud et al., 2013).

Myelosuppression in dogs may be alleviated through the use of lithium carbonate (10 mg/kg PO q12h) or, in dogs and cats, recombinant human granulocyte colony–stimulating factor (G-CSF; Neupogen; 5 μ g/kg subcutaneously q24h). Although several studies have reported the beneficial role of G-CSF or granulocyte-macrophage colony–stimulating factor (GM-CSF) in dogs and cats, it is unlikely that these agents will find their way into the clinic owing to their high cost (≈$70-$150/day) and the fact that dogs and cats can mount an antibody response to this protein of human origin and inactivate it; moreover, in dogs with chemotherapy-induced neutropenia, the activity of endogenous G-CSF is extremely high, and neutrophil counts return to normal within 36 to 72 hours, the same interval reported for "response" to G-CSF. For this reason, G-CSF is typically reserved for patients that received accidental chemotherapy overdoses and in which the predicted duration of neutropenia is unknown.

GASTROINTESTINAL TOXICITY

Although less common than myelosuppression, gastrointestinal toxicity is a relatively common complication of cancer chemotherapy in pets. From a clinical standpoint, two major types of gastrointestinal complications can occur: the combination of anorexia, nausea, vomiting, and gastroenterocolitis.

Although results of controlled studies are not available, nausea and vomiting are not apparently as common in pets as they are in humans receiving similar drugs and dosages. Drugs associated with nausea and vomiting include dacarbazine (DTIC), cisplatin, doxorubicin (primarily in cats), methotrexate, actinomycin D, cyclophosphamide, and 5-fluorouracil (5-FU; see Table 77.1).

Acute anorexia, nausea, and vomiting caused by injectable drugs are usually prevented by administering the offending agents by slow IV infusion. If these problems persist despite this approach, antiemetics such as metoclopramide can be given at a dosage of 0.1 to 0.3 mg/kg IV, subcutaneously, or PO every 8 hours. Other antiemetics effective in dogs with chemotherapy-induced emesis are butorphanol (Torbugesic, Fort Dodge Labs, Fort Dodge, IA) at a dosage of 0.1 to 0.4 mg/kg intramuscularly or intravenously every 6 to 8 hours; ondansetron (Zofran, GlaxoSmithKline, Research Triangle Park, NC) at a dosage of 0.1 to 0.3 mg/kg immediately before chemotherapy and every 6 hours thereafter; or maropitant (Cerenia, Zoetis, Madison, NJ) at a dosage of 2 mg/kg, PO every 24 hours. (For additional information on this subject, see Chapter 28.) Our preferred approach is to use maropitant in these situations.

Methotrexate and cyclophosphamide, two drugs commonly administered PO, can also cause anorexia, nausea, and vomiting. Methotrexate commonly causes anorexia and vomiting 2 or 3 weeks after the start of therapy in dogs; these adverse effects are usually controlled with antiemetics as described earlier. If these problems persist, it may be necessary to discontinue methotrexate treatment. Cyclophosphamide tends to induce anorexia or vomiting in some cats. Cyproheptadine (Periactin, Merck Sharp & Dohme, West Point, PA) at a dosage of 1 to 2 mg (total dose) PO q8-12h is quite effective as an appetite stimulant and antinausea agent in cats; an alternative option is mirtazapine (3.75 mg PO q24h for cats; 3.75-30 mg PO q24h for dogs).

In our experience, chemotherapy-associated anorexia in dogs is more difficult to manage because nonspecific appetite stimulants such as cyproheptadine and mirtazapine do not seem to be effective. In these cases, oral antiemetics can be considered, mainly ondansetron and maropitant, which can be beneficial to decrease the duration of anorexia in some dogs. The novel Entyce (capromorelin oral solution, Aratana Therapeutics, Leawood, KS) is also an appetite stimulant in both dogs and cats with chemotherapy or cancer-induced anorexia (3 mg/kg PO q24h).

Gastroenterocolitis is uncommon in patients receiving anticancer agents. Drugs that occasionally cause this include methotrexate, 5-FU, actinomycin D, and doxorubicin. It occurs rarely in association with other alkylating agents such as cyclophosphamide. Of the drugs mentioned in the previous paragraphs, only doxorubicin and methotrexate appear to be of clinical relevance. On the basis of the author's experience, Collies and Collie crosses, Old English Sheepdogs, Cocker Spaniels, and West Highland White Terriers appear to be extremely susceptible to doxorubicin-induced enterocolitis, independently of *ABCB1* mutations.

Doxorubicin-induced enterocolitis is characterized by the development of hemorrhagic diarrhea (with or without vomiting), primarily of large bowel type, 3 to 7 days after the administration of the drug; it is more common in dogs than in cats. Supportive fluid therapy (if necessary) and treatment with therapeutic doses of bismuth subsalicylate–containing products (Pepto-Bismol, 3-15 mL or 1-2 tabs PO q8-12h) are generally effective in controlling the clinical signs in dogs, which usually resolve in 3 to 5 days. The administration of Pepto-Bismol from days 1 to 7 of the treatment may alleviate or prevent these signs in dogs at risk for gastroenterocolitis (i.e., one of the breeds mentioned, a patient with a history of this toxicity). The use of bismuth subsalicylate should be avoided in cats. Gastroenteritis associated with the PO administration of methotrexate usually occurs after 2 weeks of administration; the treatment is the same as that used for doxorubicin-induced enterocolitis.

HYPERSENSITIVITY REACTIONS

Acute type I hypersensitivity reactions occasionally occur in dogs receiving parenteral L-asparaginase or doxorubicin and are common in dogs treated with IV etoposide or taxol derivatives; in the latter two, there is a reaction to the solubilizing agent (Tween 80, Cremophor EL). As discussed earlier, a water-soluble form of etoposide is now available. The reaction to doxorubicin does not appear to be a true hypersensitivity reaction, however, because this agent can induce direct mast cell degranulation independently of immunoglobulin E (IgE) mediation. Etoposide can be safely administered to dogs PO. Hypersensitivity reactions to anticancer agents are extremely rare in cats and thus are not discussed.

Clinical signs in dogs with hypersensitivity reactions to anticancer agents are similar to those in dogs with other types of hypersensitivity reactions (i.e., they are primarily cutaneous and gastrointestinal). Typical signs appear during or shortly after administration of the agent and include head shaking (caused by ear pruritus), generalized urticaria and erythema, restlessness, occasionally vomiting or diarrhea, and rarely collapse caused by hypotension.

Most systemic anaphylactic reactions can be prevented by pretreating the patient with H_1 antihistamines (i.e., intramuscular diphenhydramine, 1-2 mg/kg 20-30 minutes before administration of the drug) and by administering certain drugs (e.g., L-asparaginase) subcutaneously or intramuscularly rather than through an IV route. If the agent cannot be given by any other routes (i.e., doxorubicin), it should be diluted and administered by slow IV infusion.

The treatment of acute hypersensitivity reactions includes immediate discontinuation of the agent and the administration of H_1 antihistamines (i.e., diphenhydramine, 0.2-0.5 mg/kg by slow IV infusion), dexamethasone sodium phosphate (1-2 mg/kg IV), and fluids if necessary. If the systemic reaction is severe, epinephrine (0.1-0.3 mL of a 1:1000 solution intramuscularly or intravenously) should be used. Once the reaction subsides (and if it was mild), the administration of certain drugs such as doxorubicin may be continued. Injectable H_1 antihistamines should be used with caution in cats (if at all) because they can cause acute central nervous system depression leading to apnea.

DERMATOLOGIC TOXICITY

It is rare for anticancer agents to cause dermatologic toxicity in small animals. However, three types of dermatologic toxicities can occur: local tissue necrosis (caused by extravasation), delayed hair growth and alopecia, and hyperpigmentation. More recently, the newest chemotherapeutic agent that is conditionally approved for use in dogs with lymphoma, rabacfosadine (Tanovea, VetDC, Fort Collins, CO) has been reported to have a unique dermatologic toxicity discussed later.

Local tissue necrosis resulting from the extravasation of vincristine, vinblastine, actinomycin D, doxorubicin, or Tanovea is occasionally seen in dogs receiving these drugs but is extremely rare in cats. Indeed, according to anecdotal reports, cats have accidentally received full doses of doxorubicin perivascularly without developing tissue necrosis. The pathogenesis of this toxicity is poorly understood, but it is thought to be mediated by release of free radicals. Every effort should be made to ensure that these drugs are administered intravascularly. In addition to this complication, some retrievers (e.g., Labrador and Golden Retrievers) appear to experience pruritus or discomfort around the site of the IV injection even when the drug is known to have been administered intravascularly. This pain and discomfort frequently lead to licking and the development of a pyotraumatic dermatitis ("hot spot") within hours of the injection. In these dogs, applying a bandage over the injection site or placing an Elizabethan collar prevents this type of reaction.

To prevent or minimize the probability of extravascular injection of caustic drugs, they should be administered through small-gauge (22- to 23-gauge), indwelling, IV, over-the-needle catheters or through 23- to 25-gauge butterfly catheters. We use the former to administer doxorubicin and the latter to administer the vinca alkaloids and actinomycin D. Caustic drugs should be properly diluted before administration (i.e., vincristine to a final concentration of 0.1 mg/mL and doxorubicin to a concentration of 0.5 mg/mL) and the patency of the intravascular injection site ensured by intermittently aspirating until blood appears in the catheter. In the authors' clinics, doxorubicin is not administered by IV constant-rate infusion because such patients are more likely to undergo extravasation. If the site is not patent, the catheter should be placed in another vein. Recommendations for the management of extravascular injections are controversial; other than cold-packing the area for a few days, authors cannot agree as to whether diluting the extravasated drug with saline solution is a good or bad idea. For the management of perivascular doxorubicin, see next paragraph.

If, despite these precautions, a local tissue reaction occurs, it develops approximately 1 to 7 days after the perivascular injection of vinca alkaloids or actinomycin D and 7 to 15 days after doxorubicin extravasation. Tissue necrosis resulting from doxorubicin extravasation is far more severe than that associated with the extravasation of other agents because the drug is extremely caustic and persists in tissues for up to 16 weeks. If perivascular administration of doxorubicin has occurred (and the clinician has recognized it during or immediately after the administration), dexrazoxane (Zinecard, Pfizer) can be administered at 5 to 10 times the dose of doxorubicin given (i.e., for 30 mg of doxorubicin, 150-300 mg of dexrazoxane should be given). Dexrazoxane is rather expensive, so it is not routinely used in small animal patients. One of the authors has evaluated carvedilol (Coreg, GlaxoSmithKline) in a limited number of dogs that received perivascular doxorubicin. In three dogs that received treatment immediately after drug extravasation (at a dosage of 0.1-0.4 mg/kg q12-24h), there were no visible signs of necrosis. In three dogs that developed necrosis after perivascular doxorubicin administration, carvedilol resulted in rapid healing of the area (i.e., within 2-3 weeks). Clinical signs of extravasation include pain, pruritus, erythema, moist dermatitis, and necrosis of the affected area; severe tissue sloughing may occur (Fig. 77.3). If local tissue reactions develop, they can be treated as shown in Box 77.1.

In dogs and cats undergoing chemotherapy, delayed hair growth is more common than alopecia. This is in contrast to the situation in human patients, in whom severe scalp alopecia is a predictable complication of therapy. Because most chemotherapeutic agents affect rapidly dividing tissues, cells in the anagen (growth) phase of the hair cycle are usually affected. Therefore hair is slow to regrow in areas that were clipped or shaved before or during chemotherapy. Excessive shedding is also common.

Alopecia occurs predominantly in woolly-haired (coarse-haired) dogs such as Poodles, Schnauzers, and Kerry Blue



FIG 77.3
Tissue necrosis after extravascular injection of doxorubicin in a dog. Note the full-thickness sloughing of the area.

BOX 77.1

Treatment of Local Tissue Reactions

1. Apply an antibiotic ointment (with or without corticosteroids) to the affected area and start systemic antibiotics (amoxicillin/clavulanic acid).
2. Bandage the area (and replace bandages daily).
3. Prevent self-mutilation by placing an Elizabethan collar or a muzzle.
4. If there is no bacterial contamination (ruled out on the basis of negative bacterial cultures), 10 to 20 mg of methylprednisolone acetate (Depo-Medrol, Zoetis, Madison, NJ) can be injected subcutaneously in the affected area to alleviate pruritus and inflammation.
5. If severe necrosis or gangrene caused by anaerobic contamination occurs, the area should be surgically debrided.
6. In the event of severe doxorubicin-induced soft tissue necrosis, the affected limb may need to be amputated.

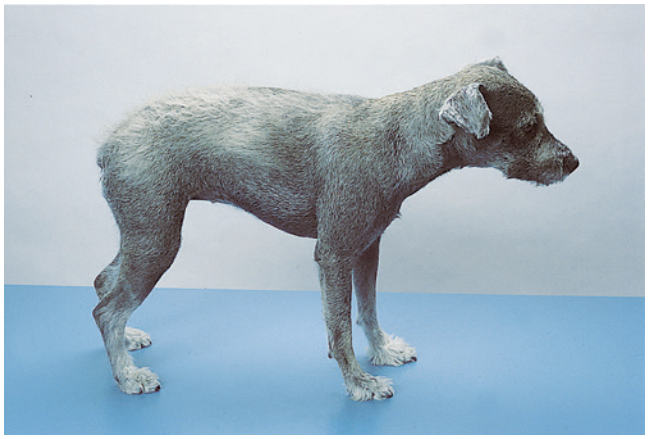


FIG 77.4
Alopecia in a 7-year-old Schnauzer undergoing doxorubicin and dacarbazine (ADIC) chemotherapy. Note the short and light-colored haircoat.

Terriers (Fig. 77.4). It primarily affects the tactile hairs in short-haired dogs and cats. Although the exact reason that chemotherapy-induced alopecia occurs in woolly-haired dogs is unknown, a prolonged anagen phase and synchronous hair growth, comparable with those occurring in human scalp hair, may make these dogs prone to this toxic effect. Drugs commonly associated with delayed hair growth and alopecia include cyclophosphamide, doxorubicin, 5-FU, 6-thioguanine, and hydroxyurea (Hydrea, E.R. Squibb & Sons, Princeton, NJ). Alopecia and delayed hair growth usually resolve shortly after discontinuation of the offending agent.

Hyperpigmentation is uncommon in dogs and extremely rare in cats receiving chemotherapy. Cutaneous hyperpigmentation affecting the face, ventral abdomen, and flanks is common in dogs receiving doxorubicin- and bleomycin-containing protocols. Occasionally, dogs on hydroxyurea develop generalized erythema.

Dermatologic toxicity has been identified in multiple cohorts of dogs receiving Tanovea; this dermatopathy develops in up to 45% of dogs, and generally consists of pruritic, focal otitis externa or focal erythemic skin lesions on the dorsum and in the inguinal region. This generally resolves with the institution of supportive treatments (antibiotics for dermatitis, corticosteroids) and treatment interruption.

PANCREATITIS

Pancreatitis is a well-recognized entity in human patients undergoing chemotherapy. Offending drugs in humans include corticosteroids, azathioprine, 6-mercaptopurine, L-asparaginase, cytosine arabinoside, and combination chemotherapy. Sporadic reports of pancreatitis in dogs (but not in cats) receiving chemotherapeutic and immunosuppressive agents have also appeared in the literature.

The author has documented acute pancreatitis in several dogs receiving L-asparaginase or combination chemotherapy. Dogs in the latter group were receiving COAP (cyclophosphamide, vincristine, cytosine arabinoside, prednisone); ADIC (doxorubicin, DTIC); or VAC (vincristine, doxorubicin, cyclophosphamide) chemotherapy. Clinical signs developed 1 to 5 days after the start of chemotherapy and consisted of anorexia, vomiting, and depression. Physical examination findings in these dogs were unremarkable, and abdominal pain was rare. The patients were treated with IV fluids, and the clinical signs resolved within 3 to 10 days in most dogs.

It is difficult to prevent chemotherapy-induced pancreatitis because it is not a predictable complication. As a further precaution, dogs receiving drugs with the potential to cause pancreatitis may be fed a low-fat diet.

CARDIOTOXICITY

Cardiotoxicity is a relatively uncommon complication of doxorubicin therapy in dogs; it is extremely rare in cats (one author has personally given cats more than 20 doses of doxorubicin without signs of cardiotoxicity). Two types of doxorubicin-induced cardiac toxicities are observed in dogs: an acute reaction occurring during or shortly after administration and a chronic cumulative toxicity. Acute doxorubicin toxicity is characterized by cardiac arrhythmias (mainly sinus tachycardia) that develop during or shortly after administration. This phenomenon is thought to stem from doxorubicin-induced histamine-mediated catecholamine release because the sinus tachycardia and hypotension can be prevented by pretreatment with H_1 and H_2 antihistamines. Several weeks or months after repeated doxorubicin injections, persistent arrhythmias, including ventricular premature contractions, atrial premature contractions, paroxysmal

ventricular tachycardia, second-degree atrioventricular blocks, and intraventricular conduction defects, can develop. These rhythm disturbances are usually associated with the development of a dilated cardiomyopathy, similar to that which occurs spontaneously in Doberman Pinschers and Cocker Spaniels.

The hallmark of chronic doxorubicin toxicity is a dilated cardiomyopathy that allegedly develops after a total cumulative dose of approximately 240 mg/m^2 is exceeded in the dog; however, we have administered higher cumulative doses without overt cardiac problems in a large number of dogs (see later). The histologic lesions seen in dogs with doxorubicin-induced cardiomyopathy consist of vacuolation of myocytes, with or without myofibril loss. Clinical signs of toxicity in dogs are those of congestive heart failure (usually left-sided). Therapy consists of discontinuation of the offending drug and the administration of cardiac drugs such as digitalis glycosides or nonglycoside inotropic agents (e.g., pimobendan). Once cardiomyopathy develops, the prognosis is poor because the myocardial lesions are irreversible.

It is critical to monitor patients receiving doxorubicin to prevent potentially fatal cardiomyopathy. In this respect, dogs (and possibly cats) with underlying rhythm disturbances or impaired myocardial contractility, as shown by decreased fractional shortening on echocardiogram, should not receive doxorubicin. It is also recommended that high-risk dogs receiving doxorubicin undergo echocardiographic evaluation every three doxorubicin cycles (9 weeks) to assess myocardial contractility and that the drug be discontinued if decreased fractional shortening occurs. Endomyocardial biopsy specimens are commonly obtained in people receiving doxorubicin in an effort to detect submicroscopic lesions, but this is impractical in dogs. The value of serum cardiac troponin I concentrations to detect early myocardial damage from doxorubicin is questionable in dogs.

Several protocols have been devised in an attempt to minimize doxorubicin-induced cardiomyopathy in dogs. Administering the doxorubicin slowly in a diluted solution (≈0.5 mg/mL over 30 minutes) seems to be the most effective; one of the authors (GC) has administered 8 to 10 doses of doxorubicin to a large number of dogs without obvious cardiotoxicity. This is due to the fact that cardiotoxicity of doxorubicin is directly related to the peak plasma concentration of the drug.

Dexrazoxane (Zinecard, Pfizer) offers a promising means of reducing the chronic cardiotoxicity induced by doxorubicin; doxorubicin doses in excess of 500 mg/m^2 have been administered to dogs receiving the agent without causing significant cardiotoxicity. Recently, carvedilol (0.1-0.4 mg/kg PO q12-24h) has been used successfully to prevent or decrease the probability of developing doxorubicin-associated cardiomyopathy in people (Kalay et al., 2006); one of the authors (GC) has successfully used carvedilol in dogs with subclinical myocardial dysfunction that needed doxorubicin.

UROTOXICITY

The urinary tract in small animals is rarely affected by adverse reactions to anticancer agents. Only two specific complications are of clinical importance in pets with cancer: nephrotoxicity and sterile hemorrhagic cystitis. Transitional cell carcinomas of the urinary bladder associated with chronic cyclophosphamide therapy have also been reported in dogs.

Nephrotoxicity is rarely observed in dogs and cats undergoing chemotherapy. Although several potentially nephrotoxic drugs are commonly used in these species, only doxorubicin (primarily in cats), cisplatin (in dogs), and intermediate to high doses of methotrexate (in dogs) are of concern to clinicians. The author's clinic does not use cisplatin frequently because of its potential to induce nephrotoxicity.

Doxorubicin may be a nephrotoxin in cats, and the limiting cumulative toxicity in this species may be renal rather than cardiac. This is generally seen after repeated doses of doxorubicin in cats, and for this reason, the authors commonly monitor kidney values and urine specific gravities in cats receiving repeated doxorubicin. If increases in creatinine and/or SDMA concentrations, or decreases in urine specific gravity develop, doxorubicin discontinuation should be considered. Doxorubicin may cause nephrotoxicosis in dogs with preexisting renal disease and in those concomitantly receiving other nephrotoxins such as aminoglycoside antibiotics or cisplatin. The administration of cisplatin using forced diuresis protocols minimizes the prevalence of nephrotoxicity in dogs. Due to its potential for nausea/vomiting and nephrotoxicity, the authors' clinics do not use cisplatin.

Sterile hemorrhagic cystitis (SHC) is a relatively common complication of long-term cyclophosphamide therapy in dogs; rarely, it may also occur acutely after a single dose of cyclophosphamide. This toxicity is not clinically relevant in cats. Acute clinical signs and urinalysis changes compatible with SHC developed after the first injection in three dogs treated at one clinic with IV cyclophosphamide, 100 mg/m^2, and four dogs receiving PO cyclophosphamide, 300 mg/m^2. SHC results from the caustic effects of one of the cyclophosphamide metabolites (acrolein) on the bladder epithelium. It develops in approximately 5% to 25% of dogs treated with cyclophosphamide, usually after an average of 18 weeks of therapy. Subjectively, it appears that the prevalence of SHC is higher when using cyclophosphamide in metronomic protocols. Furosemide or prednisone administered concomitantly with cyclophosphamide appears to decrease the prevalence of cystitis.

Forced diuresis appears to minimize the severity of this complication or prevent it. The authors usually recommend administering the cyclophosphamide in the morning, allowing the pet to urinate frequently (if it is an indoor dog), and administering prednisone on the same day that the animal receives the cyclophosphamide (if the protocol calls for prednisone administration). In addition, if giving bolus doses of cyclophosphamide to dogs, furosemide should be used to decrease the potential for SHC. An alternative method for

decreasing the risk of SHC is calculating the total dose of cyclophosphamide for a dog to receive (i.e., 200-250 mg/m^2 in the typical multiagent protocol for lymphoma) and splitting administration over 2-4 days. In a recent study, splitting administration of cyclophosphamide over 3 days without concurrent furosemide administration in dogs with lymphoma, 0/57 dogs to develop SHC (these dogs also experienced an 82% complete remission, suggesting that the efficacy was likely not affected by this dosing regimen) (Best et al., 2013). Additionally, a recent study evaluating the use of concurrent furosemide during metronomic administration of cyclophosphamide also subjectively decreased the prevalence of SHC to 3.6% (versus up to 32%) (Chan et al., 2016).

Clinical signs of sterile hemorrhagic cystitis are similar to those of other lower urinary tract disorders and include pollakiuria, hematuria, and dysuria. Urinalysis typically reveals blood and mildly to moderately increased numbers of white blood cells but no bacteria. Treatment of this complication consists of discontinuing the cyclophosphamide, forcing diuresis, diminishing the inflammation of the bladder wall, and preventing secondary bacterial infections. The cystitis resolves in most dogs within 1 to 4 months after the cyclophosphamide is discontinued. The author administers furosemide at a dosage of 2 mg/kg PO every 12 hours for its diuretic effects, prednisone at a dosage of 0.5 to 1 mg/kg PO every 24 hours for its antiinflammatory (and diuretic) effect, and an ST combination at a dose of 13 to 15 mg/kg PO every 12 hours to prevent secondary bacterial contamination. If the clinical signs worsen despite this approach, the instillation of 1% formalin solution in water into the bladder can be attempted. Gross hematuria resolved within 24 hours and did not recur in two dogs thus treated. The intravesical infusion of a 25% to 50% dimethylsulfoxide solution may also alleviate the signs of cystitis in dogs.

HEPATOTOXICITY

Chemotherapy-induced hepatotoxicity is extremely rare in dogs and cats. With the exception of the hepatic changes induced by corticosteroids in dogs, methotrexate, cyclophosphamide, lomustine, and azathioprine (Imuran, Burroughs Wellcome, Research Triangle Park, NC) have been implicated as or confirmed to be hepatotoxins in dogs. In our experience, the hepatotoxicity caused by anticancer drugs in small animals is of little or no clinical relevance, with the exception of lomustine.

A recent report describes a low prevalence of hepatotoxicity (<10%) in dogs receiving lomustine (CCNU) for lymphoma or mast cell tumors. The authors clinics have documented marked increases in alanine transaminase (ALT) activities (>1000 IU/L) and mild increases in alkaline phosphatase (ALP) activities (<500 IU/L) within 3 weeks of starting lomustine therapy in several dogs. Most dogs had decreases in the ALT and ALP concentrations after lengthening the dosing interval, decreasing the individual dosage, or both. In a recent study of 50 dogs receiving CCNU, increased liver enzyme activity occurred in 84% of dogs receiving CCNU alone and in 68% of dogs on concurrent Denamarin (Nutramax, Lancaster, SC) at therapeutic doses. Dogs receiving CCNU alone had significantly greater increases in ALT, aspartate aminotransferase, alkaline phosphatase, and bilirubin, and a significantly greater decrease in serum cholesterol concentrations than dogs receiving concurrent Denamarin. Dogs receiving CCNU alone were significantly more likely to have treatment delayed or discontinued because of increased ALT activity (Skorupski et al., 2011). For this reason, Denamarin should be used concurrently with CCNU when possible.

Dogs with immune-mediated disorders receiving chronic azathioprine therapy rarely develop increases in liver enzyme activities that respond to discontinuation of the drug.

NEUROTOXICITY

Anticancer agent–induced neurotoxicity is also extremely rare in dogs and cats. Neurotoxicosis occurs infrequently in dogs receiving 5-FU, although it is common in cats (for this reason, this drug should not be used in cats). Neurotoxicity can also occur in dogs and cats that ingest 5-FU intended for human use (i.e., prescribed for the owners). Clinical signs occur shortly (3-12 hours) after ingestion of the drug and consist primarily of excitation and cerebellar ataxia, resulting in death in approximately one third of the dogs and in most cats. Neurotoxicity was also documented in 25% of dogs receiving a combination of actinomycin D, 5-FU, and cyclophosphamide (the CDF protocol) for the management of metastatic or nonresectable carcinomas at one of the authors' clinics. This prevalence is considerably higher than that seen in association with the use of 5-FU in combination with other drugs and may be a result of drug interactions.

PULMONARY TOXICITY

Chemotherapy-induced pulmonary toxicity appears to be a rare adverse effect in dogs and cats. Lomustine has been associated with the development of pulmonary fibrosis in cats. This was seen after a high cumulative dose; however, it was associated with death after an episode of acute respiratory distress in one patient.

Similarly, there are multiple reports of pulmonary fibrosis in 5% to 15% of dogs treated with Tanovea; in most patients, it was fatal. Anecdotally, the concurrent use of prednisone may help decrease this specific toxicity. For this reason, we recommend not using Tanovea in breeds predisposed to development of pulmonary fibrosis, mainly West Highland White Terriers and other terrier breeds; we also recommend having baseline thoracic radiographs on dogs receiving this agent.

Bleomycin has also been associated with pulmonary toxicity in humans, leaving this as a potential concern for

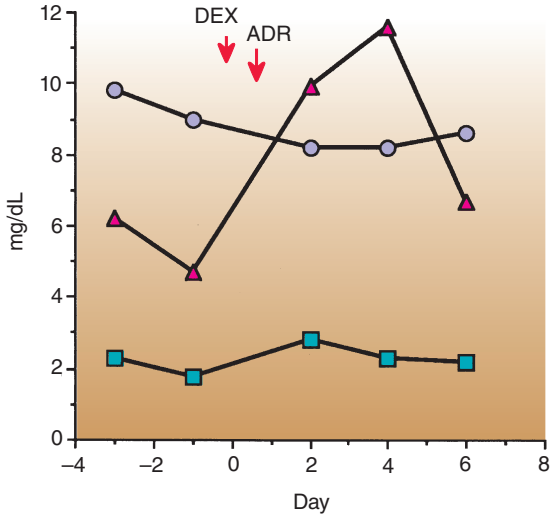


FIG 77.5
Serum phosphorus (Δ), calcium (○), and creatinine (□) concentrations in a dog with acute tumor lysis syndrome after chemotherapy for a primary pulmonary lymphoma. Note the increase in the serum phosphorus concentrations, with a mild decrease in the calcium concentrations and minor increases in the serum creatinine concentrations. *ADR,* Doxorubicin; *DEX,* dexamethasone. (From Couto CG: Management of complications of cancer chemotherapy, *Vet Clin North Am* 20:1037, 1990.)

veterinary use. Lastly, cisplatin can cause fatal pulmonary hypertension and edema in cats, and for this reason, is contraindicated for use in this species.

ACUTE TUMOR LYSIS SYNDROME

In human patients, the rapid lysis of certain tumor cells (e.g., lymphoma cells) shortly after chemotherapy may lead to a syndrome of hyperuricemia, hyperphosphatemia, and hyperkalemia, either singly or in combination. This clinical entity is referred to as *acute tumor lysis syndrome* and is thought to be secondary to the release of high quantities of intracellular phosphate, uric acid, and nucleic acid metabolites. The intracellular concentration of phosphorus in human lymphoma and leukemic cells is 4 to 6 times higher than that in normal lymphocytes, and the same appears to be true for dogs.

In dogs ATLS has been reported to occur only in association with lymphomas treated with chemotherapy, radiation therapy, or both, and is characterized by hyperphosphatemia, with or without azotemia, hyperkalemia, hypocalcemia, metabolic acidosis, and hyperuricemia. It is rare in cats. Clinical signs include depression, vomiting, and diarrhea, and occur within hours of the start of chemotherapy.

At one author's clinic, 10 cases of canine ATLS were documented in dogs with lymphoma during a period in which approximately 2000 dogs with lymphoma were treated with chemotherapy. In most dogs, the pretreatment serum creatinine concentrations or the tumor burden was high; one of the dogs had high liver enzyme activities. Within 1 to 7 days of the start of chemotherapy, lethargy, vomiting, and bloody diarrhea developed in affected dogs, and the serum phosphorus concentrations increased markedly (Fig. 77.5). Aggressive fluid therapy and the correction of acid-base and electrolyte disturbances resulted in resolution of the clinical signs within 3 days in 6 dogs; the remaining 2 dogs died as a result of ATLS.

Suggested Readings

Best MP, Fry DR. Incidence of sterile hemorrhagic cystitis in dogs receiving cyclophosphamide orally for three days without concurrent furosemide as part of a chemotherapeutic treatment for lymphoma: 57 cases (2007-2012). *J Am Vet Med Assoc.* 2013;243:1025.

Chan CM, et al. Incidence of sterile hemorrhagic cystitic in tumor-bearing dogs concurrently treated with oral metronomic cyclophosphamide chemotherapy and furosemide: 55 cases (2009-2015). *J Am Vet Med Assoc.* 2016;249:1408.

Charney SC, et al. Risk factors for sterile hemorrhagic cystitis in dogs with lymphoma receiving cyclophosphamide with or without concurrent administration of furosemide: 216 cases (1990-1996). *J Am Vet Med Assoc.* 2003;222:1388.

Couto CG. Management of complications of cancer chemotherapy. *Vet Clin N Am.* 1990;20:1037.

Hakim H, et al. Gut microbiome composition predicts infection risk during chemotherapy in children with acute lymphoblastic leukemia. *Clin Infect Dis.* 2018;67:541.

Harvey HJ, et al. Neurotoxicosis associated with use of 5-fluorouracil in five dogs and one cat. *J Am Vet Med Assoc.* 1977;171:277.

Hosoya K, et al. Prevalence of elevated alanine transaminase activity in dogs treated with CCNU (lomustine). *Vet Comp Oncol.* 2009;7:244.

Kalay N, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol.* 2006;48:2258.

Knapp DW, et al. Cisplatin toxicity in cats. *J Vet Intern Med.* 1988;1:29.

Kristal O, et al. Hepatotoxicity associated with CCNU (lomustine) chemotherapy in dogs. *J Vet Intern Med.* 2004;18:75.

Laing EJ, et al. Treatment of cyclophosphamide-induced hemorrhagic cystitis in five dogs. *J Am Vet Med Assoc.* 1988;193:233.

Mealey KL, Meurs KM. Breed distribution of the *ABCB1*-1Δ (multidrug sensitivity) polymorphism among dogs undergoing *ABCB1* genotyping. *J Am Vet Med Assoc.* 2008;233:921.

Peterson JL, et al. Acute sterile hemorrhagic cystitis after a single intravenous administration of cyclophosphamide in three dogs. *J Am Vet Med Assoc.* 1572;201:1992.

Pflug N, et al. Efficacy of antineoplastic treatment is associated with the use of antibiotics that modulate intestinal microbiota. *Oncoimmunology.* 2016;5(6):e1150399.

Pierro J, et al. Febrile neutropenia in cats treated with chemotherapy. *Vet Comp Oncol.* 2016;15:550.

Shaffer K, Bach J, Chun R. Prospective study evaluating the incidence of bacteraemia and bacteruria in afebrile and febrile neutropaenic dogs undergoing chemotherapy. *Vet Med Surg.* 2016;14:281.

Skorupski KA, et al. Prospective randomized clinical trial assessing the efficacy of denamarin for prevention of CCNU-induced hepatopathy in tumor-bearing dogs. *J Vet Intern Med.* 2011;25:838.

Sorenmo KU, et al. Case-control study to evaluate risk factors for the development of sepsis (neutropenia and fever) in dogs receiving chemotherapy. *J Am Vet Med Assoc*. 2010;236:650.

Thamm DH, Vail DM. Aftershocks of cancer chemotherapy: managing adverse effects. *J Am Anim Hosp Assoc*. 2007;43:1.

Vail DM. Supporting the veterinary cancer patient on chemotherapy: neutropenia and gastrointestinal toxicity. *Top Comp Anim Med*. 2009;24:133.

Veterinary Cooperative Oncology Group. Veterinary cooperative oncology group - common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol*. 2011;14:417.

Viaud S, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science*. 2013;342:971.

Weller RE. Intravesical instillation of dilute formalin for treatment of cyclophosphamide-induced cystitis in two dogs. *J Am Vet Med Assoc*. 1978;172:1206.

CHAPTER 78

Approach to the Patient With a Mass



APPROACH TO THE CAT OR DOG WITH A SOLITARY MASS

It is common for the practicing veterinarian to evaluate a clinically healthy dog or cat in which a single mass is found during a routine physical examination or in which the owner has detected a mass and is concerned about it. The mass can be superficial (e.g., enlarged prescapular lymph node, dermal mass, or subcutaneous mass) or deep (e.g., splenic mass, enlarged mesenteric lymph node), and often the clinician wonders how to proceed and what to recommend to the owner.

In this situation, there are several possible approaches:

1. Do nothing and see if the mass "goes away."
2. Evaluate the mass cytologically.
3. Evaluate the mass histopathologically.
4. Do a complete workup, including complete blood count (CBC), serum biochemistry profile, radiography, abdominal ultrasonography, and urinalysis.

The first option (i.e., do nothing and see if the mass goes away) is not really an option because the presence of any mass is abnormal, and it should therefore be evaluated. As a general rule, most masses, with the notable exception of inflammatory lesions, histiocytomas in young dogs, and transmissible venereal tumors, do not regress spontaneously.

At our clinics, the typical first step in evaluating a solitary mass is to perform a fine-needle aspiration (FNA) to obtain material for cytologic evaluation (see Chapter 74). Using this simple, relatively atraumatic, quick, and inexpensive procedure, the clinician can arrive at a highly presumptive or definitive diagnosis in the vast majority of animals. After identifying the nature of the mass (i.e., benign neoplastic, malignant neoplastic, inflammatory, or hyperplastic), the clinician can recommend additional tests to the owner.

Performing a biopsy for histopathology constitutes another valid alternative. However, the cost, the trauma to the patient, and the time it takes for the pathologist's report to become available make biopsy a less-attractive option than FNA. An intensive workup of a cat or dog with a solitary mass (i.e., option 4) may not be warranted because additional diagnostic information regarding the mass is rarely gained from these procedures. However, the presence of metastatic lesions on thoracic radiographs may suggest that the mass in question is a malignant tumor.

If a cytologic diagnosis of a benign neoplasm is made (e.g., lipoma), the clinician faces two options: to do nothing and observe the mass or surgically excise it. Because benign neoplasms in cats and dogs are rarely premalignant (with the notable exception of solar dermatitis/carcinoma in situ preceding the development of squamous cell carcinomas), if a benign neoplasm is definitively diagnosed, a sound approach is to recommend a wait-and-see attitude. In those cases, the mass should be measured using calipers and recorded in the medical record; if the mass enlarges, becomes inflamed, or ulcerates, then surgical excision is recommended. However, the clinician should keep in mind that most benign neoplasms are more easily excised when they are small (i.e., it is not advisable to wait until the mass becomes quite large). To some owners, the option of surgically excising the mass shortly after diagnosis is more appealing; this can be scheduled at the same time of a dental prophylaxis, for example.

If a cytologic diagnosis of malignancy is obtained (or if the findings are suggestive of or compatible with malignancy), additional evaluation is warranted. Different approaches are indicated, depending on the cytologic diagnosis (i.e., carcinoma versus sarcoma versus round cell tumor), the patient, the family, and the clinician. However, with the exception of mast cell tumors (i.e., pulmonary metastases are extremely rare in dogs and cats with this tumor type), thoracic radiographs should be obtained to search for metastatic disease in dogs and cats with most types of malignant neoplasms. Two lateral views (i.e., right and left) and a ventrodorsal (or dorsoventral) view are recommended to increase the likelihood of detecting metastatic lesions. If available, a computed tomography (CT) can detect masses smaller than those detectable on plain radiography; however, this has not yet become a routine staging diagnostic at the authors' clinics due to the fact that this procedure

requires general anesthesia and is more expensive. Plain radiographs of the affected area may also be indicated to look for soft tissue and bone involvement. Abdominal ultrasonography or CT may be indicated for further staging in patients with certain neoplasms (e.g., hemangiosarcoma, intestinal neoplasms, mast cell tumors). A minimum database consisting of a CBC, serum biochemistry profile, and urinalysis may provide additional clinical information (e.g., paraneoplastic syndromes, concurrent organ failure), and assess the general health of the patient in preparation for potential treatment.

If the mass is malignant and there is no evidence of metastatic disease, surgical excision is usually recommended. If there are systemic or metastatic lesions, the pathologist feels comfortable with the cytologic diagnosis, and the tumor is likely to respond to chemotherapy (e.g., lymphoma, hemangiosarcoma), chemotherapy constitutes the best viable option (see Chapter 75). However, as discussed in Chapter 75, surgical resection of the primary mass (e.g., mammary carcinoma) in a patient with metastatic lesions may provide considerable palliation and prolong good-quality survival. If an assertive diagnosis cannot be made on the basis of the cytologic findings, an incisional or excisional biopsy of the mass is advisable. The authors' clinics almost never recommend euthanasia in dogs and cats with metastatic lesions and good quality of life because survival times in excess of 6 months (without chemotherapy) are common in animals with most metastatic neoplasms. Metronomic chemotherapy may result in long-standing stable or slowly progressive metastatic disease (Fig. 78.1).

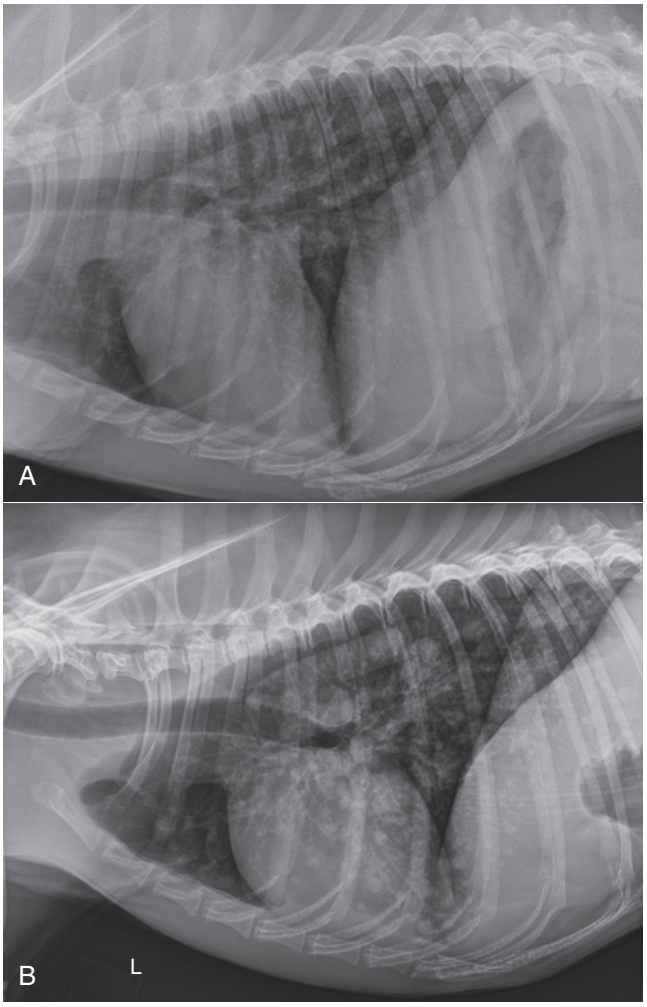


FIG 78.1
Thoracic radiographs in a 10-year-old, mixed-breed dog with a nonresectable thyroid carcinoma before **(A)** and after 756 days of metronomic chemotherapy **(B).**

APPROACH TO THE PATIENT WITH METASTATIC LESIONS

Radiographic or ultrasonographic evidence of metastatic cancer is occasionally found during the routine evaluation of an animal with a suspected or confirmed malignancy, or during the evaluation of a cat or dog with obscure clinical signs. In such instances, the clinician should be familiar with both the biologic behavior of the common neoplasms and with their characteristic radiographic and ultrasonographic patterns (Table 78.1). Suter et al. (1974) described the typical radiographic appearances of various metastatic malignancies. In addition, the owner should be questioned regarding any prior surgeries in the pet (e.g., excision of a mass that was thought to be benign but may have been the primary malignancy).

If a cytologic or histopathologic diagnosis of malignancy has already been made and the metastatic lesions are detected while staging the patient, treatment options can be discussed with the owner at this point (assuming that the metastatic lesions have arisen from the previously diagnosed primary tumor). As a general rule, cytologic or histopathologic evaluation of one or more of these lesions should be performed so that the clinician can best advise the owner as to the appropriate course of action.

A cytologic diagnosis of metastatic lung lesions can usually be obtained through blind or ultrasonography-, fluoroscopy-, or CT-guided percutaneous FNA of the lungs. To do this, the area to be aspirated (i.e., the one with the highest density of lesions radiographically or the easily identified and accessible lesions) is clipped and aseptically prepared. For blind percutaneous lung aspirates, the patient should be in sternal recumbency or standing; a 25- or 27-gauge, 2- to 3-inch (5- to 7.5-cm) needle (depending on the size of the animal) coupled to a 12- to 20-mL syringe is rapidly advanced through an intercostal space along the cranial border of the rib to the depth required (previously determined on the basis of the radiographs), and suction is applied two or three times and then released; the needle is then withdrawn. Smears are made as described in Chapter 74. When aspirating lungs, the clinician is likely to obtain a fair amount of air or blood (or both) in the syringe. Rare complications associated with this technique include pneumothorax (patients should be closely observed for 2-6 hours after the procedure and dealt with accordingly if pneumothorax develops) and bleeding. As a

general rule, FNA of the lungs should not be performed in cats or dogs with coagulopathies. In most patients, metastatic lesions are easily diagnosed using this simple approach.

If an FNA of the lungs fails to yield a diagnostic sample, a lung biopsy performed with a biopsy needle (under ultrasonographic, fluoroscopic, or CT guidance) or through a thoracotomy or thoracoscopy should be contemplated. This procedure is associated with an extremely low morbidity and should be recommended if owners are considering treatment.

Metastatic lesions in other organs or tissues (e.g., liver, bone) can also be diagnosed on the basis of FNA findings.

TABLE 78.1

Metastatic Behavior of Some Common Neoplasms in Dogs and Cats

NEOPLASM	SPECIES	COMMON METASTATIC SITES
HSA	D	Liver, lungs, omentum, kidney, eye, CNS
OSA	D	Lungs, bone
SCC—oral	C, D	Lymph nodes, lungs
aCA—mammary	C, D	Lymph nodes, lungs
aCA—anal sac	D	Lymph nodes
aCA—prostate	D	Lymph nodes, bone, lungs
TCC—bladder	D	Lymph nodes, lungs, bone
MEL—oral	D	Lymph nodes, lungs
MCT	D	Lymph nodes, liver, spleen
MCT	C	Spleen, liver, bone marrow

aCa, Adenocarcinoma; *C,* cat; *CNS,* central nervous system; *D,* dog; *HSA,* hemangiosarcoma; *MCT,* mast cell tumor; *MEL,* malignant melanoma; *OSA,* osteosarcoma; *SCC,* squamous cell carcinoma; *TCC,* transitional cell carcinoma.

The clinician should remember that nodular lesions of the liver or spleen in dogs with a primary malignancy should not necessarily be considered metastatic. FNA or biopsies of such lesions frequently reveal normal hepatocytes (i.e., regenerative hepatic nodule) or extramedullary hematopoiesis/lymphoreticular hyperplasia.

In addition, an ultrasonographically "normal" liver or spleen in a patient with suspected metastases may contain abundant malignant cells. For example, in dogs with lymphoma and increased ALT activity, FNA of ultrasonographically normal liver oftentimes yields neoplastic lymphoid cells. The authors occasionally find large (i.e., 4-6 cm) metastatic lesions in the liver of dogs with normal ultrasonographic appearance. Ultrasonographic features of internal lymph nodes may assist in classifying the lymphadenopathy as metastatic or reactive; for example, it has been reported that the resistive index (RI) and pulsatility index (PI) were significantly higher in neoplastic than in reactive medial iliac and mesenteric lymph nodes (Prieto et al., 2009).

Primary bone lesions or bone metastases can easily be aspirated using a hypodermic needle (20- to 22-gauge) that is inserted blindly or under ultrasonographic guidance; if this fails to yield cells, a 16- or 18-gauge bone marrow aspiration needle can be used. If a cytologic diagnosis cannot be made, a core (needle) biopsy can be performed.

As discussed in Chapter 75, cats and dogs with metastatic neoplasms can now be treated fairly successfully using conventional or metronomic chemotherapy. To do this, however, it is necessary to know the histologic (or cytologic) tumor type. The clinician should always bear in mind that euthanasia is a viable option for some owners.

APPROACH TO THE PATIENT WITH A MEDIASTINAL MASS

Several lesions are found as anterior mediastinal masses (AMMs) during physical examination or plain thoracic radiography (Table 78.2). Some of these lesions are malignant neoplasms; therefore diagnosis and treatment should be approached aggressively in such animals.

TABLE 78.2

Anterior Mediastinal Masses in Cats and Dogs

LESION	CAT	DOG	COMMENTS
Thymoma	Common	Common	See text
Lymphoma	Common	Common	See text
Thyroid adenocarcinoma	Rare	Rare	
Lipoma	Rare	Rare	Low radiographic density
Branchial cysts	Rare	Rare	Cystic on ultrasound
Thymic hematomas	?	Rare	Traumatic, rodenticides?
Heart base tumors	?	Rare	Brachiocephalic breeds

?, Questionable.

Clinicopathologic Features and Diagnosis

When evaluating a cat or dog with an AMM, the clinician should consider several issues before recommending a specific treatment. As discussed previously (see Chapter 75), the treatment recommended depends on the specific tumor type (i.e., surgical excision may be curative for dogs and cats with thymomas, whereas chemotherapy is indicated for those with lymphoma). Because lymphomas and thymomas are the most common AMMs in small animals, the ensuing discussion is limited to these two neoplasms. Other neoplasms that originate in anterior mediastinal structures include chemodectomas (heartbase tumors), ectopic thyroid carcinomas, and lipomas, among others. Nonneoplastic lesions of the mediastinum include mainly thymic or mediastinal hematomas, granulomatous lymphadenitis (e.g., blastomycosis), and ultimobranchial cysts.

Paraneoplastic syndromes such as generalized or focal myasthenia gravis, polymyositis, exfoliative dermatitis, lymphocytosis, neutropenia, and second neoplasms have been well characterized in cats and dogs with thymoma. Aplastic anemia, a paraneoplastic syndrome common in humans with thymoma, is uncommon in small animals with this tumor type. Hypercalcemia is a common finding in dogs with mediastinal lymphoma, but it can also occur in dogs with thymoma.

In cats, the age at the time of presentation points to a specific diagnosis. In other words, anterior mediastinal lymphomas are more common in young cats (1-3 years old), whereas thymomas are more common in older cats (>8 years old). It is also important to know the feline leukemia virus (FeLV) status in this species because most cats with mediastinal lymphomas are viremic (i.e., FeLV positive), whereas most cats with thymoma are not. FeLV-negative mediastinal lymphomas have been described in young to middle-age Siamese cats and can occasionally be seen in other cats.

In dogs most AMMs are diagnosed in older animals (older than 5-6 years of age); therefore age cannot be used as a means of distinguishing between lymphomas and thymomas. However, a large proportion of dogs with mediastinal lymphoma are hypercalcemic, whereas most dogs with thymomas are not (although hypercalcemia can also occur in dogs with this neoplasm). Peripheral blood lymphocytosis can be present in dogs and cats with either lymphoma or thymoma; in most dogs with lymphoma, the circulating lymphocytes are morphologically abnormal. The presence of neuromuscular signs in a dog or cat with an AMM suggests the existence of a thymoma or of lymphoma with central nervous system involvement.

Thoracic radiographs are of little help in differentiating thymomas from lymphomas. The two neoplasms are similar in appearance, although lymphomas appear to originate more frequently in the dorsal anterior mediastinum, whereas thymomas originate more often in the ventral mediastinum (Fig. 78.2). Thymomas also occasionally "hug" the heart in the ventrodorsal radiographic view and can have sharp or irregular edges. The prevalence of pleural effusion in dogs and cats with either thymoma or lymphoma is similar; thus the finding cannot be used as a means to distinguish between these two tumor types. However, neoplastic cells are often seen in the pleural effusion in dogs and cats with lymphoma but are typically absent in those with thymoma.



FIG 78.2
Typical radiographic features of thymoma *(arrows)* in a dog. The mass originates in the ventral mediastinum, unlike most lymphomas, which usually originate in the dorsal mediastinal region. Percutaneous fine-needle aspiration of this mass yielded findings diagnostic for thymoma, and the dog underwent a thoracotomy with complete resection of the mass.

Ultrasonographic evaluation of the AMM should be attempted before more invasive diagnostic techniques are used. Ultrasonographically, most thymomas have mixed echogenicity, with discrete hypoechoic to anechoic areas that correspond to true cysts on cross section (Patterson and Marolf, 2014). The lack of a supporting stroma in lymphomas usually confers a hypoechoic to anechoic density to the mass, which therefore may look diffusely cystic. In addition to aiding in the presumptive diagnosis of a given tumor type, ultrasonography may provide information regarding the resectability of the mass and assists in obtaining a specimen for cytologic evaluation (see next paragraph). In patients with thymoma, a thoracic CT scan may help in planning surgery.

Transthoracic FNA of AMMs constitutes a relatively safe and reliable evaluation technique. After sterile preparation of the thoracic wall overlying the mass (see Chapter 74), a 2- to 3-inch (5- to 7.5-cm), 25-gauge needle is used to sample the mass. This can be done blindly (if the mass is so large that it is pressing against the interior thoracic wall) or guided by radiography (using three views to establish a three-dimensional location), fluoroscopy, ultrasonography, or CT. Despite the fact that there are large vessels within the anterior mediastinum, postaspiration bleeding is extremely rare if the animal remains motionless during the procedure. Alternatively, if the mass is large enough to be in close contact with the internal thoracic wall, a transthoracic needle biopsy can be performed to allow histopathologic evaluation.

Cytologically, mediastinal lymphomas are composed of a monomorphic population of lymphoid cells that are mostly immature (i.e., low nuclear-to-cytoplasmic ratio, dark blue cytoplasm, clumped chromatin pattern, and nucleoli); in cats, most cells in anterior mediastinal lymphomas are heavily vacuolated and resemble human Burkitt lymphoma cells (Fig. 78.3). Thymomas are cytologically heterogeneous and composed primarily of a population of small lymphocytes (although large blasts are sometimes present) and occasionally a distinct population of epithelial-like cells that are usually polygonal or spindle-shaped, which can be identified either as individual cells or in sheets. Hassall corpuscles are rarely seen in Wright-stained cytologic preparations. Plasma cells, eosinophils, neutrophils, mast cells, macrophages, and melanocytes are all occasionally seen (Fig. 78.4). Flow cytometry can also be used to help differentiate mediastinal lymphoma from thymomas in dogs. The presence of >10% lymphocytes that are CD4+/CD8+ is characteristic for thymomas, whereas mediastinal lymphomas generally contained <2% CD4+CD8+ lymphocytes (Lana et al., 2006).

Treatment

As discussed in preceding paragraphs, anterior mediastinal lymphomas are best treated with chemotherapy (see Chapter 79). Radiotherapy can also be used in conjunction with chemotherapy to induce a more rapid remission. A recent publication on canine mediastinal lymphoma reported that two dogs that did undergo radiotherapy in addition to their chemotherapy protocol had prolonged progression-free survival and overall survival compared with the rest of the dogs in the study that did not undergo radiation (Moore et al., 2018). However, the animal must be deemed an appropriate candidate for anesthesia before consideration of radiotherapy, because chemical restraint in patients exhibiting severe respiratory compromise can further compound their clinical status.

Because most thymomas are benign, surgical excision is usually curative. Although in some reports the perioperative morbidity and mortality of this procedure are high (Atwater et al., 1994), in the authors' experience, most patients that undergo thoracotomies for removal of a thymoma do well and are released from the hospital in 3 to 4 days. In a review of the surgical outcome in 9 cats and 11 dogs with thymomas (Zitz et al., 2008), 8 out of 9 cats and 8 out of 11 dogs survived the immediate postoperative period and had median survival times of 30 and 18.5 months, respectively. Two cats and one dog had late recurrences.

Radiotherapy can successfully induce remission in patients with thymoma, although complete, long-lasting remission is rarely achieved. This may be due to the fact that radiotherapy eliminates only the lymphoid component of the neoplasm, whereas the epithelial component remains unchanged. Chemotherapy may be beneficial in selected cats and dogs with nonresectable thymomas or in those in which repeated anesthetic episodes or a major surgical procedure poses a severe risk. One author's clinic has used combination chemotherapy protocols commonly used for dogs and cats with lymphoma (i.e., cyclophosphamide, vincristine, cytosine arabinoside, and prednisone [COAP]; cyclophosphamide, vincristine, and prednisone [COP]; and cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; see Chapter 79) in a limited number of cats and dogs with cytologically diagnosed thymomas. As with radiotherapy, however, chemotherapy may only eliminate the lymphoid cell population, thus rarely resulting in complete or long-lasting remissions.

If a definitive diagnosis of thymoma or lymphoma cannot be obtained preoperatively, the clinician has two therapeutic

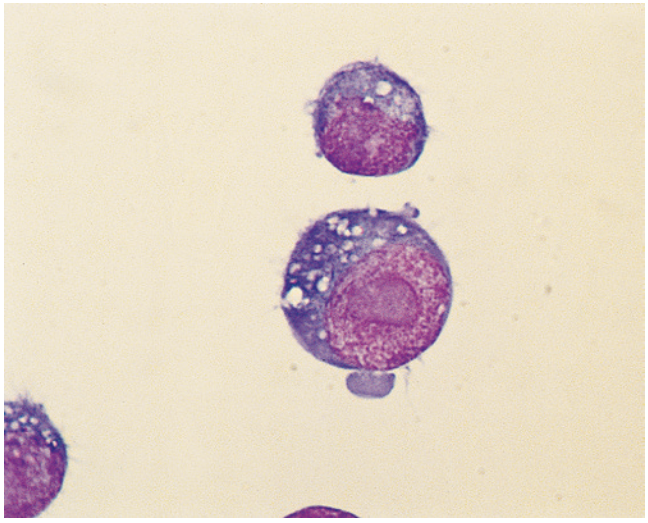


FIG 78.3
Cytologic characteristics of feline mediastinal lymphoma. Note the dark cytoplasm with abundant vacuoles typical of this neoplasm in cats (×1000).

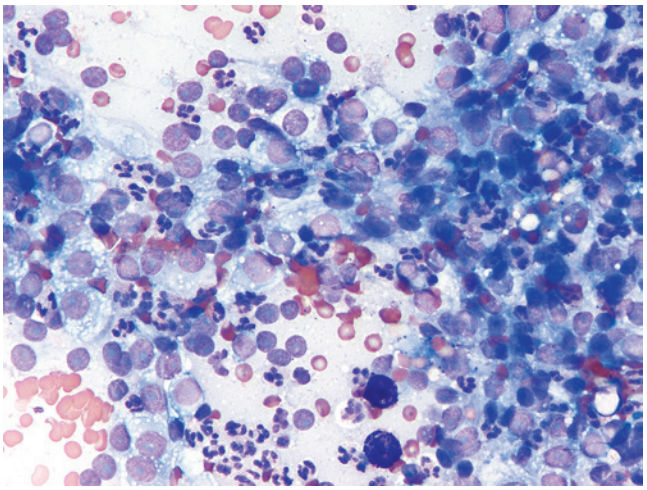


FIG 78.4
Cytologic characteristics of canine thymoma. Note the heterogeneous lymphoid cell population, which also includes neutrophils and mast cells (×1000). (Courtesy Dr. D. Pappas.)

options: (1) perform a thoracotomy and excise the mass or (2) initiate chemotherapy for lymphoma (COP, COAP, or CHOP). In the latter case, if no remission (or only a partial remission) is observed 10 to 14 days after the start of chemotherapy, the mass is most likely a thymoma, and surgical resection should be considered.

Suggested Readings

Aronsohn MG, et al. Clinical and pathologic features of thymoma in 15 dogs. *J Am Vet Med Assoc*. 1984;184:1355.

Atwater SW, et al. Thymoma in dogs: 23 cases (1980-1991). *J Am Vet Med Assoc*. 1994;205:1007.

Bellah JR, et al. Thymoma in the dog: two case reports and review of 20 additional cases. *J Am Vet Med Assoc*. 1983;183:1095.

Carpenter JL, et al. Thymoma in 11 cats. *J Am Vet Med Assoc*. 1982;181:248.

De Swarte M, et al. Comparison of sonographic features of benign and neoplastic deep lymph nodes in dogs. *Vet Radiol Ultrasound*. 2011;52:451.

Lana S, et al. Diagnosis of mediastinal masses in dogs by flow cytometry. *J Vet Intern Med*. 2006;20:1161.

Liu S, et al. Thymic branchial cysts in the dog and cat. *J Am Vet Med Assoc*. 1983;182:1095.

Moore EL, et al. Patient characteristics, prognostic factors and outcome of dogs with high-grade primary mediastinal lymphoma. *Vet Comp Oncol*. 2018;16:E45.

Nemanic S, London CA, Wisner ER. Comparison of thoracic radiographs and single breath-hold helical CT for detection of pulmonary nodules in dogs with metastatic neoplasia. *J Vet Intern Med*. 2006;20:508.

Patterson MME, Marolf AJ. Sonographic characteristics of thymoma compared with mediastinal lymphoma. *J Am Anim Hosp Assoc*. 2014;50:409.

Prieto S, et al. Pathologic correlation of resistive and pulsatility indices in canine abdominal lymph nodes. *Vet Radiol Ultrasound*. 2009;50:525.

Rae CA, et al. A comparison between the cytological and histological characteristics in thirteen canine and feline thymomas. *Can Vet J*. 1989;30:497.

Scott DW, et al. Exfoliative dermatitis in association with thymoma in 3 cats. *Fel Pract*. 1995;23:8.

Suter PJ, et al. Radiographic recognition of primary and metastatic pulmonary neoplasms of dogs and cats. *J Am Vet Radiol Soc*. 1974;15:3.

Yoon J, et al. Computed tomographic evaluation of canine and feline mediastinal masses in 14 patients. *Vet Radiol Ultrasound*. 2004;45:542.

Zitz JC, et al. Thymoma in cats and dogs: 20 cases (1984-2005). *J Am Vet Med Assoc*. 2008;232:1186.

CHAPTER 79

Lymphoma



Lymphoma (i.e., malignant lymphoma, lymphosarcoma) is a lymphoid malignancy that originates from solid organs or tissues (e.g., lymph nodes, liver, spleen, eye); this distinguishes lymphomas from lymphoid leukemias, which originate in the bone marrow (see Chapter 80).

Etiology and Epidemiology

Early reports stated that approximately 70% of cats with lymphoma are persistently infected with feline leukemia virus (FeLV) (Table 79.1). Although the prevalence of viremia in cats with lymphoma varies with the anatomic form of presentation (see later discussion), young cats with lymphoma are generally FeLV positive, whereas older cats are FeLV negative. Over the past few years, the prevalence of FeLV infection in cats with lymphoma in the United States has been decreasing, so we tend to see predominantly FeLV-negative cats with lymphoma. Feline immunodeficiency virus (FIV) infection increases the risk of developing lymphoma in cats; cats infected with FIV are almost six times more likely to develop lymphoma than noninfected cats, whereas cats coinfected with FeLV and FIV are more than 75 times more likely to develop lymphoma than noninfected cats (Shelton et al., 1990). Louwerens et al. (2005) reported an increase in the prevalence of feline lymphoma despite the decrease in the prevalence of FeLV infection; this increase was associated primarily with the gastrointestinal form, extranodal or atypical forms, and FeLV-negative mediastinal forms in young to middle-aged Siamese and oriental breeds. *Helicobacter* spp. may play a role in the development of gastric lymphoma in cats (Bridgeford et al., 2008). *Borrelia* spp. infection has been linked to the development of non-Hodgkin lymphoma in people and in a horse (Ferreri et al., 2009); however, this has not been described in dogs. A T-cell multicentric lymphoma associated with infection with a novel *Ehrlichia* spp (Panola Mountain *Ehrlichia*) that responded to doxycycline was recently reported (Qurollo et al., 2013).

In dogs, the etiology of lymphomas is considered multifactorial because no single etiologic agent has been identified. However, a genetic component is evident in that the neoplasm is highly prevalent in certain breeds and bloodlines (Modiano et al., 2005). For example, Boxers, Shih Tzus, and Siberian Huskies have primarily T-cell tumors, whereas Cocker Spaniels and Basset Hounds have predominantly B-cell lymphoma; B- and T-cell tumors are almost equally distributed in Golden Retrievers.

The age of cats with lymphoma at the time of presentation is bimodal, with the first peak occurring in cats that are approximately 2 years of age and the second peak in cats that are approximately 10 to 12 years of age. The cats that make up the first peak are mainly FeLV positive, whereas those that make up the second peak are predominantly FeLV negative. As mentioned earlier, the prevalence of FeLV-positive cats with lymphoma in the United States continues to decrease. Most dogs with lymphoma are middle-aged or older (6-12 years of age); however, lymphoma can occur in dogs of any age (even in puppies).

Clinical Features

Four anatomic forms of presentation occur in dogs and cats with lymphoma:

1. *Multicentric,* characterized by generalized lymphadenopathy; hepatic, splenic, or bone marrow involvement; or a combination of these
2. *Mediastinal,* characterized by mediastinal lymphadenopathy, with or without bone marrow infiltration
3. *Alimentary,* characterized by solitary, diffuse, or multifocal gastrointestinal tract infiltration, with or without intraabdominal lymphadenopathy
4. *Extranodal,* affecting any organ or tissue (e.g., renal, neural, ocular, cutaneous)

The distribution of the different anatomic forms differs between cats and dogs. The multicentric form is the most common in dogs, accounting for more than 80% of all the lymphomas in this species. In cats, the alimentary form is the most common, representing more than 70% of the cats with this neoplasm.

The clinical findings in dogs and cats with lymphoma are related to the anatomic form of presentation. Patients with

TABLE 79.1

Prevalence of Feline Leukemia Virus Infection in Cats With Lymphoma

ANATOMIC FORM	FeLV POSITIVE (%)
Alimentary	30
Mediastinal	90
Multicentric	80
Cutaneous	0



FIG 79.1
Massive mandibular lymphadenopathy in a dog with multicentric lymphoma. (Courtesy Dr. Bill Kisseberth.)

the multicentric form are evaluated because of vague, nonspecific clinical signs, or more frequently, the owners detect one or more subcutaneous masses (i.e., enlarged lymph nodes, Fig. 79.1) during grooming or petting in an otherwise healthy pet, and this prompts them to seek veterinary care. Occasionally, dogs and cats with lymphoma are evaluated because of nonspecific clinical signs such as weight loss, anorexia, and lethargy. If the enlarged lymph nodes mechanically obstruct lymphatic drainage, edema can occur; if they compress the airway, coughing may occur. Dogs with lymphoma and hypercalcemia (see later) frequently present for polyuria and polydipsia, and are often times clinically unwell.

Physical examination of dogs and cats with multicentric lymphoma usually reveals marked to massive generalized lymphadenopathy, with or without hepatomegaly, splenomegaly, or extranodal lesions (e.g., ocular, cutaneous, renal, neural). The affected lymph nodes are enlarged, painless, and freely movable. A syndrome of reactive (hyperplastic) lymphadenopathy that occurs in cats can mimic the clinicopathologic features of multicentric lymphoma but is usually easily distinguished cytologically.

Cats and dogs with mediastinal lymphoma are usually evaluated because of dyspnea, coughing, or dysphagia/regurgitation (the latter is more common in cats) of recent onset. Polyuria and polydipsia are also common presenting complaints in dogs with mediastinal lymphoma and hypercalcemia; tumor-associated hypercalcemia is rare in cats with lymphoma. The respiratory and upper digestive tract signs are caused by compression from enlarged anterior mediastinal lymph nodes, although malignant pleural effusion can contribute to the severity of the respiratory tract signs. On physical examination, the abnormalities are usually confined to the thoracic cavity and consist of decreased bronchovesicular sounds, normal pulmonary sounds displaced to the dorsocaudal thoracic cavity, a dull sound heard on percussion of the ventral thoracic cavity, and a noncompressible anterior mediastinum (in cats). Unilateral or bilateral Horner syndrome may occur in cats (and occasionally dogs) with mediastinal lymphoma. Some dogs with mediastinal lymphoma have marked head and neck edema caused by compression from enlarged lymph nodes (anterior vena cava syndrome).

Cats and dogs with alimentary lymphoma usually display gastrointestinal tract signs such as anorexia, vomiting, diarrhea, or weight loss. Occasionally, signs compatible with an intestinal obstruction or peritonitis (caused by rupture of a lymphomatous mass) can occur. Physical examination typically reveals an intraabdominal mass or masses (e.g., enlarged mesenteric or ileocecocolic lymph nodes or intestinal masses) and thickened bowel loops (in patients with diffuse small intestinal lymphoma). Rarely, polypoid lymphomatoid masses can protrude through the anus in dogs with colorectal lymphoma.

The clinical signs and physical examination findings in cats and dogs with extranodal lymphomas are extremely variable and depend on the location of the lesions. In general, the clinical signs stem from the compression or displacement of normal parenchymal cells in the affected organ (e.g., anterior uveitis or hyphema in ocular lymphoma, variable neurologic signs in central nervous system [CNS] lymphoma). The typical clinical signs and physical examination findings in cats and dogs with extranodal lymphomas are summarized in Table 79.2. Common extranodal forms in dogs include cutaneous and ocular lymphomas; in cats they include nasopharyngeal, ocular, renal, and neural lymphomas.

Cutaneous lymphoma is one of the most common extranodal forms of lymphoma in dogs but is rare in cats. The clinical signs and characteristics of the lesions are extremely variable, and they can mimic any primary or secondary skin lesion. Dogs with mycosis fungoides (an epitheliotropic T-cell lymphoma) are usually first evaluated because of chronic alopecia, desquamation, pruritus, and erythema, eventually leading to plaque and mass formation (Fig. 79.2). Mucocutaneous and mucosal lesions are relatively common, but generalized lymph node involvement may not occur initially. A characteristic lesion in dogs with this form of lymphoma is a circular, raised, erythematous, donut-shaped, dermoepidermal mass that contains normal skin in the center (Fig. 79.3). Diffuse swelling and erythema are also common (Fig. 79.4, *A*). Most of the cats with cutaneous

TABLE 79.2

Clinical Signs and Physical Examination Findings in Dogs and Cats With Extranodal Lymphomas

ORGAN INVOLVED	CLINICAL PRESENTATION	PHYSICAL FINDING(S)
CNS	Solitary or multifocal CNS signs	Any neurologic finding
Eye	Blindness, infiltrates, photophobia	Infiltrates, uveitis, RD, glaucoma
Kidney	PU-PD, azotemia, erythrocytosis*	Renomegaly, renal masses
Lung	Coughing, dyspnea	None, radiographic changes
Skin	Any primary or secondary lesion	Any primary or secondary lesion

CNS, Central nervous system; *PU-PD*, polyuria/polydipsia; *RD*, retinal detachment.
*Only in dogs.



FIG 79.2
Diffuse desquamative dermatopathy in a 13-year-old female spayed dog with mycosis fungoides (a specific type of epidermotropic cutaneous T-cell lymphoma). Clinical signs and lesions were present for almost 2 years.



FIG 79.3
Typical doughnut-shaped lesion in a Rottweiler with cutaneous T-cell lymphoma.

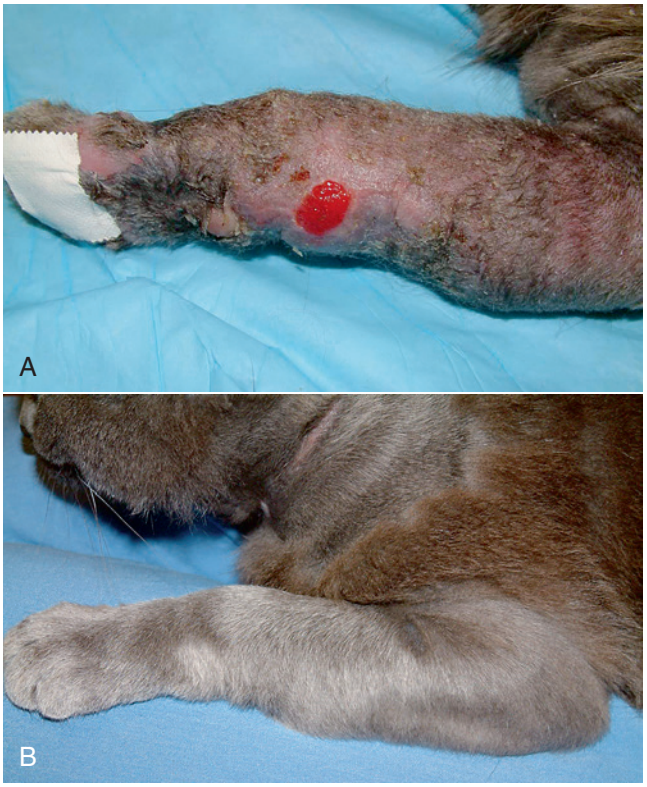


FIG 79.4
Diffuse distal limb swelling, erythema, and ulceration in a cat with epidermotropic cutaneous T-cell lymphoma, before **(A)** and after chemotherapy **(B).**

lymphoma reported in the literature and seen by the authors have been negative for FeLV viremia.

Ocular lymphoma occurs in both dogs and cats. In dogs, it is commonly associated with the multicentric form, whereas both primary ocular involvement and ocular involvement associated with the multicentric form are common in cats. A variety of signs and lesions may be present in these patients, including photophobia, blepharospasm, epiphora, hyphema, hypopyon, ocular masses, third eyelid infiltration, anterior uveitis, chorioretinal involvement, and retinal detachment.

Nasopharyngeal lymphoma is relatively common in cats but is extremely rare in dogs. Clinical signs are similar to those seen in cats with any upper respiratory tract disorder and include sneezing, unilateral or bilateral nasal discharge (ranging from mucopurulent to frankly hemorrhagic), stertorous breathing, exophthalmos, and facial deformity (Fig. 79.5); this is one of the most common forms of extranodal lymphoma seen in cats at the authors' clinics.

Renal lymphoma is relatively common in cats but uncommon in dogs. Cats with this anatomic form are first evaluated because of vague clinical signs, usually secondary to azotemia. On physical examination, the cat is often emaciated, typically has pale mucous membranes from anemia, and has large, irregular, and firm kidneys; both kidneys are commonly affected. There is a purported association between

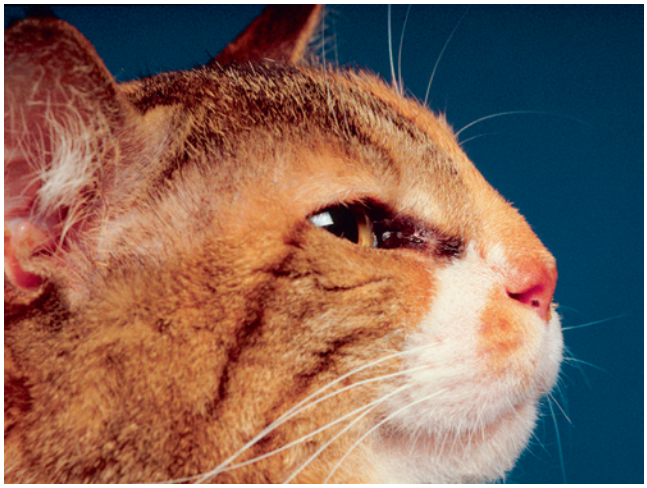


FIG 79.5
Facial deformity and nasal discharge associated with intranasal lymphoma in a 6-year-old cat.

renal and CNS lymphoma in cats, so some oncologists recommend using antineoplastic drugs that achieve high CNS concentrations (i.e., cytosine arabinoside, lomustine) in the treatment of cats with renal involvement in an attempt to prevent secondary CNS dissemination (see later).

Dogs and cats with neural lymphoma are evaluated because of a variety of neurologic signs that reflect the location and extent of the neoplasm. Although CNS signs are most common, peripheral nerve involvement may occur occasionally in cats. Three forms of presentation are clinically recognized: solitary epidural lymphoma, neuropil (intracranial or intraspinal) lymphoma (also called *true CNS lymphoma*), and peripheral nerve lymphoma. Solitary epidural lymphoma is common in young FeLV-positive cats. Neural lymphomas can be primary (e.g., epidural lymphoma), or they may be secondary to the multicentric form; as discussed earlier, secondary CNS involvement may occur in cats with renal lymphoma. Additionally, dogs that have been receiving chemotherapy for multicentric lymphoma can develop late CNS relapse; these patients develop acute onset of neurologic signs, usually while the multicentric neoplasm is still in remission. This late CNS relapse is likely related to the fact that most drugs used to treat lymphoma do not cross the blood-brain barrier when used at standard doses; thus the CNS becomes a sanctuary for tumor cells. In our clinics, CNS signs in any dog with lymphoma before or during treatment are attributed to this neoplasm (and treated accordingly) until proven otherwise.

A variety of differential diagnoses should be considered in a dog or cat with suspected lymphoma. The clinician should always bear in mind that lymphomas are great imitators; they can mimic numerous different neoplastic and nonneoplastic disorders. The differential diagnoses for cats and dogs with lymphoma are similar to those in patients with leukemia (see Chapter 80).

Occasionally, dogs with lymphoma are evaluated because of clinical signs secondary to a paraneoplastic syndrome (i.e., molecularly mediated distant effects of the neoplasm). Paraneoplastic syndromes that have been encountered in dogs with lymphoma include hypercalcemia, monoclonal and polyclonal gammopathies, immune-mediated cytopenias (typically immune-mediated hemolytic anemia or immune-mediated thrombocytopenia), polyneuropathy, and hypoglycemia. Only hypercalcemia and gammopathies have been documented in cats with this neoplasm, although they are considerably less frequent than in dogs. Of all these syndromes, humoral hypercalcemia of malignancy in dogs is of main clinical relevance and typically resolves with the treatment. Most paraneoplastic syndromes resolve when patients are treated with chemotherapy.

Hematologic and serum biochemical features

A variety of nonspecific hematologic and serum biochemical abnormalities can be detected in patients with lymphoma. The hematologic abnormalities result from infiltration of the bone marrow with neoplastic cells, splenic hypofunction or hyperfunction (caused by neoplastic infiltrates), chronic disease, or paraneoplastic immune-mediated abnormalities. Certain hematologic abnormalities (i.e., monocytosis, eosinophilia, leukemoid reactions) may result from the local or systemic production of bioactive substances by the tumor cells (e.g., hematopoietic growth factors, interleukins). With the new flow cytometry (FCM)-based hematology analyzer, neoplastic cells in circulation are often "counted" as monocytes, so monocytosis should always prompt careful evaluation of the graphics or a blood smear review. Given the fact that these analyzers evaluate 10,000 to 15,000 leukocytes per run, it is common to identify neoplastic cells in circulation in dogs with lymphoma (Fig. 79.6).

The serum biochemical abnormalities result from either the production of bioactive substances by the tumor cells or from organ failure secondary to neoplastic infiltration. In general, the complete blood count (CBC) and biochemical profile are not diagnostic in cats and dogs with lymphoma, unless there are unclassified cells identified as abnormal lymphoid cells on evaluation of the blood smear or the graphics from the analyzer.

Common hematologic abnormalities include nonregenerative anemia, leukocytosis, neutrophilia (with or without a left shift), monocytosis, eosinophilia (usually in cats), abnormal lymphoid cells in peripheral blood (i.e., leukemic phase of lymphoma), thrombocytopenia, isolated or combined cytopenias, and leukoerythroblastic reactions, among others. Lymphocytosis is rare in dogs and cats with lymphoma; when present, it is usually of low magnitude (i.e., <10,000-12,000/μL). Erythrocytosis occurs in approximately half of the dogs with renal lymphoma, but it is extremely uncommon in cats (see Chapter 84).

Serum biochemical abnormalities are more common in dogs than in cats with lymphoma and consist mainly of hypercalcemia or gammopathies. Hypercalcemia is one of the most common paraneoplastic abnormalities in dogs with lymphoma, occurring in approximately 20% to 40% of the patients; it is extremely rare in cats, and it is more prevalent

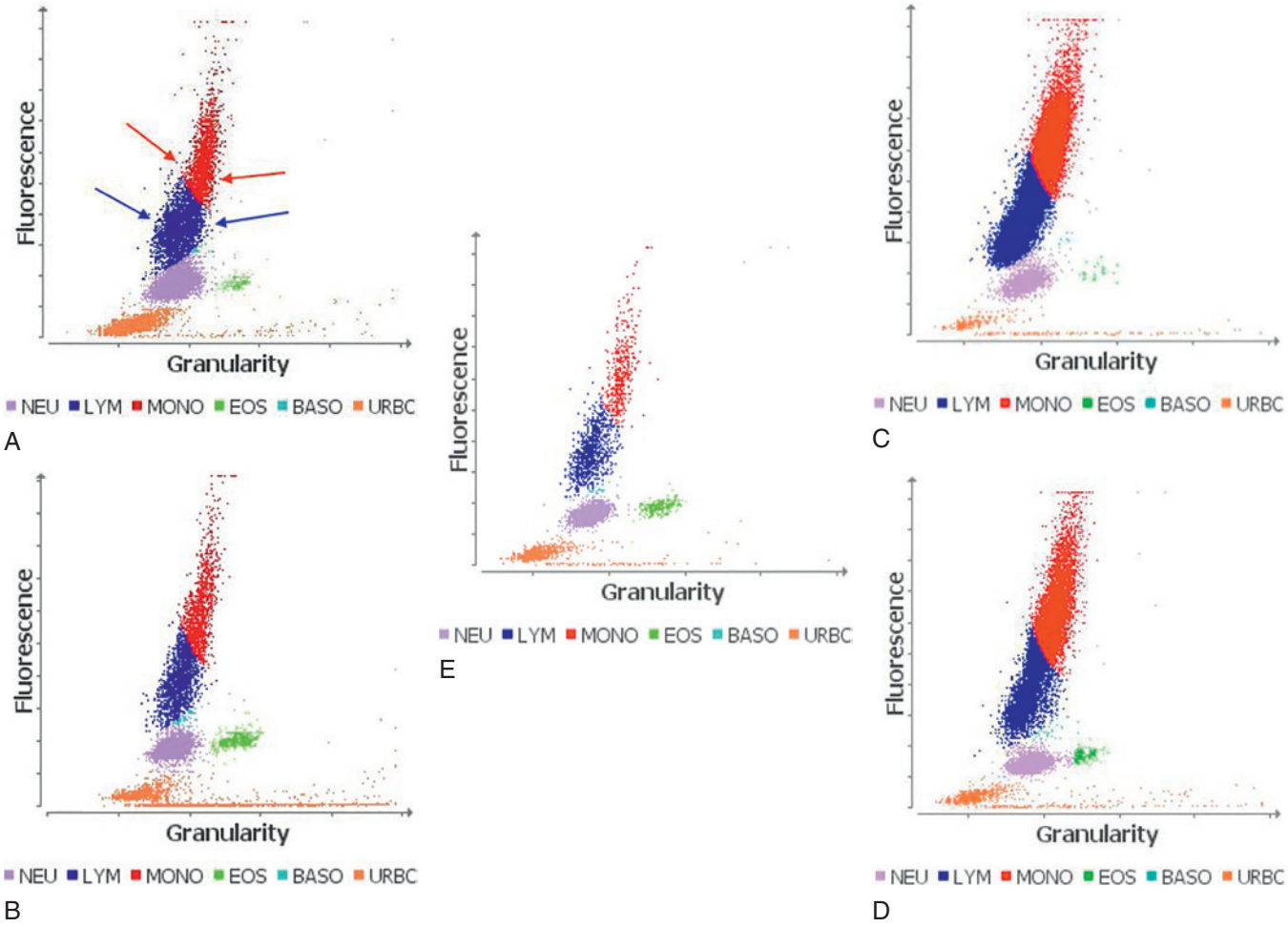


FIG 79.6
Leukocyte graphics (dot plots) from four dogs with lymphoma obtained with a ProCyteDx (Idexx Laboratories, Westbrook, ME). Note the difference in the lymphocyte (*blue arrrows*) and monocyte (*red arrows*) clouds when compared with a normal dog, and the straight line between both populations. *Panels A and B,* small and intermediate cell lymphomas; *panels C and D,* large cell lymphomas; *panel E,* normal dog.

in dogs with mediastinal lymphoma than in those with the multicentric, alimentary, or extranodal forms. In most dogs with lymphoma and hypercalcemia, the tumor is of T-cell origin.

Numerous molecular mechanisms underlie hypercalcemia in dogs with lymphoma, but in most cases, hypercalcemia is thought to occur as a result of the production of a parathyroid hormone-like protein, called *PTHrP (PTH-related protein),* by the neoplastic cells. Markedly increased serum concentrations of 1,25-vitamin D have been documented in dogs with lymphoma and hypercalcemia by one of the authors (GC).

Hyperproteinemia is another paraneoplastic abnormality that occurs rarely in cats and dogs with lymphoma. It may be secondary to the production of a monoclonal protein by the lymphoma cells and can result in the development of hyperviscosity syndrome. In a recent study of serum protein electrophoresis in 155 cats, only one cat had a monoclonal gammopathy associated with lymphoma (Taylor et al., 2010). Polyclonal gammopathies may also be present in cats and dogs with lymphoma. Recently, we identified high serum SDMA concentrations in some dogs and cats with lymphoma or lymphoid leukemia.

Imaging

Radiographic abnormalities in cats and dogs with lymphoma vary with the different anatomic forms but in general are secondary to lymphadenopathy or organomegaly (i.e., hepatomegaly, splenomegaly, renomegaly); occasionally, the infiltration of other organs (e.g., lungs) may lead to the appearance of additional radiographic abnormalities.

Radiographic changes in cats and dogs with multicentric lymphoma include sternal or tracheobronchial lymphadenopathy or both (Fig. 79.7); interstitial, bronchoalveolar, or mixed pulmonary infiltrates; pleural effusion (rare); intra-abdominal lymphadenopathy (e.g., mesenteric or iliac); hepatomegaly; splenomegaly; renomegaly; or intraabdominal masses. Rarely, lytic or proliferative bone lesions are identified on plain abdominal or thoracic radiographs.

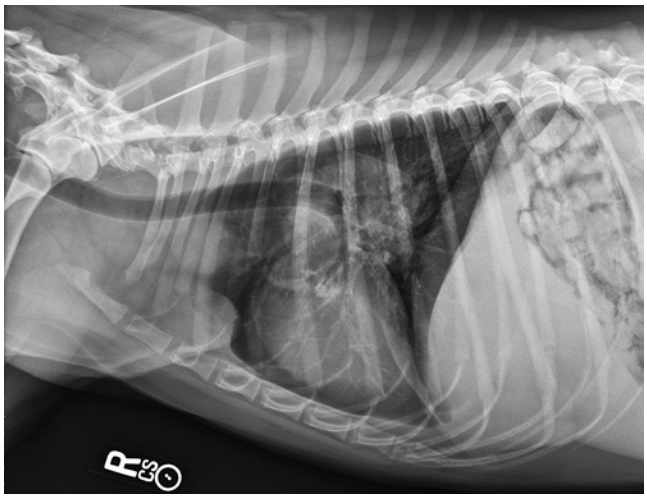


FIG 79.7
Mediastinal, hilar, and sternal lymphadenopathy in a dog with multicentric lymphoma.

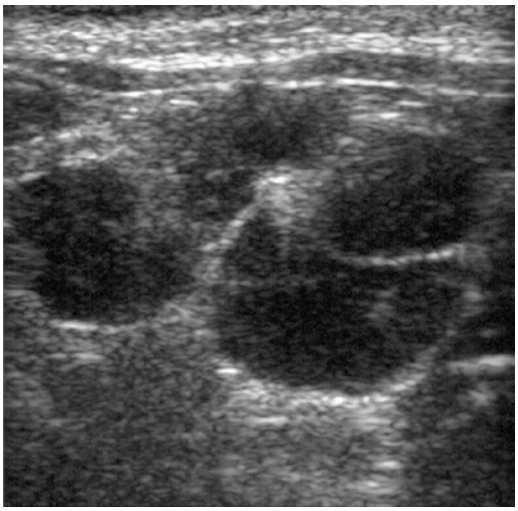


FIG 79.8
Mesenteric lymphadenopathy in a 12-year-old cat with diarrhea associated with an intestinal small cell lymphoma. Note the marked enlargement of the affected lymph node (3 × 5 cm).

In cats and dogs with mediastinal lymphoma, radiographic changes are usually limited to the finding of an anterior (or, more rarely, posterior) mediastinal mass, with or without pleural effusion. In cats and dogs with alimentary lymphoma, abnormalities are rarely detected on plain abdominal radiographs (<50%). When present, they vary in nature but include mainly hepatomegaly, splenomegaly, and midabdominal masses. Positive contrast–enhanced radiography of the upper gastrointestinal tract usually reveals abnormalities in most animals. In a series of dogs with alimentary lymphoma evaluated at one authors' clinic (GC), abnormalities were found in all dogs that underwent positive contrast–enhanced radiography of the upper gastrointestinal tract and included mucosal irregularities, luminal filling defects, and irregular thickening of the wall, suggestive of infiltrative mural disease.

Ultrasonography constitutes an invaluable tool for evaluating cats or dogs with suspected or confirmed intraabdominal lymphoma. The technique is also helpful in the evaluation of mediastinal masses in both species (see Chapter 78). Changes in the echogenicity of parenchymal organs (i.e., liver, spleen, kidneys) detected by this technique usually reflect changes in organ texture secondary to neoplastic infiltration. In addition, enlarged lymphoid structures or organs can easily be identified using this technique. Several abnormalities are commonly detected ultrasonographically in cats and dogs with intraabdominal lymphoma, including hepatomegaly; splenomegaly; changes in the echogenicity of liver or spleen (mixed echogenicity or multiple hypoechoic areas); diffuse, focal, or multifocal intestinal thickening; lymphadenopathy (Fig. 79.8); splenic masses; and effusion. Cats with lymphoma of the small intestine are more likely to have thickening of the muscularis when compared with cats with inflammatory bowel disease (Zwingenberger et al., 2010). Fine-needle aspiration (FNA) and needle biopsy can also be easily performed using this technique to guide the placement of the needle. Ultrasonography is neither sensitive nor specific for the evaluation of liver lesions; a high proportion of dogs with hepatic lymphoma have normal ultrasonographic appearance. Therefore obtaining a sample for cytology in patients with ultrasonographically normal liver is recommended in dogs with lymphoma or suspected lymphoma.

Diagnosis

The clinical signs and physical examination findings described in preceding paragraphs are usually suggestive of lymphoma. However, before instituting therapy, the clinician must confirm the diagnosis cytologically, histopathologically, or, less frequently, using molecular techniques. In addition, a minimum database consisting of a CBC, serum biochemistry profile, and urinalysis should be obtained if the owners are contemplating treatment.

From a cytologic standpoint, lymphomas can be classified as small-, intermediate-, or large-cell types. As a general rule, small-cell lymphomas are slowly progressive (i.e., indolent), whereas large-cell lymphomas are more aggressive. Intermediate-cell lymphomas can be indolent or aggressive. In most dogs and cats with large-cell multicentric, superficial extranodal, mediastinal, or alimentary lymphoma, a diagnosis can easily be obtained by cytologic evaluation of FNA of the affected organs or lymph nodes. The techniques for FNA and the cytologic features of lymphoma are described in detail in Chapter 74 (Fig. 79.9).

In the authors' practices, lymphomas can be diagnosed cytologically in over 90% of dogs and 70% to 75% of cats evaluated. In other words, in only 10% of the dogs and 25% to 30% of the cats is it necessary to perform a histopathologic,

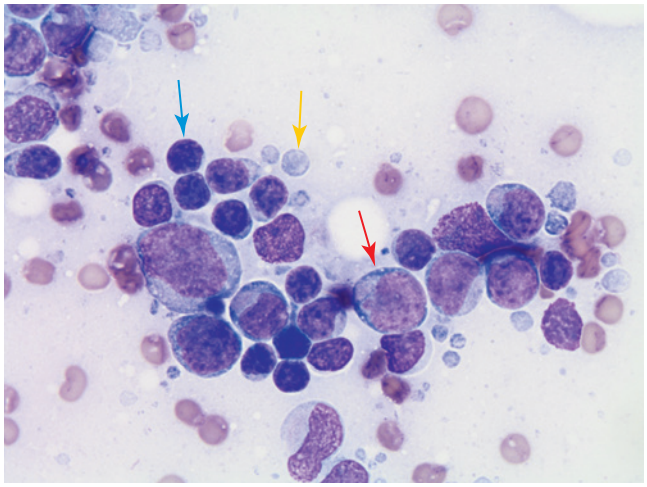


FIG 79.9
Cytologic features of large cell lymphoma in a dog. Large, neoplastic lymphoid cells *(red arrow),* intermixed with normal small lymphocytes *(blue arrow).* Note lymphoglandular bodies *(yellow arrow),* islands of cytoplasms from broken neoplastic cells.

TABLE 79.3
TNM Staging System for Dogs and Cats With Lymphoma

STAGE	CLINICAL FEATURES
I	Solitary lymph node involvement
II	More than one lymph node enlarged but on one side of the diaphragm (i.e., cranial or caudal)
III	Generalized lymph node involvement
IV	Stage III findings, plus hepatomegaly and/or splenomegaly
V	Any of the above, plus bone marrow or extranodal involvement Substage a: asymptomatic Substage b: sick

TNM, Tumor, node, metastasis.

flow cytometric, or molecular evaluation of a lymph node or mass to establish a diagnosis.

Pathologists have advocated the use of an adaptation of the human World Health Organization's histopathologic classification of non-Hodgkin lymphomas for several decades. Recently, Valli et al. (2013) proposed a modified system that may have prognostic implications. However, it includes more than 30 different categories of tumors, usually requires histopathologic evaluation of an entire lymph node, and specific diagnoses may not be consistent among pathologists. In this scheme, the authors (and others) recognized a subset of multicentric indolent lymphomas, in which survival times with minimal treatment (see later) are common. These subtypes include mainly mantle zone lymphoma (MZL-intermediate cell, B-cell) and T zone lymphoma (TZL-small cell, T-cell) (Deravi et al., 2017; Flood-Knapik et al., 2013; Valli et al., 2013). Most dogs with TZL are Golden Retrievers, Shih Tzus, and Labrador Retrievers. The combination of cytologic appearance and FCM allows for classification of these tumors as indolent (Deravi et al., 2017; Flood-Knapik et al., 2013). There is also a specific splenic indolent lymphoma in dogs, termed marginal zone lymphoma; this tumor usually presents as a solitary splenic mass (as opposed to diffuse splenomegaly) and can be effectively treated with splenectomy alone, resulting in prolonged survival times (O'Brien et al., 2013).

Until there is conclusive evidence that the histopathologic classification of canine and feline lymphomas offers conclusive prognostic or therapeutic information, the surgical removal of a lymph node or extranodal mass for histopathologic evaluation in a patient with a cytologic diagnosis of lymphoma is not generally indicated. A diagnosis based on cytologic findings rather than histopathologic findings yielded by an excisional lymph node biopsy also offers two major benefits: (1) It is associated with minimal or no morbidity, and (2) it is financially acceptable to most owners (i.e., approximate cost of a lymph node aspirate is $200-$300; the cost for biopsy and histopathologic evaluation is $500-$700).

New diagnostic methodologies commonly used in patients with lymphoma in our clinics include immunophenotyping by FCM and clonal analysis by polymerase chain reaction (PCR). In the former, a sample of the affected organ/tissue is obtained by FNA and placed in appropriate transport media. In the laboratory, these cells are incubated with specific antibodies that recognize epitopes specific for T or B cells. FCM evaluation of the sample allows to immunophenotype the cell population as T or B cell derived. Immunophenotyping by FCM is now performed by some diagnostic reference laboratories. Immunophenotyping can also be carried out on lymph node or tissue biopsies immunohistochemically or previously submitted cytology slides by immunocytochemistry. Clonal analysis by PCR (or PCR for antigen receptor rearrangement [PARR]) also requires an FNA or a small biopsy specimen. Specific laboratories will evaluate the population of cells in question by PCR to determine if they are monoclonal or polyclonal. This technique has high sensitivity and specificity for distinguishing reactive lymphadenopathy from lymphoma in dogs and cats. As a general rule, the authors use FCM to immunophenotype lymphomas and PARR when the diagnosis of lymphoma is in question (i.e., to confirm or rule out lymphoma).

After a diagnosis of lymphoma is confirmed, it is customary to stage the disease to obtain a prognosis. A staging system devised by the World Health Organization has been used routinely for the staging of cats and dogs with lymphoma (Table 79.3). In this system, derived from the tumor, node, metastasis (TNM) staging system for neoplasms in humans, clinical and clinicopathologic information from the

patient is used in an attempt to determine the extent of disease and correlate it with the prognosis. Unfortunately, it has little prognostic value (i.e., animals with stage I disease have survival times similar to those of animals with stage IV disease). The only prognostic information of clinical relevance in this system is the fact that asymptomatic (i.e., substage a) dogs with lymphoma have a better prognosis than "sick" (i.e., substage b) dogs. As discussed earlier, with the novel FCM analyzer's use for in-house CBCs, circulating neoplastic cells are frequently identified in the graphics; therefore these patients who would have previously been classified as stage III, now undergo "stage migration" to stage V disease.

A staging system that takes into account tumor bulk and FeLV status in cats with lymphoma provides some prognostic information. Until a new system is devised, it is advisable to determine the prognosis on the basis of the patient's overall clinical condition, the FeLV status (in cats), and any constitutional signs or severe hematologic and biochemical abnormalities the patient may have. Another important issue is that, even though a specific staging protocol may be of some prognostic value in patients treated with a given chemotherapy protocol, it may not be so when a different drug combination is used. Moreover, at this time the effectiveness of more aggressive protocols in dogs and cats with advanced-stage lymphoma is unknown.

At least a CBC, a serum biochemistry profile, and a urinalysis should be performed in all cats and dogs with lymphoma whose owners are contemplating therapy. In addition, FeLV and FIV tests should be performed in cats. The resulting minimum database can provide a wealth of information that can help the owner (and clinician) decide whether the patient should be treated. In addition, once a decision to treat the pet has been made, the nature of any clinicopathologic abnormalities usually dictates the treatment or treatments used. For example, in a dog with pronounced cytopenias caused by lymphomatous infiltration of the bone marrow, a highly myelosuppressive chemotherapy combination will almost certainly result in severe neutropenia and sepsis; it should therefore be avoided. L-asparaginase is a useful initial treatment in this situation, as it does not have myelosuppressive effects.

In cats and dogs with suspected CNS lymphoma, it is advisable to perform cerebrospinal fluid (CSF) analysis and advanced imaging (i.e., computed tomography [CT] scan or magnetic resonance imaging [MRI]). The finding of high numbers of neoplastic lymphoid cells and an increased protein concentration in a CSF sample is diagnostic for lymphoma. Because of their poor accessibility, the diagnosis of extradural masses usually requires the collection of a surgical specimen for cytologic or histopathologic evaluation. As discussed earlier, the authors' clinics assume that any dog or cat with lymphoma and central neurologic signs has CNS involvement until proven otherwise, and it is treated appropriately (see later).

As previously discussed, immunophenotyping of canine and feline lymphoma has become routine for most oncologists. This can be done by immunocytochemistry, immunohistochemistry, FCM, or PARR. But the main question is: Should every dog or cat with lymphoma be immunophenotyped before initiating therapy? The blanket answer is "no." Phenotype has been shown to change the prognosis, mainly in dogs with multicentric lymphoma; however, in our experience, it rarely changes the initial treatment approach. In dogs, a T-cell phenotype is quite likely if the patient is a Boxer, has hypercalcemia or a mediastinal mass, or has cutaneous involvement.

Although multiple previously published reports suggest that dogs with large-cell T-cell lymphoma treated with standard combination chemotherapy have a worse prognosis for remission and survival than dogs with B-cell tumors; in one of the author's experience (GC), this is not the case. In a previous study, T-cell phenotype was not a negative prognostic factor in dogs with lymphoma treated with COP- or CHOP-based protocols (Hosoya et al., 2007). This is likely because most dogs with T-cell lymphoma received lomustine (CCNU), a drug that may be more effective in patients with T-cell phenotype.

Treatment

Once a diagnosis of lymphoma is established, the prognosis and potential therapeutic options should be discussed with the pet's family. Remission rates in cats and dogs with lymphoma treated with various chemotherapy protocols are approximately 65% to 75% and 80% to 90%, respectively. Most cats with multicentric or mediastinal lymphoma treated with multiple-agent chemotherapy protocols are expected to live 6 to 9 months; approximately 20% to 30% of the cats live more than 1 year. Cats with small cell intestinal lymphoma typically live in excess of 2 years, with response rates of >90%. Most dogs with lymphoma treated with multiagent chemotherapy are expected to live 8 to 16 months; approximately 20% to 30% of the dogs are alive 2 years after diagnosis. The approximate survival time in untreated cats and dogs with lymphoma is 4 to 8 weeks. The reasons for the shorter survival times in cats as compared with dogs with lymphoma is that their initial response rates (especially, the complete response rates) are lower, and along with this, remissions appear to be difficult to reinduce once their disease has relapsed. In addition, the retrovirus-associated nonlymphomatous disorders that affect cats with lymphoma lead to shortened survival times (i.e., FeLV infection is a negative prognostic factor in cats with lymphoma).

In our experience, even if a patient has stage I nodal or extranodal lymphoma at the time of presentation, systemic dissemination of the disease usually occurs within weeks to months of diagnosis. However, occasionally solitary oral or cutaneous lymphomas may behave as true stage I diseases (i.e., there is no systemic dissemination). Therefore the mainstay of treatment for patients with lymphoma is chemotherapy, given the fact that lymphomas are (or will become) systemic neoplasms. Surgery, radiotherapy, or both can be used to treat localized lymphomas before or during chemotherapy. Half-body irradiation and bone marrow

transplantation have been used to some degree in dogs with lymphoma, and radiotherapy can also be a useful technique for treating cats with nasal or solitary epidural lymphoma (see Suggested Readings). General guidelines for the management of patients with lymphoma are presented here, although each author has a different mainstay protocol.

There are two main chemotherapeutic approaches in dogs and cats with lymphoma: induction chemotherapy, followed by maintenance (and reinduction) or more aggressive chemotherapy for a finite period of time, at the end of which no maintenance chemotherapy is used. The former is usually done with a less aggressive COP (cyclophosphamide, vincristine, and prednisone)–based protocol, whereas the latter is usually based on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)–type protocols. An example of the latter is one of several University of Wisconsin (UW) protocols. CHOP-based protocols are similar to those used in people with high-grade lymphomas.

COP-Based Protocols

One of the authors (GC) favors COP-based protocols in dogs and cats with large-cell lymphoma. The treatment is divided into several phases, or strategies: induction of remission, intensification, maintenance, and reinduction of remission or "rescue" (Box 79.1). Immediately after diagnosis, a relatively "nonaggressive" multiple-agent COP-based chemotherapy protocol is used to *induce remission.* During this phase, which lasts 6 to 8 weeks, patients are evaluated weekly by a veterinarian, at which time they receive an intravenous (IV) injection of an antimitotic agent (vincristine) in addition to



BOX 79.1

Chemotherapy Protocols Used by the Author to Treat Dogs and Cats* With Lymphoma

1. Induction of Remission

a. COP protocol

Cyclophosphamide: 200-300 mg/m^2 BSA, PO, every 3 weeks (dogs or cats)‡
Vincristine: 0.5 mg/m^2 BSA, IV, once a week
Prednisone: 40-50 mg/m^2 BSA, PO, q24h for a week; then 20-25 mg/m^2 BSA, PO, every other day or dexamethasone 4-5 mg total dose, PO, q1-3 weeks (in cats only)

b. COAP protocol †

Cyclophosphamide: 200-300 mg/m^2 PO q3 weeks
Vincristine: 0.5 mg/m^2 IV weekly
Cytosine arabinoside: 100 mg/m^2 daily as an IV drip or SC for only 2 days in cats and 4 days in dogs
Prednisone: 50 mg/m^2 PO q24h for 1 week; then 20 mg/m^2 PO q48h or dexamethasone 4-5 mg total dose, PO, q1-3 weeks (in cats only)

c. UW-25 protocol (This protocol uses no maintenance chemotherapy—for additional information see text.)

Week 1: Vincristine 0.5-0.75 mg/m^2 IV; Asparaginase 400 IU/kg, IM or SC; Prednisone 2 mg/kg PO q24h
Week 2: Cyclophosphamide 200-250 mg/m^2 IV; Prednisone 1.5 mg/kg PO q24h
Week 3: Vincristine 0.5-0.75 mg/m^2 IV; Prednisone 1 mg/kg PO q24h
Week 4: Doxorubicin 30 mg/m^2 (or 1 mg/kg if <10 kg) IV; Prednisone 0.5 mg/kg PO q24h
Week 5: **No treatment**
Week 6: Vincristine 0.5-0.75 mg/m^2 IV
Week 7: Cyclophosphamide 200-250 mg/m^2 IV
Week 8: Vincristine 0.5-0.75 mg/m^2 IV
Week 9: Doxorubicin 30 mg/m^2 (or 1 mg/kg if <10 kg) IV
Week 10: **No treatment**
Week 11: Vincristine 0.5-0.75 mg/m^2 IV
Week 13: Cyclophosphamide 200-250 mg/m^2 IV
Week 15: Vincristine 0.5-0.75 mg/m^2 IV
Week 17: Doxorubicin 30 mg/m^2 (or 1 mg/kg if <10 kg) IV
Week 18: **No treatment**
Week 19: Vincristine 0.5-0.75 mg/m^2 IV
Week 21: Cyclophosphamide 200-250 mg/m^2 IV
Week 23: Vincristine 0.5-0.75 mg/m^2 IV
Week 25: Doxorubicin 30 mg/m^2 (or 1 mg/kg if <10 kg) IV

2. Intensification

Dogs

L-Asparaginase: 10,000-20,000 IU/m^2 SC or IM (one or two doses)
or
Vincristine: 0.5-0.75 mg/m^2 IV q1-2 weeks

Cats

Doxorubicin: 1 mg/kg IV q3 weeks
or
Mitoxantrone: 4-6 mg/m^2 IV q3 weeks

3. Maintenance§

a. LMP protocol

Chlorambucil: 20 mg/m^2 PO q2 weeks
Methotrexate: 2.5 mg/m^2 PO two or three times per week
Prednisone: 20 mg/m^2 PO q48h or dexamethasone 4-5 mg total dose PO q1-3 weeks (in cats only)

b. Lomustine/prednisone protocol

Lomustine: 60-70 mg/m^2 PO q3 weeks in dogs or 10 mg total dose q3 weeks in cats
Prednisone: 2 mg/kg PO q24h, taper when remission obtained or dexamethasone 4-5 mg total dose, PO, q1-3 weeks (in cats only)

c. COP protocol

Use as previously discussed every other week for six treatments, then every third week for six additional treatments, then try to maintain the animal on one treatment every fourth week. Maintenance therapy is continued until the tumor relapses.

BOX 79.1

Chemotherapy Protocols Used by the Author to Treat Dogs and Cats* With Lymphoma—cont'd

4. Rescue

Dogs

a. D-MAC protocol (14-day cycle)
   Dexamethasone: 0.5 mg/lb (1 mg/kg) PO or SC on days 1 and 8
   Actinomycin D: 0.75 mg/m^2 as IV push on day 1
   Cytosine arabinoside: 200-300 mg/m^2 as IV drip over 4 hours *or* SC on day 1
   Melphalan: 20 mg/m^2 PO on day 8‖
b. AC protocol (21-day cycle)
   Doxorubicin: 30 mg/m^2 (or 1 mg/kg for dogs <10 kg) IV on day 1
   Cyclophosphamide: 100-150 mg/m^2 PO on days 15 and 16
c. Rescue CHOP-based protocol (21-day cycle)
   Cyclophosphamide: 200-300 mg/m^2 PO on day 10
   Doxorubicin: 30 mg/m^2 (or 1 mg/kg for dogs <10 kg) IV on day 1
   Vincristine: 0.75 mg/m^2 IV on days 8 and 15
   Prednisone: 20-25 mg/m^2 PO q48h
d. MOPP protocol (28-day protocol; repeat continuously until relapse)
   Mechlorethamine: 3 mg/m^2 IV on day 0, 7
   Vincristine: 0.7 mg/m^2 IV on days 0,7
   Procarbazine: 50 mg/m^2 PO q24h for days 0-13
   Prednisone: 30-40 mg/m^2 PO q24h for days 0-13
e. Combination L-asparaginase, lomustine, and prednisone
   Lomustine: 60-70 mg/m^2 PO q3 weeks
   L-asparaginase: 400 u/kg SC or IM q3 weeks
   Prednisone: 2 mg/kg PO q24h, taper when remission obtained
f. Dacarbazine: 800-1000 mg/m2 q14-21d
g. Lomustine: 60-80 mg/m^2 q21d
h. Rabacfosadine: 0.82-1 mg/kg IV over 30 minutes q3 weeks

Cats

a. ACD protocol (21-day cycle)
   Doxorubicin: 1 mg/kg IV on day 1
   Cyclophosphamide: 200-300 mg/m^2 PO on day 10 or 11
   Dexamethasone (4-5 mg total dose q1-2 weeks can be added to this protocol)
b. MiCD protocol (21-day cycle)
   Mitoxantrone: 4-6 mg/m^2 as IV drip over 4-6 hours on day 1
   Cyclophosphamide: 200-300 mg/m^2 PO on day 10 or 11
   Dexamethasone (4-5 mg total dose q1-2 weeks can be added to this protocol)
c. MiCA protocol (21-day cycle)
   Mitoxantrone: 4-6 mg/m^2 in IV drip over 4-6 hours on day 1
   Cyclophosphamide: 200-300 mg/m^2 PO on day 10 or 11
   Cytosine arabinoside: 200 mg/m^2 in IV drip over 4-6 hours (mixed in the same bag with mitoxantrone) on day 1
   Dexamethasone (4-5 mg total dose q1-2 weeks can be added to this protocol)

5. "Low-Budget" Protocols

Prednisone: 50 mg/m^2 PO q24h for 1 week; then 25 mg/m^2 PO q48h
Chlorambucil: 20 mg/m^2 PO q2 weeks
Lomustine: 60 mg/m^2 PO q3 weeks in dogs; 10 mg (total dose) q3 weeks in cats
Prednisone and chlorambucil: doses as above
Prednisone and lomustine: doses as above

*Unless otherwise specified, protocols can be used in both dogs and cats.
†Use for 6-10 weeks, then use LMP.
‡The duration of chemotherapy using this protocol is variable.
§Use until relapse occurs, then go to "rescue."
‖After four doses, substitute chlorambucil (20 mg/m^2 PO q2 weeks) for melphalan.
BSA, Body surface area; *IM,* intramuscular; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.

undergoing a routine physical examination (with or without a CBC). If at the end of this phase, the patient is considered to be in complete remission (CR; i.e., all neoplastic masses have completely disappeared), the *maintenance* phase is initiated. During this phase, a multiple-agent chemotherapy protocol consisting of three drugs (chlorambucil [Leukeran], methotrexate, and prednisone [LMP]) administered orally is used so that the patient requires less intensive monitoring (once every 6-8 weeks). The owners are then instructed to closely monitor the size of the lymph nodes in their pets; when the nodes start enlarging (i.e., relapse), a fourth drug is added to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m^2 IV q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months. Alternatively, in suspected or confirmed T-cell tumors (in dogs), a maintenance protocol consisting of lomustine (60-70 mg/m^2 orally [PO] q3-6 weeks) and prednisone can be used, utilizing the same strategy for relapse as in dogs on LMP.

The maintenance or modified maintenance phase continues until the tumor relapses (i.e., is out of remission), at which time the *reinduction* phase begins. This phase is similar to the induction phase in that intensive treatments are used. Once remission is obtained, the patient is started

again on a modified maintenance protocol. If at the end of the induction phase the patient is not in a CR, the author recommends that *intensification* with L-asparaginase be done before the maintenance phase is initiated. In addition to the chemotherapeutic approach discussed in this section, a variety of protocols have been used successfully in the treatment of cats and dogs with lymphoma. (See Suggested Readings for additional information.)

Induction of remission

As previously discussed, one author's (GC) protocol of choice for the induction of remission is COP. The agents in this protocol consist of cyclophosphamide, vincristine, and prednisone; these drugs are currently available as generic products and are relatively inexpensive. The dosages are specified in Box 79.1. These drugs belong to three different categories, have different mechanisms of action, and do not have superimposed toxicities. In dogs or cats with CNS or ocular involvement, cytosine arabinoside can be added by the subcutaneous (SC) route or as a continuous rate infusion for 6 to 8 hours (COAP protocol); given its short half-life and S-phase–specific mechanism of action, an IV bolus injection results in minimal cell kill. SC administration of this drug is painful in cats (and in some dogs). The induction phase lasts 6 to 8 weeks, and weekly chemotherapy visits are necessary during this time.

During the induction phase, toxicity is minimal (<15%) and client compliance is high because most of the toxic signs are hematologic (i.e., cytopenias) and usually do not result in clinical signs that can be detected by the owners. The dose-limiting toxicity of this induction protocol is hematologic (i.e., myelosuppression leading to neutropenia), and it occurs in less than 10% of the patients; the neutrophil nadir usually occurs around day 7 or 8 because two myelosuppressive agents (i.e., cyclophosphamide and cytosine arabinoside) are given during the initial 2 to 4 days of treatment in the COAP protocol. In most cases, the neutropenia is mild (2000-3500 cells/μL). The neutropenia can be severe if the animals have neoplastic bone marrow infiltration before the initiation of treatment, have FeLV- or FIV-associated myelodysplasia or other retrovirus-associated bone marrow disorders, or receive the cytosine arabinoside by constant-rate IV infusion rather than by the SC route. Also, anecdotally, neutropenia appears to be common in Cocker Spaniels and West Highland White Terriers receiving this protocol. Dosage adjustments in cats and dogs that develop neutropenia are described in Chapter 77. Gastrointestinal toxicity is minimal to nonexistent; however, cats receiving cyclophosphamide can occasionally become anorectic. Consequently, this drug should be administered once every 3 weeks in cats (as opposed to every other day as in dogs; see Box 79.1). If anorexia develops, treatment with cyproheptadine, an antiserotonin drug, at a dosage of 1 to 2 mg per cat PO every 12 h or mirtazapine at a dosage of 1.875 to 3.75 mg per cat PO every 1 to 3 days is indicated. Capromorelin, is a novel appetite stimulant (Entyce, Aratana Therapeutics, Leawood, KS) given at a dosage of 3 mg/kg PO every 24 h. Hair loss is also minimal, and it occurs primarily in woolly-haired dogs (e.g., Poodle, Bichon Frise); cats (and some dogs) may also shed their tactile hairs during treatment.

During this phase, owners are instructed to monitor their pet's appetite and activity level, measure their lymph nodes (if peripheral lymphadenopathy was present initially), and take their pet's rectal temperature if they are unwell (pyrexia is usually secondary to neutropenia and bacteremia or sepsis). If pyrexia develops, owners are instructed to contact their veterinarian immediately so that their pet can undergo a complete physical examination and CBC (for additional information, see Chapter 77). Treatment with COP results in CR within 1 to 14 days of the start of therapy in most animals (>85% in dogs, >70% in cats) (Figs. 79.9 and 79.10, *A* and *B*). This remission is usually maintained throughout the induction phase.

In dogs with diffuse large-cell alimentary lymphoma, the authors both use a CHOP-based protocol (see Box 79.1) because, on the basis of experience, the response rate to COP is low. This protocol is more expensive and slightly more likely to cause adverse effects than the COP protocol.



FIG 79.10
Mixed-breed dog with multicentric lymphoma before **(A)** and 7 days after initiating chemotherapy **(B).** Note complete disappearance of mandibular lymphadenopathy and ventral facial edema.

Lomustine (CCNU) is typically used in dogs with epitheliotropic T-cell lymphoma (see Box 79.1) and, as discussed earlier, for one of the authors (GC), as part of the maintenance or reinduction protocol in dogs with other large-cell T-cell lymphomas.

In dogs and cats with multicentric lymphoma (or any other anatomic form) coexisting with neurologic or ocular signs, one author (GC) usually uses the COAP protocol but administers the cytosine arabinoside as a continuous IV infusion (200-400 mg/m^2 as an IV infusion over 24 hours for 1-4 days) to attain high concentrations of this drug in the CNS. This protocol tends to cause marked myelosuppression in cats, so cytosine arabinoside is typically administered as a 12- to 24-hour infusion (200 mg/m^2) in this species. More information on the treatment of dogs and cats with suspected or confirmed CNS lymphoma is given later in this chapter.

Maintenance

The protocol recommended by one of the authors (GC) for the maintenance phase of treatment is LMP ("lump"), which consists of chlorambucil, methotrexate, and prednisone (see Box 79.1). These drugs also act by three different mechanisms of action and have differing toxicities. The advantages of this protocol include its reduced cost compared with the cost of the induction phase; its ease of administration (all the drugs are administered orally by the owners); its minimal toxicity; and the fact that intensive monitoring by a veterinarian is not necessary.

The toxicities associated with LMP maintenance chemotherapy are minimal. Of the three drugs in this protocol, methotrexate is the only one associated with moderate to severe toxicity. Approximately 25% of dogs and cats receiving methotrexate develop gastrointestinal tract signs consisting of anorexia, vomiting, or diarrhea. Anorexia and vomiting are more common than diarrhea, and usually occur after the patient has been receiving the drug for more than 2 weeks. In these cases, treatment with an antiemetic such as metoclopramide on the days the animal receives the methotrexate, at a dosage of 0.1 to 0.3 mg/kg PO q8h, alleviates or eliminates the upper gastrointestinal tract signs. Use of maropitant (Cerenia, Pfizer Animal Health, Kalamazoo, Mich) at a dosage of 2 mg/kg PO q24h for dogs, and 1 mg/kg PO q24h for cats can also be considered to prevent chemotherapy-associated nausea and vomiting. Gastroprotectants such as famotidine (0.5-1 mg/kg PO q12h) may also be effective in preventing or minimizing this adverse effect. In cases of methotrexate-associated diarrhea, treatment with a bismuth subsalicylate–containing product (Pepto-Bismol) may also alleviate or eliminate the signs; however, it may be necessary to discontinue the drug. Hematologic toxicity associated with LMP therapy is minimal to nonexistent. In a small proportion of cats (i.e., <5%) receiving chlorambucil for weeks to months, serum biochemical abnormalities consistent with cholestasis that resolve with discontinuation of the drug may develop. Tonic or tonic-clonic convulsions can also rarely occur in cats receiving chlorambucil.

During this phase the patient is examined every 6 to 8 weeks, at which time a complete physical examination and a CBC are performed. As with the induction protocols, owners are instructed to monitor their pet's activity, appetite, behavior, and lymph node size. As discussed previously, is it recommended that the owners of pets with multicentric lymphoma are instructed to closely monitor the size of the lymph nodes; when the nodes start enlarging (i.e., relapse), a fourth drug can be added to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m^2 IV q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months.

Most patients treated with this protocol remain in remission for approximately 3 to 6 months. If a relapse occurs, reinduction of remission (as discussed next) is instituted. After remission is reinduced, animals can be treated with a modified maintenance protocol, as described in previous paragraphs.

CHOP-Based Protocols

When using CHOP-based protocols (favored by one of the authors—KC), a 4 to 6 month protocol without long-term maintenance is used. Typically, weekly to twice monthly chemotherapy with a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone is used for a total of 4 cycles; the main difference between the UW-19 and UW-25 protocol are a longer interval between treatments during the second half of the protocol. As stated earlier, these drugs have differing mechanisms of action and do not have superimposed toxicities, again fulfilling the criteria for traditional multiagent chemotherapy described in Chapter 76. Doxorubicin can be associated with a slightly higher risk of gastrointestinal adverse effects than the other drugs in this protocol, and the author (KC) generally uses Cerenia after each dose of doxorubicin to help limit this toxicity. Fasting before doxorubicin administration has also been associated with a lower frequency of delayed vomiting, so this should also be considered. During treatment, similarly to the previously described recommendations, owners are instructed to monitor their pet's appetite, activity level, lymph node size (if peripheral lymphadenopathy was present initially), and take their pet's rectal temperature if they are unwell. Additionally, the patient is examined every 1 to 2 weeks, at which time a complete physical examination and CBC are performed. After completion of the 4 to 6 month protocol, patients are examined every 4 to 6 weeks, to assess for relapse of their lymphoma, and if any overt abnormalities were present on CBC or chemistry panel before diagnosis (i.e., circulating neoplastic cells, liver enzyme elevation, etc.), this bloodwork is repeated. If no previous abnormalities were present, then full bloodwork is rechecked every 3 months to assess for development of any concerning findings related to relapse of lymphoma.

These conventional CHOP-based chemotherapy protocols have been associated with remission rates of approximately 85% to 95% in dogs with high-grade lymphoma, and 60% to 70% in cats with high-grade lymphoma. The typical

MSTs reported for dogs with multicentric lymphoma are 10 to 12 months. Cats treated with CHOP-based protocols for high-grade lymphoma experience overall lower MSTs than dogs; however, approximately 30% of cats have long-term survivals of over 1 to 2 years.

Should You Use COP-Based or CHOP-Based Protocols?

Clinicians have been debating the relative merits of COP- and CHOP-based protocols for several years. However, due to the fact that most institutions or clinicians prefer one protocol over the other (illustrated by the differing protocols used in this chapter by both authors), most reports on COP-based protocols are 10 to 20 years old, and most reports of COP- or CHOP-based chemotherapy studies have remission times as endpoints rather than survival times, a definitive answer is not readily available. There is no clear advantage of one protocol over the other, so it is recommended that the clinician make decisions based on various factors (e.g., the owner's perception, the patient's clinical signs, other concurrent illnesses, the veterinarian's "comfort" with a given protocol or drug, etc.). See Figures 79.12 and 79.13.

Intensification

If a dog with large-cell lymphoma is undergoing induction therapy (with either COP- or CHOP-based protocols), but only partial remission (PR) is obtained, intensification with one or two doses of L-asparaginase (10,000-20,000 IU/m^2 intramuscular [IM] or SC, repeated once at a 2- to 3-week interval) may be indicated. This drug can rapidly induce CR in most dogs with lymphoma that have shown only PR while receiving COP or CHOP. Additionally, in patients that are unwell or have cytopenias, we frequently induce the initial remission, before initiation of either COP or CHOP, with L-asparaginase, given the lack of adverse effects and the high probability of response. This can be quite beneficial for dogs that are sick from their lymphoma and cannot tolerate traditional chemotherapy. Caution is recommended in dogs with a history of pancreatitis or in those that are at high risk for acute pancreatitis (i.e., obese, middle-aged female dogs), as asparaginase can cause pancreatitis; however, in our experience, this is an uncommon adverse effect. L-asparaginase appears to be less effective in cats than in dogs, only inducing remission in approximately 30% of cats.

Reinduction of remission or rescue

Virtually every dog and cat with lymphoma treated with either COP- or CHOP-based chemotherapy protocols will eventually relapse; this generally occurs 3 to 6 months after the start of induction therapy with COP (median: ≈4 months), and 8 to 9 months after initiation of the CHOP. At this time, reinduction of remission is indicated. In our experience, remission can be reinduced one to four additional times in most dogs with relapsing lymphoma. Reinduction of remission is usually not as successful in cats (i.e., remission is difficult to reinduce in most cats with relapsing lymphoma). Therefore the following discussion on "rescue" pertains mostly to dogs with lymphoma.

Numerous "rescue" protocols have been described in the literature, and as a general rule, the practitioner may have difficulty deciding what protocol to choose since the final decision is frequently based on personal experience. Typically, if a patient has completed the induction phase of COP or the entirety of the CHOP protocol before relapse, reinduction with one of these protocols is considered the most likely to induce another remission. There are also alternative rescue chemotherapy options consisting of multi- or single-agent protocols that can be considered for use if the COP or CHOP protocol is unsuccessful at reinducing remission, or the owner opts to proceed with an alternative protocol.

One author (GC) currently uses the D-MAC protocol (see Box 79.1) as the first alternative to COP, which consists of dexamethasone, melphalan, cytosine arabinoside, and actinomycin D (Alvarez et al., 2006). This protocol results in a greater than 70% remission rate in dogs with relapsing lymphoma; it has a relatively low toxicity compared with that of doxorubicin-containing protocols, and it is necessary for the owner to go to the veterinarian only once every 2 weeks (instead of every week). The median duration of remission using the D-MAC protocol was 61 days (range 2-467+ days) in a previous study (Alvarez et al., 2006). Previous use of doxorubicin and failure to induce remission with the induction protocol were negative prognostic factors for response to this protocol. Thrombocytopenia occurred in 56% of the dogs, neutropenia in 17%, and gastrointestinal toxicity in 22%; 3 of the 56 dogs required hospitalization because of toxicity. Because the long-term use of melphalan is associated with severe chronic thrombocytopenia, chlorambucil, 20 mg/m^2, is substituted for melphalan after four cycles. If complete or partial remissions are achieved after the administration of four to six cycles of D-MAC, the patient can be started on a maintenance protocol again. If the response to D-MAC is poor (i.e., the disease progresses), GC then pursues the CHOP protocol (see Box 79.1). This protocol calls for two or three cycles of CHOP; if CR is obtained, the patient is started on maintenance chemotherapy at the end of the second or third CHOP cycle. The maintenance protocol in these animals also includes LMP, with the possible addition of vincristine (0.5-0.75 mg/m^2 IV once weekly to every other week, alternating weeks with the chlorambucil) or cytosine arabinoside (200-400 mg/m^2 SC every other week, alternating weeks with the chlorambucil). After a second relapse occurs, GC generally proceeds with an additional D-MAC or CHOP protocol for two additional cycles, as described in the preceding paragraph.

If a CHOP-based protocol is unsuccessful at reinducing a remission, or owners opt to not proceed with another CHOP-based protocol, KC generally discusses different rescue options with owners to decide which protocol is most suitable. The main considerations include whether the owners are able to commit to weekly or every other week office visits, finances, and the health of the patient at relapse. The protocols commonly considered are listed in Box 79.1, with the single-agent protocols (e.g., dacarbazine, CCNU) having response rates of approximately 30% to 40% and the

combination protocols (e.g., MOPP, L-asparaginase/CCNU/prednisone, DMAC) having response rates of 60% to 80%. One exception, single-agent rabacfosadine, has recently been evaluated for the use of dogs with relapsed B-cell lymphoma, and an overall response rate of 74% was reported (Saba et al., 2018).

After the second and third relapses, the percentage of patients in which remission can be easily reinduced decreases with each subsequent cycle. This likely stems from the development of multiple-drug resistance by the tumor cells. The authors usually advise owners that after each subsequent relapse, the probability and duration of remission are about half of those in the previous one. Other protocols that have been successful in reinducing remission in dogs with lymphoma are listed in Box 79.1. Although the probability of reinducing remission is considerably lower in cats than in dogs, one of the protocols listed in Box 79.1 can be used for this purpose.

In cats, the authors generally consider doxorubicin- or mitoxantrone-containing protocols, as well as CCNU, which have shown some degree of success (see Box 79.1); asparaginase-containing protocols may also be used but are generally not as effective as in dogs.

Management of dogs with indolent lymphomas

A diagnosis of indolent lymphoma can be made on the basis of histopathology or using a combination of historical, physical examination, cytologic, and FCM findings. For example, a middle-aged Shih Tzu with long-standing mild to moderate generalized lymphadenopathy and a small-cell lymphoma based on cytology likely has a TZL. We manage these patients either with chlorambucil and prednisone (see earlier), with or without vincristine, or with a short course of COP followed by chlorambucil and prednisone. Survival times of 1 to 2 years are common. In one study, the use of CHOP in these patients resulted in significantly shorter survival times (Flood-Knapik et al., 2013). As discussed before, splenectomy alone typically results in long-term survival in dogs with splenic indolent lymphoma (O'Brien et al., 2013).

Management of solitary and extranodal lymphomas

The clinician faces a dilemma when confronted with a dog or cat with a solitary lymphoma, regardless of whether it is nodal (i.e., stage Ia disease) or extranodal (i.e., a solitary cutaneous or oral mass). Should the mass (or lymph node) be treated in the same manner as other solitary malignancies (i.e., by wide surgical excision)? Should the patient be treated primarily with chemotherapy? Should the patient be treated with a combination of surgery, irradiation, and chemotherapy? Unfortunately, there are no correct answers to these questions.

In our experience, seemingly solitary lymphomas become (or already are) systemic in most animals. Exceptions include some oral and some cutaneous solitary T-cell lymphomas. Although cures have been achieved through surgical excision or irradiation of solitary lymphomas, they are extremely rare. Therefore it is important not to underestimate the malignant behavior of this neoplasm by treating the patient with only localized treatment modalities such as surgery or radiotherapy. The following guidelines can be used in this subset of patients. As a general rule, these patients should be thoroughly staged before consideration of any localized therapy to ensure that visible systemic disease is not present before local therapy:

1. If the tumor is easily resectable (e.g., cutaneous mass, superficial lymph node, intraocular mass) and the surgical procedure does not pose a considerable risk to the patient, the mass should be resected and the animal treated with chemotherapy.
2. If the mass is difficult or impossible to resect or if a major surgical procedure would pose an undue risk for the patient, then systemic chemotherapy with or without radiotherapy of the primary lesion should be pursued.

Radiotherapy constitutes an excellent treatment modality for dogs and cats with solitary lymphomas because the tumor cells are extremely radiosensitive. Marked responses (CR or PR) can be seen within hours or days of the start of such treatment. Different sources and protocols have been used in cats and dogs with lymphoma, but in general 3 to 5 Gy per fraction is delivered daily or three times weekly for a total of 6 to 10 fractions (total dose, 30-50 Gy). One of the authors has successfully used coarse fractionation radiotherapy (7 Gy once a week for 4 treatments) followed by maintenance chemotherapy (discussed later) in dogs with solitary oral T-cell lymphomas. A previous study supports a major role for radiotherapy of oral mucocutaneous lymphomas, where median survival times in excess of 2 years were obtained (Berlato et al., 2012). Additionally, special settings in which radiotherapy may be beneficial include CNS lymphomas (see following paragraphs) and upper airway lymphomas that cause respiratory compromise.

Another decision the clinician must make if chemotherapy is to be used is which protocol to use and for how long. There are also no specific guidelines for this. Generally, the authors use similar protocols for the more typical lymphomas in this situation (e.g., COP, CHOP-based protocols).

Central nervous system lymphoma

The treatment of choice for cats and dogs with primary or secondary epidural lymphoma is multiple-agent chemotherapy with or without radiotherapy. If radiotherapy facilities are not available, multiple-agent chemotherapy alone is an effective approach. It is our clinical impression that the surgical excision of such masses does not provide a therapeutic advantage over chemotherapy alone or radiotherapy plus chemotherapy, given the fact that the latter two forms of treatment can consistently induce rapid remissions (i.e., within 12-36 hours of the initiation of therapy, see Fig. 79.11). However, because surgery may be necessary to confirm the diagnosis, surgical excision of the mass may be attempted at that time. If radiotherapy is available, it is quite effective. The COAP protocol alone can also be effective in inducing remission in cats with epidural lymphoma. One of the authors (KC) has also used CHOP-based



FIG 79.11
Cat with retroorbital and intranasal lymphoma before **(A)** and 24 hours after administration of asparaginase, cytosine arabinoside, and dexamethasone **(B).**

protocols with cytarabine arabinoside used in place of cyclophosphamide.

In cats and dogs with lymphoma of the neuropil (i.e., true CNS lymphoma), chemotherapy with or without radiotherapy is the preferred protocol. Intrathecal chemotherapy can be used in cats and dogs with confirmed or highly likely neuropil lymphoma. The drug of choice is cytosine arabinoside because it is almost nontoxic, it is inexpensive, and it is easy to administer. However, IV administration of this drug as a constant rate infusion (CRI) at dosages of 200 to 600 mg/m^2 over 24 to 72 hours achieves similar results and is the preferred approach. Responses to intrathecal or IV CRI cytosine arabinoside are usually quite spectacular. Dogs and cats that are tetraparetic, demented, or comatose usually regain normal neurologic status within 6 to 48 hours of receiving the first dose of this agent. In addition, disappearance of the neoplastic cells from the CSF occurs within hours of the injection.

The authors frequently induce clinical and cytologic remission (i.e., normal neurologic status and disappearance of neoplastic cells from CSF) in cats and dogs with primary or secondary CNS lymphoma treated with COAP (using cytosine arabinoside as an IV infusion) or CHOP with cytosine arabinoside as an IV infusion in place of cyclophosphamide. As previously discussed, an alternative drug that crosses the blood-brain barrier and is effective in eliminating lymphoma cells is lomustine (CCNU; see Box 79.1) administered at a dosage of 60-70 mg/m^2 PO every 3 weeks in dogs and at a dosage of 10 mg/cat every 3 to 6 weeks in cats; the authors have seen marked improvement or disappearance of neurologic signs in dogs and cats with lymphoma treated with this drug and corticosteroids.

Despite the fact that remissions are easily attained in dogs and cats with CNS lymphoma, they are often relatively short in duration compared with disease in other anatomic locations. Most dogs and cats with CNS lymphoma relapse within

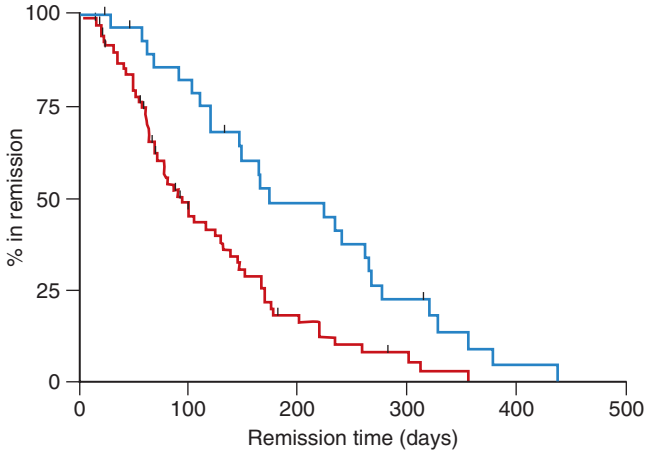


FIG 79.12
Kaplan-Meier curves for duration of first remission in dogs with multicentric lymphoma treated with COAP *(red line)* or CHOP *(blue line)*. The median duration of remission was significantly longer in dogs treated with CHOP chemotherapy (P <0.01). (From Hosoya et al., 2007.)

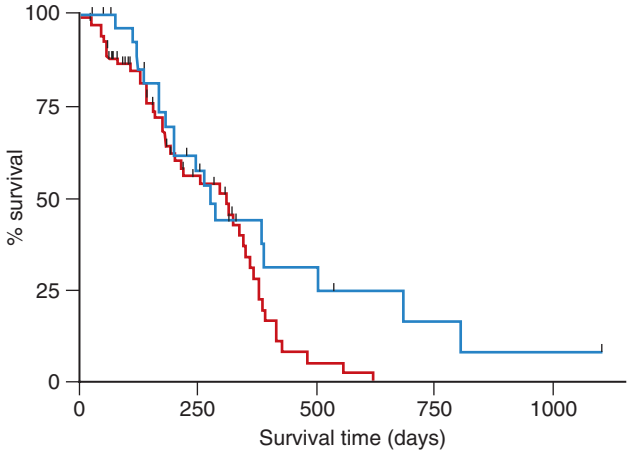


FIG 79.13
Kaplan-Meier survival curves in dogs with multicentric lymphoma treated with COAP *(red line)* or CHOP *(blue line)*. The median duration of remission was not significantly different between groups (P = 0.09). (From Hosoya et al., 2007.)

2 to 4 months of diagnosis; however, prolonged remissions (i.e., 6-12 months) are possible.

Ocular lymphoma

Ocular lymphoma can be treated using a variety of modalities. However, the eye behaves similarly to the blood-brain barrier in that adequate intraocular concentrations of chemotherapeutic agents are usually difficult to attain. If the clinician and owner want to try to preserve the animal's eye, there are several alternatives to enucleation. As in animals with CNS lymphoma, the administration of cytosine arabinoside as a slow IV drip usually results in remission of the tumor (see Fig. 79.11). Lomustine is also effective in dogs and cats with intraocular lymphoma.

Cutaneous lymphoma

Cutaneous lymphoma is the one of the most common extranodal form of lymphoma in dogs seen in most clinics in the United States. In dogs with cutaneous involvement secondary to multicentric lymphoma, the authors use a standard chemotherapy protocol (i.e., COP- or CHOP-based protocols). In dogs with epitheliotropic T-cell lymphomas, we use lomustine (CCNU)-containing protocols. Two studies have evaluated the use of lomustine for epitheliotropic cutaneous T-cell lymphoma, reporting an overall response rate of approximately 80%, with 20% to 30% attaining CR and 50% to 60% attaining PR. The overall median duration of response in these studies was approximately 90 days, with most dogs experiencing progressive disease resulting in death. More recently, rabacfosadine has also been used for epitheliotropic cutaneous lymphoma, which resulted in a response rate of 45%, and a progression free-survival of 37.5 days (Morges et al., 2014). This is an alternative treatment option if lomustine has been unsuccessful, or if there are contraindications for its use. As discussed earlier, radiotherapy is effective in localized cutaneous/mucocutaneous T-cell lymphomas. Fig. 79.4 depicts a cat with cutaneous lymphoma before and after chemotherapy.

Alimentary lymphoma

Both authors use standard chemotherapy protocols (i.e., COP or COAP, CHOP-based protocols) in dogs and cats with solitary mural or nodal (e.g., mesenteric or ileocecocolic lymph node) involvement of large-cell lymphoma. Even though surgery is not necessarily indicated for these dogs and cats, a fair number are referred after exploratory surgery and an incisional or excisional biopsy has been performed. In general, the response in these animals is good; however, it can be short-lived. Dogs and cats with diffuse large-cell intestinal lymphoma usually respond poorly to chemotherapy. Responses to doxorubicin-containing protocols (i.e., CHOP) appear to be better than those to COP, although survival times are overall short (4-6 months). Dogs with colorectal lymphoma and cats with gastric lymphoma tend to respond extremely well to COP- or CHOP-based chemotherapy, with documented remission times in excess of 3 years in these subsets of patients. Recently, a study of 31 dogs with colorectal lymphoma reported a progression free-survival of 1318 days and a disease-related MST of 1845 days. These dogs underwent chemotherapy, and a portion of them also underwent either radiation therapy or surgical resection (Desmas et al., 2017). In cats with gastric lymphoma, prolonged survival may be related to the fact that *Helicobacter* spp. may play a role in the development of gastric lymphoma, as *H. pylori* does in people; all cats with gastric lymphoma should be treated with combination chemotherapy and antibiotics proven effective in cats with *Helicobacter* infection.

In cats with epitheliotropic intestinal lymphoma, a common, small lymphocytic form of the disease in older individuals, a more conservative approach is recommended, which has been associated with excellent results. A combination of chlorambucil (20 mg/m^2 PO q2 weeks) plus prednisolone (1-2 mg/kg PO q24-48h) or dexamethasone (4 mg/cat PO q1-2 weeks) is administered; if clinical signs do not improve within 3 or 4 weeks, vincristine can be added (0.5 mg/m^2 IV q1-2 weeks). Most cats treated with this protocol have marked improvement of the clinical signs and typically gain weight; survival times of 1 to 2 years are common with treatment. Interestingly, some of the cats exhibit no appreciable decrease in mesenteric lymph node size, despite the remarkable clinical improvement. For these cats, the author uses the approach of "treating the patient, not the disease" (i.e., as long as the patient feels well and is free of clinical signs, the current treatment is continued). Recently, this disease entity has also been documented in dogs by one of the authors (KC), and similar to cats, treatment with a combination of chlorambucil and prednisone may results in long-term survivals (Couto et al., 2018).

"Low-Budget" Lymphoma Protocols

Quite frequently, the clinician is evaluating a dog or cat with lymphoma that should benefit from chemotherapy, but because of finances or other issues (e.g., time commitment), the owners are not interested in the standard multiagent chemotherapy approach. The authors have used one of the following quite successfully: prednisone alone, prednisone and chlorambucil, chlorambucil alone, lomustine alone, or prednisone and lomustine. Although the duration of remission is shorter than when using COP- or CHOP-based protocols, most of these patients (and their owners) can enjoy prolonged (i.e., months), good-quality survival times. These protocols are listed in Box 79.1.

Suggested Readings

Alvarez FJ, et al. Dexamethasone, melphalan, actinomycin D, cytosine arabinoside (DMAC) protocol for dogs with relapsed lymphoma. *J Vet Intern Med.* 2006;20:1178.

Berlato D, et al. Radiotherapy in the management of localized mucocutaneous oral lymphoma in dogs: 14 cases. *Vet Comp Oncol.* 2012;10:16.

Bridgeford EC, et al. Gastric *Helicobacter* species as a cause of feline gastric lymphoma: a viable hypothesis. *Vet Immunol Immunopathol.* 2008;123:106.

Burton JH, et al. Evaluation of a 15-week CHOP protocol for the treatment of canine multicentric lymphoma. *Vet Comp Oncol.* epub ahead of print May 2012.

Chun R, et al. Evaluation of a high-dose chemotherapy protocol with no maintenance therapy for dogs with lymphoma. *J Vet Intern Med*. 2000;14:120.

Chun R. Lymphoma: which chemotherapy protocol and why? *Top Companion Anim Med*. 2009;24:157.

Couto KM, et al. Clinical characteristics and outcome in dogs with small cell T-cell intestinal lymphoma. *Vet Comp Oncol*. 2018;14:547.

Deravi N, et al. Specific immunotypes of canine T cell lymphoma are associated with different outcomes. *Vet Immunol Immunopathol*. 2017;191:5.

Desmas I, et al. Clinical presentation, treatment and outcome in 31 dogs with presumed primary colorectal lymphoma (2001-2013). *Vet Comp Oncol*. 2017;15:504.

Ferreri AJM, et al. Infectious agents and lymphoma development: molecular and clinical aspects. *J Intern Med*. 2009;265:421.

Flood-Knapik KE, et al. Clinical, histopathological and immunohistochemical characterization of canine indolent lymphoma. *Vet Comp Oncol*. 2013;11:272.

Greenberg CB, et al. Phase II clinical trial of combination chemotherapy with dexamethasone for lymphoma in dogs. *J Am Anim Hosp Assoc*. 2007;43:27.

Hosoya K, et al. COAP or UW-19 treatment of dogs with multicentric lymphoma. *J Vet Intern Med*. 2007;21:1355.

Ito D, et al. A tumor-related lymphoid progenitor population supports hierarchical tumor organization in canine B-cell lymphoma. *J Vet Intern Med*. 2011;25:890.

Kiselow MA, et al. Outcome of cats with low-grade lymphocytic lymphoma: 41 cases (1995-2005). *J Am Vet Med Assoc*. 2008;232:405.

Lana SE, et al. Utility of polymerase chain reaction for analysis of antigen receptor rearrangement in staging and predicting prognosis in dogs with lymphoma. *J Vet Intern Med*. 2006;20:329.

Lane AE, et al. Use of recombinant human granulocyte colony-stimulating factor prior to autologous bone marrow transplantation in dogs with lymphoma. *Am J Vet Res*. 2012;73:894.

Louwerens M, et al. Feline lymphoma in the post-feline leukemia virus era. *J Vet Intern Med*. 2005;19:329.

Modiano JF, et al. Distinct B-cell and T-cell lymphoproliferative disease prevalence among dog breeds indicates heritable risk. *Cancer Res*. 2005;65:5654.

Mooney SC, et al. Treatment and prognostic factors in lymphoma in cats: 103 cases (1977-1981). *J Am Vet Med Assoc*. 1989;194:696.

Morges MA, et al. Phase II evaluation of VDC-1101 in canine cutaneous T-cell lymphoma. *J Vet Intern Med*. 2014;28.

O'Brien D, et al. Clinical characteristics and outcome in dogs with splenic marginal zone lymphoma. *J Vet Intern Med*. 2013;27:949.

Qurollo BA, et al. Infection with Panola Mountain Ehrlichia sp. in a dog with atypical lymphocytes and clonal T-cell expansion. *J Vet Intern Med*. 2013;27:1251.

Rau SE, Barber LG, Burgess KE. Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. *J Vet Intern Med*. 2010;24(6):1452–1457. doi:10.1111/j.1939-1676.2010.0611.x. [Epub 2010 Oct 12].

Risbon RE, et al. Response of canine cutaneous epitheliotropic lymphoma to lomustine (CCNU): a retrospective study of 46 cases (1999-2004). *J Vet Intern Med*. 2006;20:1389.

Saba CF, et al. Rabacfosadine for relapsed canine B-cell lymphoma: efficacy and adverse event profiles of 2 different doses. *Vet Comp Oncol*. 2018;16:76.

Saba CF, Thamm DH, Vail DM. Combination chemotherapy with L-asparaginase, lomustine, and prednisone for relapsed or refractory canine lymphoma. *J Vet Intern Med*. 2007;21:127.

Shelton GH, et al. Feline immunodeficiency virus and feline leukemia virus infection and their relationships to lymphoid malignancies in cats: a retrospective study. *J AIDS*. 1990;3:623.

Stein TJ, et al. Treatment of feline gastrointestinal small-cell lymphoma with chlorambucil and glucocorticoids. *J Am Anim Hosp Assoc*. 2010;46:413.

Taylor SS, et al. Serum protein electrophoresis in 155 cats. *J Fel Med Surg*. 2010;12:643.

Teske E, et al. Prognostic factors for treatment of malignant lymphoma in dogs. *J Am Vet Med Assoc*. 1994;205:1722.

Valli VE, et al. Canine lymphomas: association of classification type, disease stage, tumor subtype, mitotic rate, and treatment with survival. *Vet Pathol*. 2013;50:738.

Willcox JL, et al. Autologous peripheral blood hematopoietic cell transplantation in dogs with B-cell lymphoma. *J Vet Intern Med*. 2012;26:1155.

Williams LE, et al. CCNU in the treatment of canine epitheliotropic lymphoma. *J Vet Intern Med*. 2006;20:136.

Withers SS, et al. Fasting reduces the incidence of delayed-type vomiting associated with doxorubicin treatment in dogs with lymphoma. *Transl Oncol*. 2014;doi:10.1016/j.tranon.2014.04.014. pii: S1936-5233(14)00049-7. [Epub ahead of print].

Zwingenberger AL, et al. Ultrasonographic evaluation of the muscularis propria in cats with diffuse small intestinal lymphoma or inflammatory bowel disease. *J Vet Intern Med*. 2010;24:289.

CHAPTER 80

Leukemias



DEFINITIONS AND CLASSIFICATION

Leukemias are malignant neoplasms that originate from hematopoietic precursor cells in the bone marrow. Because these cells are unable to undergo terminal differentiation or apoptosis, they self-replicate as a clone of usually immature (and nonfunctional) cells. The neoplastic cells may or may not appear in peripheral circulation; thus the confusing terms *aleukemic* and *subleukemic* are used to refer to leukemias in which neoplastic cells proliferate within the bone marrow but are absent or scarce in the circulation.

Leukemias can be classified into two broad categories according to the cell line of origin: *lymphoid* and *myeloid* (or nonlymphoid; Table 80.1). The term *myeloproliferative disease* has also been used to refer to myeloid leukemias (particularly in acute forms in cats), but we will use *myeloid leukemias* throughout this chapter. On the basis of their clinical course and the cytologic features of the leukemic cell population, leukemias are also classified as *acute* or *chronic*. Acute leukemias are characterized by an aggressive biologic behavior (i.e., death ensues shortly after diagnosis, sometimes even if the patient is treated) and by the presence of immature (blast) cells in bone marrow or blood. Chronic leukemias have a protracted, often indolent course, and the predominant cell in the blood is a well-differentiated, late precursor (i.e., lymphocyte in chronic lymphocytic leukemia [CLL] and neutrophil in chronic myeloid leukemia [CML]). In dogs (and possibly in cats) CML can undergo *blast transformation* (blast crisis), during which the disease behaves like an acute leukemia and is usually refractory to therapy. Additionally, CLL can transform into an aggressive high-grade lymphoma, referred to as Richter syndrome; this has recently been described in dogs, where it carries a poor prognosis, with a median survival time (MST) of 41 days reported in a small cohort of dogs (Comazzi et al., 2017).

As opposed to humans, acute leukemias in dogs and cats may be difficult to classify morphologically as myeloid or lymphoid on the basis of the evaluation of Giemsa-, Wright-, or Diff-Quik–stained blood or bone marrow smears because poorly differentiated blasts look similar under the light microscope. In veterinary medicine, cytochemical stains are used in some diagnostic laboratories to establish whether the blasts are lymphoid or myeloid and also to subclassify myeloid leukemias, as described later (i.e., myeloid versus monocytic versus myelomonocytic). These cytochemical stains reveal the presence of different enzymes in the cytoplasm of the blasts, which aids in establishing their origin (Table 80.2); however, in most diagnostic laboratories immunophenotyping (see next paragraph) is the standard for diagnosis.

Immunophenotyping of canine and feline leukemic cells using monoclonal antibodies via immunocytochemistry or flow cytometry is now available in teaching institutions and most commercial diagnostic laboratories; however, although there are several validated antibodies for lymphoid cells, there is a paucity of myeloid markers that work consistently in dogs and cats. In most laboratories CD3, CD4, CD5 (in cats), and CD8 are used as T-lymphocyte markers, whereas CD21 and CD79a are B-lymphocyte markers. Acute myeloid leukemias (AMLs) are diagnosed in dogs with cells negative for lymphoid markers and positive for CD45 (panleukocyte marker) and CD34 (stem cell marker). Monocytic/monoblastic leukemias are diagnosed if cells are negative for lymphoid markers and positive for CD45 and CD14. CD41 and CD61 are megakaryocyte markers. Recently, ALP cytochemical staining has been proposed to differentiate AML and acute lymphoid leukemia (ALL) (Stokol et al., 2014); AML cells have more intense ALP staining patterns than those in ALL. Fig. 80.1 depicts flow cytometry dot plots from a cat with CLL. Clinical correlations between immunophenotype and prognosis have been investigated in few studies; however, no definitive difference in prognosis has been established among phenotypes (Novacco et al., 2015a). It is still possible that, with additional investigation, especially with more frequent availability of flow cytometric analysis, specific phenotypes may be associated with different prognoses.

A classification scheme for acute leukemia in people was devised by a group of French, American, and British investigators (the FAB scheme) and was based on the morphologic

TABLE 80.1

Classification of Leukemias in Dogs and Cats

CLASSIFICATION	SPECIES
Acute Leukemias	
Acute myeloid (myelogenous) leukemia (AML)	
Undifferentiated myeloid leukemia (AML-M_0)	D, C
Acute myelocytic leukemia (AML-M_{1-2})	D, C
Acute progranulocytic leukemia (AML-M_3)	—
Acute myelomonocytic leukemia (AMML; AML-M_4)	D, C
Acute monoblastic/monocytic leukemia (AMoL; AML-M_5)	D, C
Acute erythroleukemia (AML-M_6)	C, D?
Acute megakaryoblastic leukemia (AML-M_7)	D, C
Acute lymphoblastic leukemia (ALL)	
ALL-L_1	D, C
ALL-L_2	D, C
ALL-L_3	C, D?
Acute leukemia of large granular lymphocytes (LGL)	D, C?
Subacute and Chronic Leukemias	
Chronic myeloid (myelocytic) leukemia (CML)	D > C
Chronic myelomonocytic leukemia (CMML)	D
Chronic lymphoid (lymphocytic) leukemia (CLL)	D > C
Large granular lymphocyte (LGL) variant	D

C, Cat; *D,* dog; *?,* unknown.

features of the cells in Giemsa-stained smears of blood and bone marrow and the clinical presentation and biologic behavior of the disease. Because this scheme has not yet proved to be prognostically or therapeutically applicable to cats or dogs, it is not discussed here (see Suggested Readings for additional information on the FAB scheme in people and animals).

The terms *preleukemic syndrome* and *myelodysplastic syndrome* (MDS, or myelodysplasia) refer to a syndrome of hematopoietic dysfunction and specific cytomorphologic changes that precedes the development of acute myelogenous leukemia by months to years. The syndrome is

TABLE 80.2

Cytochemical Stains in Acute Leukemic Cells From Dogs and Cats

CYTOCHEMICAL STAIN	AML	AMOL	AMML	ALL
MPO	+	–	±	–
CAE	+	–	±	–
ANBE	–	+	±	±
LIP	–	+	±	–
LAP	+	–	±	±

ALL, Acute lymphoblastic leukemia; *AML,* acute myelogenous leukemia (AML-M_{0-2}); *AMML,* acute myelomonocytic leukemia (AML-M_4); *AMoL,* acute monoblastic/monocytic leukemia (AML-M_5); *ANBE,* α-naphthyl butyrate esterase; *CAE,* chloroacetate esterase; *LAP,* leukocyte alkaline phosphatase; *LIP,* lipase; *MPO,* myeloperoxidase; +, positive; –, negative; ±, positive or negative.

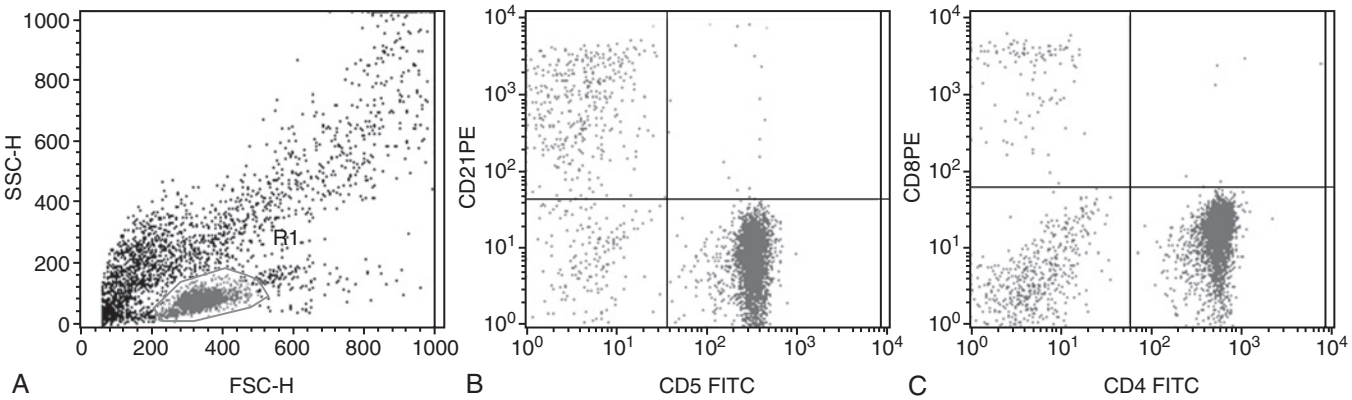


FIG 80.1
Flow cytometric analysis of peripheral blood leukocytes in a cat with chronic lymphocytic leukemia. **(A)** Leukocytes were gated to compare size (forward scatter) and complexity (side scatter). **(B)** Lymphoid cells were stained with PE and FITC to differentiate B-cell (CD21PE) and T-cell (CD5 FITC) origin. **(C)** T cells were then stained to differentiate cytotoxic T cells (CD8PE) and helper T cells (CD4 FITC). *CD4,* Helper T cells; *CD5,* T cells; *CD8,* cytotoxic T cells; *CD21,* B cells; *FITC,* fluorescein isothiocyanate; *FSC-H,* forward scatter; *PE,* phycoerythrin; *SCC-H,* side scatter. (Courtesy Dr. MJ Burkhard.)

characterized by cytopenias and a hypercellular bone marrow and is more common in cats than in dogs. The clinical and hematologic features of dogs and cats with MDS are discussed at the end of this chapter.

LEUKEMIAS IN DOGS

In dogs, leukemias constitute less than 10% of all hemolymphatic neoplasms and are therefore considered rare. At one author's previous clinic, the leukemia-to-lymphoma ratio is approximately 1:7 to 1:10. However, this ratio is artificially high because many dogs with lymphoma may be treated by their family veterinarians, whereas most dogs with leukemia are referred for treatment. Although most leukemias in dogs are considered to be spontaneous in origin, radiation and viral particles have been identified as etiologic factors in some experimental dogs with this disease.

ACUTE LEUKEMIAS

Prevalence

In the United States, AML appears to be more common than ALL in dogs, constituting approximately three fourths of the cases of acute leukemia. However, in two studies from Italy, one reported that ALL was almost twice as common as AML (Tasca et al., 2009), and the other one reported similar prevalence of the two (Novacco et al., 2015a). However, morphologically (i.e., as determined by evaluation of a Wright- or Giemsa-stained blood or bone marrow smear), most acute leukemias are initially classified as lymphoid. After cytochemical or immunocytochemical staining of the smears, or immunophenotyping is performed, approximately one third to one half of them are then reclassified as myeloid. Approximately half of the dogs with AML have myelomonocytic differentiation when cytochemical staining or immunophenotyping is performed (see Table 80.2). With the advent of immunophenotyping, most laboratories are no longer doing cytochemical stains. There is a bimodal age of presentation, with most diagnosed at 1 to 3 years of age, whereas a small proportion develop AL as adults (>7 years).

Clinical Features

The clinical signs and physical examination findings in dogs with acute leukemia are usually vague and nonspecific (Table 80.3). Most owners seek veterinary care when their dogs become lethargic or anorectic, or when persistent or recurrent fever, severe weight loss, shifting limb lameness, or other nonspecific signs develop; neurologic or ocular signs occur occasionally. Some of these signs may be quite acute (e.g., days). Splenomegaly, hepatomegaly, pallor, fever, and mild generalized lymphadenopathy are commonly detected during routine physical examination. The spleen in these dogs is usually markedly enlarged, and it has a smooth surface on palpation. Inspection of the mucous membranes in dogs with acute leukemia often reveals pallor and petechiae, ecchymoses, or both. Icterus may also be detected if marked leukemic infiltration of the liver has occurred. The generalized lymphadenopathy seen in dogs with acute leukemia is usually mild in contrast to that seen in dogs with lymphoma, in which the lymph nodes are typically massively enlarged (Fig. 80.2). In other words, the hepatosplenomegaly is more striking than the lymphadenopathy in leukemic patients. Most dogs with leukemia also have constitutional signs (i.e., they are clinically ill), whereas most dogs with lymphoma are asymptomatic. Although it is usually impossible to distinguish between acute myeloid and ALL on the basis of physical examination findings alone, some subtle differences do exist; mainly, shifting limb lameness, fever, and ocular lesions (hyphema, hypopyon) are more common in dogs with AML, whereas neurologic signs are more common in dogs with ALL.

TABLE 80.3

Clinical Signs and Physical Examination Findings in Dogs and Cats With Acute Leukemias*

FINDING	DOG	CAT
Clinical Sign		
Lethargy	>70	>90
Anorexia	>50	>80
Weight loss	>30-40	>40-50
Lameness	>20-30	>?
Persistent fever	>30-50	>?
Vomiting/diarrhea	>20-40	>?
Physical Examination Finding		
Splenomegaly	>70	>70
Hepatomegaly	>50	>50
Lymphadenopathy	>40-50	>20-30?
Pallor	>30-60	>50-70?
Fever	>40-50	>40-60?

?, Unknown.
*Results are expressed as the approximate percentage of animals showing the abnormality.

Hematologic Features

Marked hematologic changes are usually present in dogs with acute leukemia. Couto (1985) and Grindem et al. (1985b) have published detailed reviews of the hematologic features of dogs with acute leukemia. Briefly, abnormal (leukemic) cells are observed in the peripheral blood of most dogs with AML and ALL, although this is slightly more common in the latter (i.e., circulating blasts are absent in some dogs with AML; Fig. 80.3). Isolated cytopenias, bicytopenias, or pancytopenia is present in almost all dogs with AML and ALL. Leukoerythroblastic reactions are detected in approximately half of dogs with AML but are rare in dogs with ALL. The total white blood cell (WBC) and blast counts

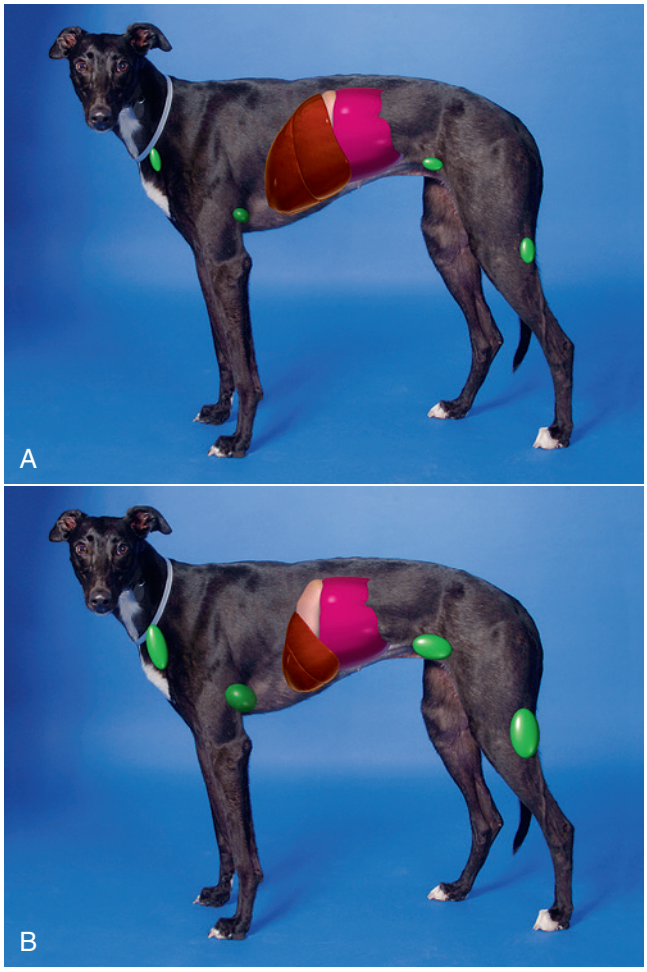


FIG 80.2
Hepatosplenomegaly and generalized lymphadenopathy in dogs with acute leukemia or multicentric lymphoma. Note the marked hepatosplenomegaly and mild lymphadenopathy in the leukemic patient **(A)** and the marked lymphadenopathy and mild hepatosplenomegaly in the dog with lymphoma **(B).** (Artwork by Tim Vojt. Reproduced with the permission of The Ohio State University.)

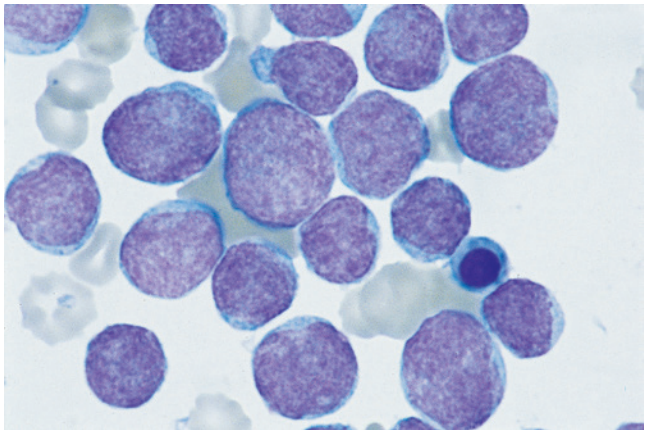


FIG 80.3
Blood smear from a dog with acute lymphoblastic leukemia and a white blood cell count of approximately 1 million/μL. Note the predominance of large, immature lymphoid cells with large nuclei, clumped chromatin, and nucleoli (×1000).

are highest in dogs with ALL (median, 298,200/μL; range, 4000-628,000/μL), and as a general rule, only dogs with ALL have WBC counts greater than 100,000/μL. Most dogs with AML and ALL are anemic, but dogs with acute monoblastic/monocytic leukemia (AMoL or AML-M_5) have the least severe anemia (packed cell volume of 30% versus 23% in all other groups). Most dogs with acute leukemias are also thrombocytopenic, although the thrombocytopenia also appears to be less severe in dogs with AML-M_5 (median, 102,000/μL; range, 39,000-133,000/μL).

With the advent of automated hematology analyzers based on flow cytometry and/or impedance, practitioners have access to "dot plots" or "cytograms" with some instruments. Visualization of dot plots in dogs with acute leukemias is helpful because some instruments "recognize" these leukemic cells as lymphocytes or monocytes (the analyzer "counts" >10,000 cells, whereas we only count 100 cells when we do a differential leukocyte count), but the shape of the "cloud" in the cytogram is quite unique (Fig. 80.4). In some dogs, the numerical values only indicate "monocytosis" or "lymphocytosis," but visualization of the dot plots is helpful from a diagnostic standpoint. In addition, in dogs with high leukemic cell counts, the abnormal cells may be counted as reticulocytes by the analyzer; this is important, because the anemia will then be classified as "regenerative" (Novacco et al., 2015b). However, all the reticulocytes are located in a relatively small area, as opposed to being widely distributed, as in dogs with true regenerative anemia.

Diagnosis

A presumptive diagnosis in dogs with acute leukemia is usually made on the basis of the history and physical examination findings; a complete blood count (CBC) is usually confirmatory, although the hematologic changes in dogs with "aleukemic leukemia" may resemble those of ehrlichiosis or other bone marrow disorders (e.g., bone marrow aplasia). Interestingly, as discussed earlier, some flow cytometry-based hematology analyzers allow for visualization of the abnormal cells in the leukocyte graphics (see Fig. 80.4); therefore the term *oligoleukemic leukemias* may be more appropriate than *aleukemic leukemia*.

To evaluate the extent of the disease, a bone marrow aspirate or biopsy may be indicated; if the patient has a high circulating blast count, a bone marrow aspirate is rarely necessary for diagnosis or prognosis. Splenic, hepatic, or lymph node aspirates for cytologic evaluation can also be obtained easily, although the information yielded may not help in establishing the diagnosis or prognosis. For example, if a dog has mild generalized lymphadenopathy and the only sample submitted to a laboratory is a lymph node, spleen, or liver aspirate, the finding of undifferentiated blasts in the smear points toward a cytologic diagnosis of either acute leukemia or lymphoma (i.e., the neoplastic lymphoid cells in lymphoma and leukemia are indistinguishable morphologically); indeed, it is quite common for the clinical pathologist to issue a diagnosis of lymphoma because it is the more common of the two diseases. In these cases, further clinical

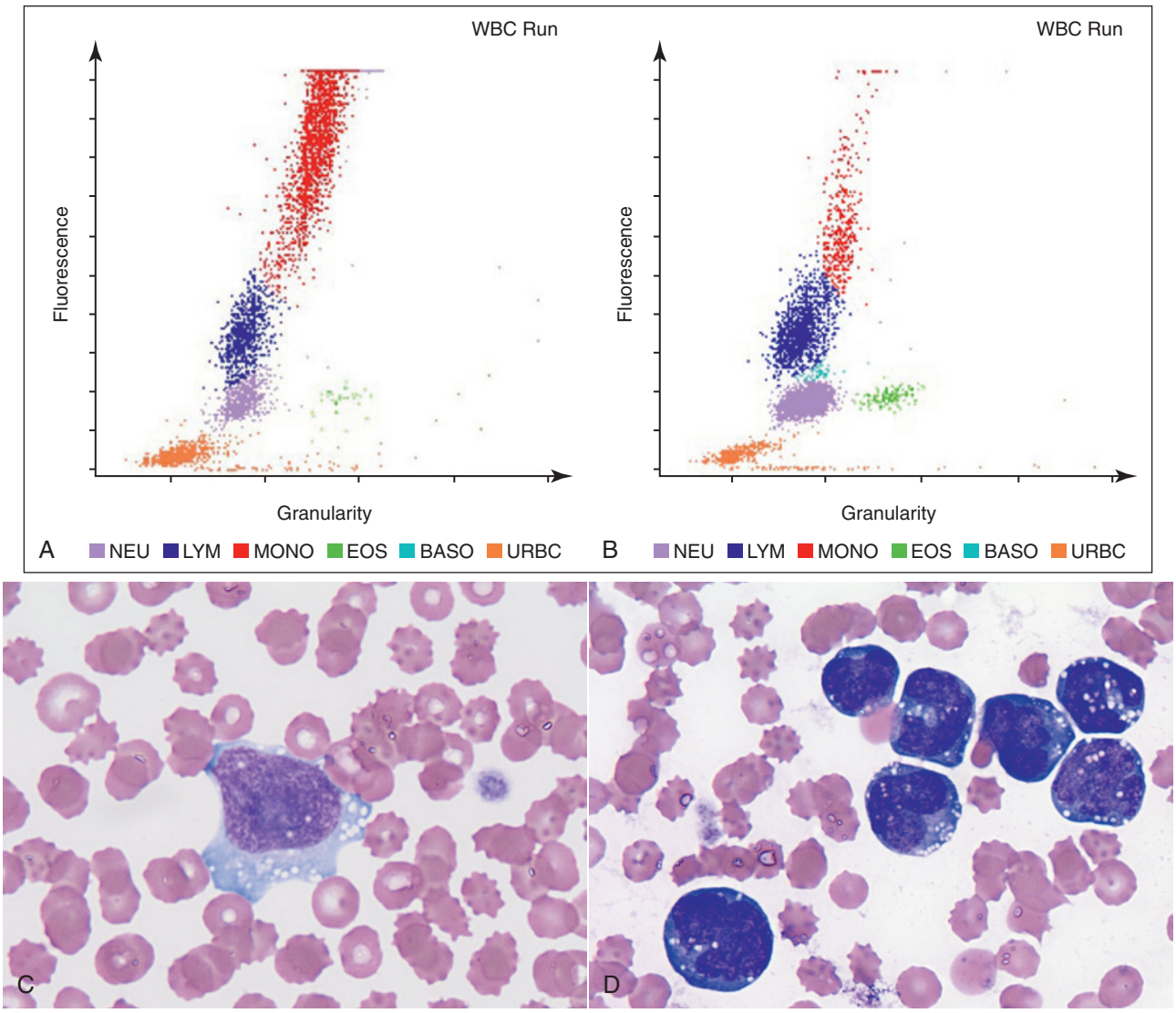


FIG 80.4
White blood cell dot plot from a ProCyte Dx in a dog with acute leukemia **(A)** compared with a normal dot plot **(B).** Note the funnel-shaped monocyte curve in red, in contrast with the well-defined, upward tapering cloud in B. The numeric values in this dog consisted of moderate neutropenia (0.96×10^9/L), mild monocytosis (2.5×10^9/L), and moderate thrombocytopenia (49×10^9/L). Monocytoid blast in peripheral blood **(C).** Bone marrow cytology reveals monocytoid precursors with a tendency toward myeloid/myelomonocytic differentiation **(D).** The final diagnosis was acute myeloid leukemia.

and clinicopathologic information (i.e., the degree and extent of lymphadenopathy, presence and degree of hepatosplenomegaly, hematologic and bone marrow biopsy, or aspiration findings) is required to establish a definitive diagnosis.

It may be difficult to diagnose the specific tumor type in a dog with generalized lymphadenopathy, hepatosplenomegaly, and a low number of circulating lymphoblasts. The main differential diagnoses are ALL and lymphoma with circulating blasts (leukemic phase of lymphoma). It is important to differentiate between these two disorders because the prognosis for dogs with lymphoma is considerably better than that for dogs with acute leukemia. These two entities may be difficult to distinguish on the basis of the clinical, hematologic, and cytologic information obtained, but the guidelines found in Box 80.1 can be used to try to arrive at a definitive diagnosis. Immunophenotyping can also be used to distinguish these two entities.

When the neoplastic cells are poorly differentiated, cytochemical staining or immunophenotyping is required to establish a definitive diagnosis (see Table 80.2). This is important if the owner is contemplating treatment because the therapy and prognosis for dogs with AML are different from those for dogs with ALL (i.e., the survival time in dogs with AML is shorter than that in dogs with ALL).

BOX 80.1

Acute Lymphoblastic Leukemia or Lymphoma With Circulating Blasts (Lymphosarcoma Cell Leukemia): Guidelines for a Clinical Diagnosis

1. If the lymphadenopathy is massive, the dog more likely has lymphoma (see Fig. 80.2).
2. If the dog is systemically ill, it is more likely ALL.
3. If bicytopenia or pancytopenia is present, ALL is the more likely diagnosis.
4. If the percentage of lymphoblasts in the bone marrow is more than 40% to 50%, the dog is more likely to have ALL.
5. If the cells are CD34 negative, it is more likely lymphoma.
6. If hypercalcemia is present, the more likely diagnosis is lymphoma.

ALL, Acute lymphoblastic leukemia.

BOX 80.2

Basic Diagnostic Principles for Dogs With Suspected Leukemia

1. If cytopenias or abnormal cells are present in peripheral blood, a bone marrow aspirate or biopsy specimen should be obtained.
2. If the spleen or liver is enlarged, a fine-needle aspirate of the affected organs should be obtained for cytologic evaluation.
3. If blasts are present, blood and bone marrow specimens should be submitted to a veterinary referral laboratory for cytochemical staining or immunophenotyping.
4. Other diagnostic tests (e.g., serologic tests or polymerase chain reaction [PCR] testing for *Ehrlichia canis*) should be performed if appropriate.

In addition to lymphoma, differential diagnoses in dogs with acute or chronic leukemias include other disorders of the mononuclear-phagocytic or hematopoietic systems, such as malignant or systemic histiocytosis; systemic mast cell disease (mast cell leukemia); and infectious diseases such as histoplasmosis, ehrlichiosis, anaplasmosis, bartonellosis, leishmaniasis, mycoplasmosis, and mycobacteriosis. Box 80.2 lists the basic principles of diagnosis that apply to all dogs with suspected leukemia.

The diagnosis of acute leukemia can be extremely straightforward (i.e., a dog that is evaluated because of weight loss, lethargy, hepatosplenomegaly, pallor, and central nervous system [CNS] signs and that has a WBC of >500,000/μL, most of which are blasts, is most likely to have ALL), or it may represent a challenge (i.e., a dog with unexplained cytopenias of prolonged duration in which aleukemic AML-M_1 subsequently develops).

Treatment

The treatment of dogs with acute leukemias is usually unrewarding. Most dogs with these diseases respond poorly to therapy, and prolonged remissions are rare. Treatment failure usually stems from one or more of the following factors:

1. Failure to induce remission (more common in AML than in ALL)
2. Failure to maintain remission
3. The presence or development of organ failure resulting from leukemic cell infiltration; this precludes the use of aggressive combination chemotherapy (i.e., because of enhanced toxicity)
4. The development of fatal sepsis, bleeding, or both caused by already existing or treatment-induced cytopenias

Prolonged remissions in dogs with AML treated with chemotherapy are extremely rare. In most dogs with AML, remissions in response to any of the protocols listed in Box 80.3 are uncommon. If patients do respond, the remission is usually extremely short-lived and survival rarely exceeds 3 months. In addition, more than half of the dogs die during induction as a result of sepsis or bleeding. In recent studies, the survival times in dogs with acute leukemias were 8 to 55 days (Bennett et al., 2016; Novacco et al., 2015a).

Furthermore, the supportive treatment required in these patients (e.g., blood component therapy, intensive care monitoring) is financially unacceptable to most owners, and the emotional strain placed on the owner is also quite high. In humans, it costs more than $1 million to treat a child with leukemia. Therefore owners should be aware of all these factors before deciding to treat their dogs.

The prognosis may be slightly better in dogs with ALL; however, responses to treatment and survival times in these patients are considerably lower than those in dogs with lymphoma. The remission rates in dogs with ALL are approximately 20% to 40%, in contrast to those in dogs with lymphomas, which approach 90%. Survival times with chemotherapy in dogs with ALL are also shorter (average, 1-3 months) than those in dogs with lymphoma (average, 12-18 months). Untreated dogs usually live less than 2 weeks. Chemotherapy protocols used in dogs with acute leukemia are listed in Box 80.3.

CHRONIC LEUKEMIAS

Prevalence

In dogs, CLL is far more common than CML; in addition, the latter is poorly characterized. One author's hospital evaluates approximately six to eight dogs with CLL a year, whereas approximately one dog with CML is evaluated every 3 to 5 years. CLL is one of the leukemias most commonly diagnosed at diagnostic referral laboratories. Small-breed dogs are more likely to develop B-cell CLL than large-breed dogs (Bromberek et al., 2016).

BOX 80.3

Chemotherapy Protocols for Dogs and Cats With Acute Leukemias

Acute Lymphoblastic Leukemia

1. OP protocol
Vincristine, 0.5 mg/m^2 IV once a week
Prednisone, 40-50 mg/m^2 PO q24h for a week; then 20 mg/m^2 PO q48h

2. COP protocol
Vincristine, 0.5 mg/m^2 IV once a week
Prednisone, 40-50 mg/m^2 PO q24h for a week; then 20 mg/m^2 PO q48h
Cyclophosphamide, 50 mg/m^2 PO q48h

3. LOP protocol
Vincristine, 0.5 mg/m^2 IV once a week
Prednisone, 40-50 mg/m^2 PO q24h for a week; then 20 mg/m^2 PO q48h
L-Asparaginase, 10,000-20,000 IU/m^2 IM or SC once every 2-3 weeks

4. COAP protocol
Vincristine, 0.5 mg/m^2 IV once a week
Prednisone, 40-50 mg/m^2 PO q24h for a week; then 20 mg/m^2 PO q48h
Cyclophosphamide, 50 mg/m^2 PO q48h
Cytosine arabinoside, 100 mg/m^2 SC daily for 2-4 days*

5. CHOP protocol
Vincristine 0.5-0.75 mg/m^2 IV week 1
Cyclophosphamide 200-250 mg/m^2 IV or PO week 2
Vincristine 0.5-0.75 mg/m^2 IV week 3
Doxorubicin 30 mg/m^2 (1 mg/kg if <10 kg) IV week 4

Acute Myelogenous Leukemia

1. Cytosine arabinoside, 5-10 mg/m^2 SC q12h for 2-3 weeks; then on alternate weeks
2. Cytosine arabinoside, 100-200 mg/m^2 in IV drip over 4 hours; repeat every 2-3 weeks
3. Mitoxantrone, 4-6 mg/m^2 in IV drip over 4 hours; repeat every 3 weeks

*The daily dose should be divided into two to four daily administrations.
IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.

Clinical Features

Like their acute counterparts, the clinical signs in dogs with CLL or CML are vague and nonspecific; however, there is a history of chronic (i.e., months), vague clinical signs in approximately half of the dogs. Many cases of chronic leukemia are diagnosed incidentally during routine annual health checks or presurgical evaluations in asymptomatic dogs. Clinical signs in dogs with CLL may include lethargy, anorexia, vomiting, mildly enlarged lymph nodes, intermittent diarrhea or vomiting, and weight loss. As mentioned previously, more than half of the dogs with CLL are asymptomatic and are diagnosed serendipitously. Physical examination findings in dogs with CLL include mild generalized lymphadenopathy, splenomegaly, hepatomegaly, pallor, and pyrexia; the last two are uncommon. The clinical signs and physical examination findings in dogs with CML appear to be similar to those in dogs with CLL.

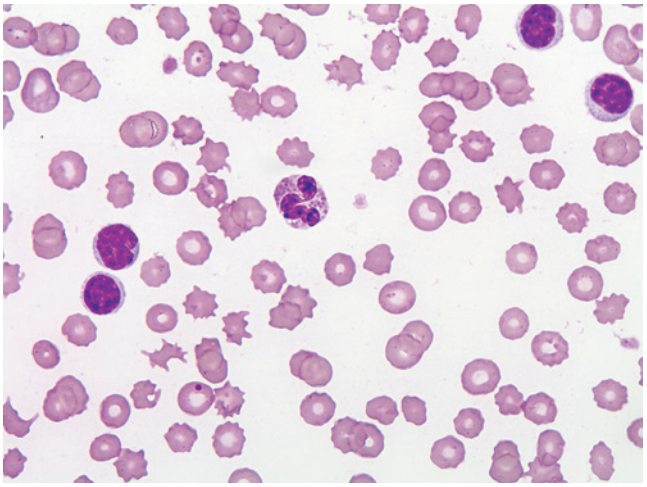


FIG 80.5
Diff-Quik–stained blood smear from a 14-year-old dog with CLL and chronic kidney disease. Note the predominance of well-differentiated small lymphocytes, smaller than the eosinophil in the center of the field, the low platelet number per field, and the presence of morphologic red blood cell changes (acanthocytes and keratoacanthocytes) (×1000).

A terminal event in dogs with CLL is the development of a diffuse large cell lymphoma, termed *Richter syndrome;* in humans Richter syndrome also includes prolymphocytic leukemia, acute leukemia, and Hodgkin lymphoma. In dogs, Richter syndrome is characterized by massive, generalized lymphadenopathy and hepatosplenomegaly. Once this multicentric lymphoma develops, chemotherapy-induced, long-lasting remissions are difficult to obtain and survival times are short. In a recent report, the MST in dogs with Richter syndrome was 41 days (Comazzi et al., 2017).

Blast crisis, which involves the appearance of immature blast cells in blood and bone marrow, occurs in humans and dogs with CML months to years after the initial diagnosis is made; in humans with CLL, acute leukemias are part of the Richter syndrome. In humans with blast crisis associated with CML, these blasts are of either myeloid or lymphoid phenotype; the origin of the blast cell in dogs with blast crises has not been determined. Blast crises in CML are uncommon.

Hematologic Features

The most common hematologic abnormality in dogs with CLL is a marked lymphocytosis resulting in leukocytosis (Figs. 80.5 and 80.6). The lymphocytes are usually morphologically normal (see Fig. 80.5), although large granular lymphocytes (LGLs) or "monocytoid" lymphocytes with abundant cytoplasm are occasionally present. The lymphocyte counts range from 8000/µL to more than 100,000/µL,

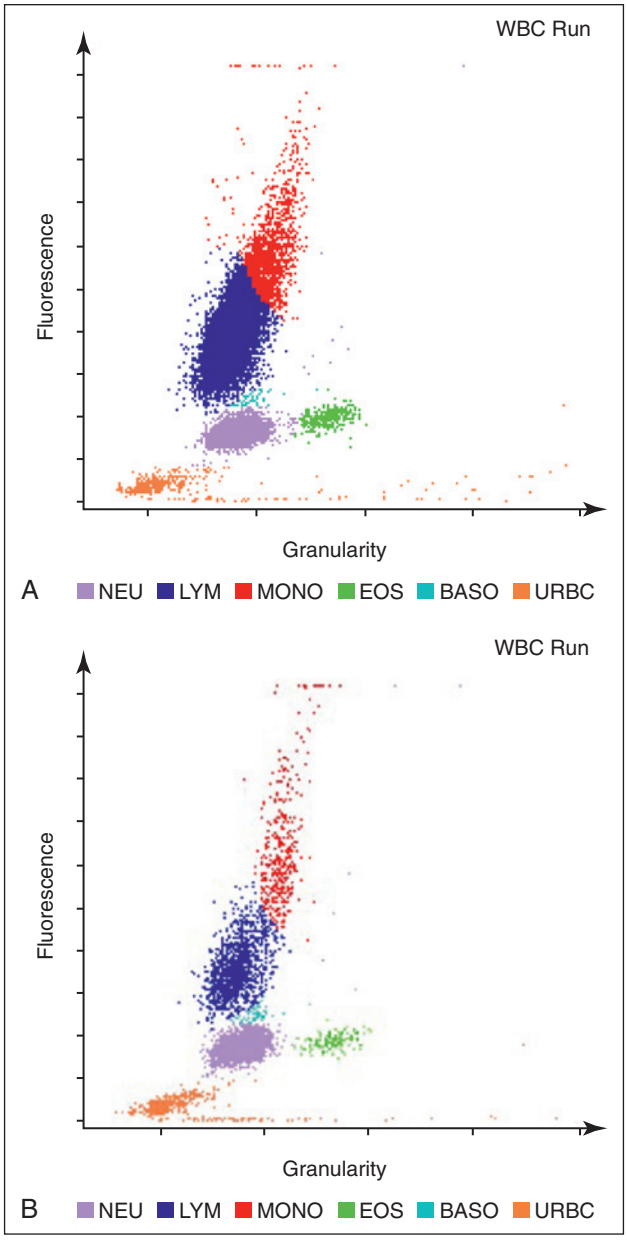


FIG 80.6
White blood cell dot plot from a ProCyte Dx in the dog with chronic lymphocytic leukemia depicted in Fig. 80.5 **(A)** compared with a normal dot plot **(B).** Note the larger, denser lymphocyte cloud in blue **(A),** positioned in the same location as that in normal dogs **(B),** suggesting that they are mature, well-differentiated lymphocytes. The straight line between the lymphocyte and monocyte clouds indicates that the instrument is "having trouble" differentiating some of the neoplastic cells from normal monocytes. The numeric values in this dog consisted of marked leukocytosis (53×10^9/L), marked lymphocytosis (39.2×10^9/L), moderate monocytosis (3.2×10^9/L), and moderate thrombocytopenia (84×10^9/L).

but lymphocyte counts of more than 500,000/μL are rare. In dogs with CLL, B-cell (i.e., CD21-positive) and T-cell (i.e., CD4/CD8-positive) CLLs were almost equally distributed (Comazzi et al., 2011). In addition to the lymphocytosis, which may be diagnostic in itself (e.g., a dog with a lymphocyte count of 100,000/μL most certainly has CLL and not an infectious disease), anemia and thrombocytopenia occur in approximately half of the dogs. Although cytologic evaluation of bone marrow aspirates in dogs with CLL usually reveals the presence of many morphologically normal lymphocytes, normal numbers of lymphocytes are occasionally detected. This is probably because the lymphocytosis in some animals with CLL, as in people, stems from disorders of recirculation rather than from the increased clonal proliferation of lymphocytes in the bone marrow. As in dogs with acute leukemias, in dogs with high-count CLL the neoplastic cells may be counted as reticulocytes by flow cytometry-based analyzers.

Monoclonal gammopathies have been reported in approximately two thirds of dogs with CLL in which serum was evaluated using protein electrophoresis. The monoclonal component is usually immunoglobulin M (IgM), but IgA and IgG components have also been reported. This monoclonal gammopathy can lead to hyperviscosity. Rarely, dogs with CLL have paraneoplastic, immune-mediated blood disorders (e.g., hemolytic anemia, thrombocytopenia, neutropenia). However, in our experience, monoclonal gammopathies are uncommon in dogs with CLL.

The hematologic features of CML in dogs are poorly characterized but include leukocytosis with a left-shift down to myelocytes (or occasionally myeloblasts), anemia, and possibly thrombocytopenia, although thrombocytosis can also occur. The hematologic findings seen during a blast crisis are indistinguishable from those seen in dogs with AML or ALL.

Diagnosis

Absolute lymphocytosis is the major diagnostic criterion for CLL in dogs. Although other diseases (e.g., ehrlichiosis, babesiosis, leishmaniasis, Chagas disease, Addison disease) should be considered in the differential diagnosis of dogs with mild lymphocytosis (i.e., 7000-20,000/μL), marked lymphocytosis (i.e., more than 20,000/μL) is almost pathognomonic for CLL. If the physical examination and hematologic abnormalities discussed in previous paragraphs (i.e., mild lymphadenopathy, splenomegaly, monoclonal gammopathy, anemia) are found, this may help establish a diagnosis of CLL in dogs with lymphocytosis, although all these changes can also be present in dogs with chronic ehrlichiosis (see Chapter 93). The phenotypic distribution after performing immunophenotyping may also establish if the cell population is monoclonal or polyclonal. In patients with lymphocytosis in which a confirmatory diagnosis of CLL cannot be made, a polymerase chain reaction (PCR) assay for clonality (PARR) will typically reveal if the cells are clonal in origin.

The diagnosis of CML may be challenging, particularly because this syndrome is poorly characterized in dogs. In our experience, most dogs with extreme neutrophilia have leukemoid reactions and not CML. Some of the markers used to diagnose CML in humans are of no use in dogs. For example, the Philadelphia 1 chromosome and the alkaline phosphatase score were originally used in humans to

differentiate CML from leukemoid reactions (i.e., CML cells have the Philadelphia 1 chromosome, and the alkaline phosphatase content of the neutrophils increases in the setting of leukemoid reactions and decreases in the setting of CML). Chromosomal analysis of the cells in question may reveal specific abnormalities that support a diagnosis of CML. As a general rule, a final diagnosis of CML should be made only after the clinical and hematologic findings have been carefully evaluated and the inflammatory and immune causes of neutrophilia have been ruled out.

Treatment

The clinician usually faces the dilemma of whether to treat a dog with CLL. If the dog is symptomatic, has organomegaly, or has concurrent hematologic abnormalities, treatment with an alkylator (with or without corticosteroids) is indicated. If there are no paraneoplastic syndromes (i.e., immune hemolysis or thrombocytopenia, monoclonal gammopathies), the authors use single-agent chlorambucil at a dosage of 20 mg/m^2 given orally (PO) once every 2 weeks (Box 80.4). If there are paraneoplastic syndromes, or the patient is symptomatic, the addition of corticosteroids (prednisone, 50-75 mg/m^2 PO q24h for 1 week, then 25 mg/m^2 PO q48h) may be beneficial.

Because the growth fraction of neoplastic lymphocytes in CLL appears to be low, a delayed response to therapy is common. In a high proportion of dogs with CLL treated with chlorambucil or chlorambucil and prednisone, it may take more than 1 month (and as long as 6 months) for the hematologic and physical examination abnormalities to improve. This is in contrast to dogs with lymphoma and acute leukemias, in which remission is usually induced in 2 to 7 days.

BOX 80.4

Chemotherapy Protocols for Dogs and Cats With Chronic Leukemias

Chronic Lymphocytic Leukemia

Chlorambucil, 20 mg/m^2 PO once every 2 weeks
Chlorambucil as above, plus prednisone, 50 mg/m^2 PO q24h for a week; then 20 mg/m^2 PO q48h

COP Protocol

Cyclophosphamide, 200-300 mg/m^2 IV or PO once every 2 weeks
Vincristine, 0.5-0.75 mg/m^2 IV once every 2 weeks (alternating weeks with the cyclophosphamide)
Prednisone as in protocol 2; this treatment is continued for 6-8 weeks, at which time protocol 1 or 2 can be used for maintenance

Chronic Myelogenous Leukemia

Hydroxyurea, 50 mg/kg PO q24h for 1-2 weeks; then q48h
Imatinib (Gleevec), 10 mg/kg PO q24h

IV, Intravenous; *PO,* by mouth.

The survival times in dogs with CLL are quite long. Indeed, even without treatment, survival times of more than 2 years are common. More than two thirds of the dogs with CLL treated with chlorambucil (with or without prednisone) at the authors' clinics have survived in excess of 2 years. In fact, most dogs with CLL do not die as a result of leukemia-related causes but rather of other senior disorders.

In a study of 202 dogs with neoplastic lymphocytosis, which likely included both dogs with CLL and dogs with leukemic phase of lymphoma, expression of CD34 on flow cytometry was associated with a negative prognosis (survival times of 16 days). Dogs with B-cell proliferation (CD21 positive) had shorter survival times than those with T-cell (CD8-positive) proliferations. Dogs with CD8-positive phenotype had longer survival times if the lymphocyte count was less than 30,000/μL (1100 days versus 131 days); among the dogs with B-cell phenotype, those with circulating small lymphocytes had a significantly longer survival than those with large lymphoid cells (MST not reached versus 129 days) (Williams et al., 2008).

Recently, Comazzi et al. (2011) reported that dogs with T-CLL that received chemotherapy had approximately 3-fold and 19-fold higher probability of surviving than dogs with B-CLL and atypical CLL, respectively. Old dogs with B-CLL survived significantly longer than did young dogs, and anemic dogs with T-CLL survived a significantly shorter time than dogs without anemia (Comazzi et al., 2011).

The treatment of dogs with CML using hydroxyurea (see Box 80.4) may result in prolonged remission, provided a blast crisis does not occur. However, the prognosis does not appear to be as good as that for dogs with CLL (i.e., survivals of 4-15 months with treatment). The treatment of blast crises is usually unrewarding. A novel therapeutic approach targeting tyrosine kinase in the neoplastic cells of humans with CML using imatinib (Gleevec) has shown to be beneficial in inducing remission; however, it is unknown if tyrosine kinase inhibitors are beneficial in dogs with this disease.

LEUKEMIAS IN CATS

ACUTE LEUKEMIAS

Prevalence

In the feline leukemia virus (FeLV)-free era, true leukemias are rare in the cat, constituting less than 15% of all hematopoietic neoplasms. Although exact figures regarding the incidences of leukemias and lymphomas are not available, these neoplasms are extremely rare in the authors' clinics.

If cytochemical staining or immunophenotyping is used to classify acute leukemias in cats, approximately two thirds are myeloid and one third are lymphoid. However, in contrast to dogs, myelomonocytic leukemias (M_4) appear to be rare in cats.

FeLV is commonly implicated as a cause of leukemias in cats; however, the role of feline immunodeficiency virus (FIV) in the pathogenesis of these neoplasms is still unclear.

Originally, it was reported that approximately 90% of cats with lymphoid and myeloid leukemias tested positive for FeLV p27 with enzyme-linked immunosorbent assay or immunofluorescence. As discussed in Chapter 78, because the prevalence of FeLV infection is decreasing, most cats with leukemia diagnosed in the authors' clinics have not been viremic for FeLV (i.e., they are FeLV negative).

Clinical Features

The clinical features and physical examination findings in cats with acute leukemias are similar to those in dogs and are summarized in Table 80.3. Shifting limb lameness and ocular or neurologic signs do not appear to be as common in cats as in dogs with myeloid leukemias.

Hematologic Features

More than three fourths of cats with AML and ALL have cytopenias; leukoerythroblastic reactions are common in cats with AML but extremely rare in those with ALL. In contrast to dogs, circulating blasts appear to be more common in cats with AML than in those with ALL.

Sequential studies of cats with myeloid leukemias have revealed that the cytomorphologic features can change from one cell type to another over time (e.g., sequential diagnoses of erythremic myelosis, erythroleukemia, and acute myeloblastic leukemia are common in a given cat). This is one of the reasons that most clinical pathologists prefer the term *myeloproliferative disorder* (MPD) to refer to this leukemia in cats.

Diagnosis and Treatment

The diagnostic evaluation of cats with suspected acute leukemia follows the same general sequence as that for dogs. If the changes in the CBC are not diagnostic, a bone marrow aspirate can provide information that may confirm the diagnosis (Fig. 80.7). In addition, cats with suspected or confirmed acute leukemias should be evaluated for circulating FeLV p27 and for serum antibodies against FIV.

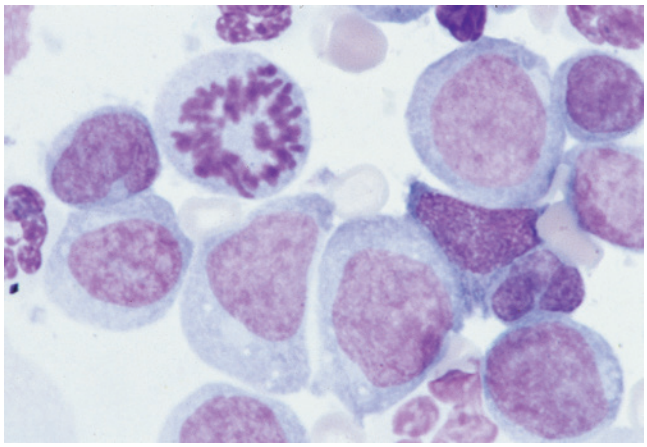


FIG 80.7
Bone marrow aspirate from a cat with peripheral blood cytopenias and absence of circulating blasts. Note the predominance of large immature myeloid cells, characterized by round to kidney-shaped nuclei. A mitotic figure is evident (×1000).

With treatment, cats with ALL apparently have better survival times than cats with AML. Survival times in cats with ALL treated with multichemotherapy range from 1 to 7 months.

There have been several published reports of cats with myeloid leukemias treated with single-agent or combination chemotherapy. The treatment protocols have included single-agent cyclophosphamide or cytosine arabinoside, as well as combinations of cyclophosphamide, cytosine arabinoside, and prednisone; cytosine arabinoside and prednisone; cyclophosphamide, vinblastine, cytosine arabinoside, and prednisone; and doxorubicin, cyclophosphamide, and prednisone. Survival times in these cats have usually ranged from 2 to 10 weeks, with a median of approximately 3 weeks. Therefore, as in dogs, intensive chemotherapy does not appear to be beneficial in cats with acute leukemias.

Low-dose cytosine arabinoside (LDA; 10 mg/m^2 subcutaneously q12h) has been used as an inductor of differentiation of the neoplastic clone. In several studies this treatment was observed to induce complete or partial remission in 35% to 70% of humans with MDS and MPD. Moreover, although myelosuppression was observed in some patients, the treatment was exceedingly well tolerated and associated with minimal toxicity.

One of the authors (GC) treated several cats with MPD using LDA and has observed in most complete or partial remissions, with transient hematologic improvement. Although no major toxicities were seen, the remissions were short-lived (3-8 weeks).

CHRONIC LEUKEMIAS

Chronic leukemias are becoming more common in cats; this may be due to the relative decrease in the prevalence of acute leukemias, or it may represent a true phenomenon. CLL is occasionally found incidentally during routine physical examination. More often, cats with CLL are seen by a veterinarian because of a protracted history of vague signs of illness, including anorexia, lethargy, and gastrointestinal tract signs.

One author's clinic (GC) previously evaluated seven FeLV-FIV–negative cats with CLL that presented primarily for anorexia and weight loss. Splenomegaly, hepatomegaly, and/or lymphadenopathy were present on physical examination in all cats. On initial evaluation, the average hematocrit was 26%, platelets averaged 258,000 cells/μL, and the total white cell count was 63,000 cells/μL. The mean lymphocyte count was 48,200 cells/μL (range, 10,000-104,000/μL) and were primarily small, well differentiated, with clumped chromatin and often a cleaved or irregular nuclear membrane (Fig. 80.8). Six of the seven cats had CD5+CD4+CD8– (T-helper cell) immunophenotype (see Fig. 80.1). Six of the seven cats (86%) responded to treatment with chlorambucil (20 mg/m^2, PO, q2 weeks) and dexamethasone (4 mg, PO, q1 week) or prednisolone (1 mg/kg, PO, q24 hours). MST was 14 months (range, 1-34 months). A recent report of

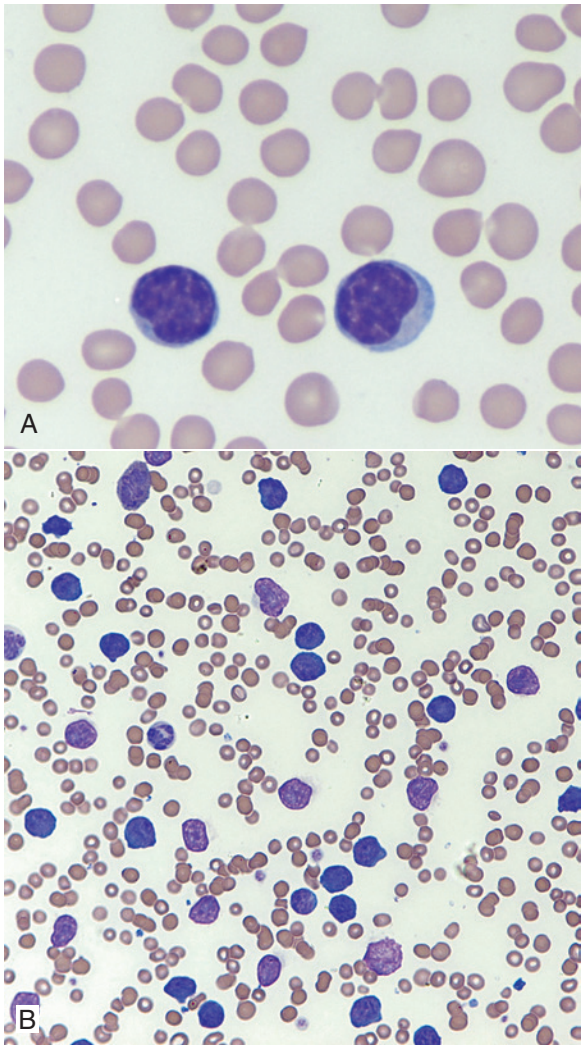


FIG 80.8
Peripheral blood smears showing lymphocyte morphology in cats with chronic lymphocytic leukemia. Note the small lymphocyte size, clumped chromatin, and cleaved nuclei. Wright-Giemsa stain; ×1000 **(A).** Blood smear showing increased number of lymphocytes per field. Wright-Giemsa stain; ×500 **(B).**

18 cats with CLL revealed similar findings (Campbell et al., 2012). Approximately 50% of the cats had clinical signs related to their disease, with the most common clinical sign being chronic weight loss. Various chemotherapy protocols were used, although chlorambucil and prednisolone were the most common; there was a response rate of 88%, with an MST of 14 months. As in dogs, CML is poorly characterized in cats.

Suggested Readings

Avery AC, Avery PR. Determining the significance of persistent lymphocytosis. *Vet Clin North Am Small Anim Pract*. 2007;37:267.

Bennett AL, et al. Canine acute leukaemia: 50 cases (1989-2014). *Vet Comp Oncol*. 2016;14:120.

Bennett JM, et al. Proposal for the classification of acute leukemias. *Br J Haematol*. 1976;33:451.

Bromberek JL, et al. Breed distribution and clinical characteristics of B cell chronic lymphocytic leukemia in dogs. *J Vet Intern Med*. 2016;30:215.

Campbell MW, Hess PR, Williams LE. Chronic lymphocytic leukaemia in the cat: 18 cases (2000-2010). *Vet Comp Oncol*. 2012;11:256.

Comazzi S, et al. Flow cytometric patterns in blood from dogs with non-neoplastic and neoplastic hematologic diseases using double labeling for CD18 and CD45. *Vet Clin Pathol*. 2006;35:47.

Comazzi S, et al. Immunophenotype predicts survival time in dogs with chronic lymphocytic leukemia. *J Vet Intern Med*. 2011;25:100.

Comazzi S, Martini V, Riondato F. Chronic lymphocytic leukemia transformation into high-grade lymphoma: a description of Richter's syndrome in eight dogs. *Vet Comp Oncol*. 2017;15:366–2017.

Couto CG. Clinicopathologic aspects of acute leukemias in the dog. *J Am Vet Med Assoc*. 1985;186:681.

Davis LL, Hume KR, Stokol T. A retrospective review of acute myeloid leukaemia in 35 dogs diagnosed by a combination of morphologic findings, flow cytometric immunophenotyping and cytochemical staining results (2007-2015). *Vet Comp Oncol*. 2017;14:937.

Grindem CB, et al. Morphological classification and clinical and pathological characteristics of spontaneous leukemia in 10 cats. *J Am Anim Hosp Assoc*. 1985a;21:227.

Grindem CB, et al. Morphological classification and clinical and pathological characteristics of spontaneous leukemia in 17 dogs. *J Am Anim Hosp Assoc*. 1985b;21:219.

Jain NC, et al. Proposed criteria for classification of acute myeloid leukemia in dogs and cats. *Vet Clin Pathol*. 1991;20:63.

Novacco M, et al. Prognostic factors in canine acute leukaemias: a retrospective study. *Vet Comp Oncol*. 2015a;14:409.

Novacco M, et al. Analytic errors in Sysmex-generated hematology results in blood from a dog with chronic lymphocytic leukemia. *Vet Clin Pathol*. 2015b;44:337.

Stokol T, et al. Alkaline phosphatase is a useful cytochemical marker for the diagnosis of acute myelomonocytic and monocytic leukemia in the dog. *Vet Clin Pathol*. 2014;44:79.

Tasca S, et al. Hematologic abnormalities and flow cytometric immunophenotyping results in dogs with hematopoietic neoplasia: 210 cases (2002-2006). *Vet Clin Pathol*. 2009;38(2).

Weiss DJ. A retrospective study of the incidence and the classification of bone marrow disorders in the dog at a veterinary teaching hospital (1996-2004). *J Vet Intern Med*. 2006;20:955.

Wilkerson MJ, et al. Lineage differentiation of canine lymphoma/leukemias and aberrant expression of CD molecules. *Vet Immunol Immunopathol*. 2005;106:179.

Williams MJ, et al. Canine lymphoproliferative disease characterized by lymphocytosis: immunophenotypic markers of prognosis. *J Vet Intern Med*. 2008;22:506.

CHAPTER 81

Selected Neoplasms in Dogs and Cats



HEMANGIOSARCOMA IN DOGS

Hemangiosarcomas (HSAs; hemangioendotheliomas, angiosarcomas) are malignant neoplasms that originate from the circulating endothelial cell precursors. They occur predominantly in older dogs (8-10 years of age) and in males; German Shepherd dogs and Golden Retrievers are at high risk for this neoplasm.

The spleen, right atrium, subcutis, and retroperitoneal space are common sites of involvement at the time of presentation; in Greyhounds, most HSAs originate in a muscle in the rear limb. Approximately 50% of the tumors originate in the spleen, 25% in the right atrium, 13% in subcutaneous tissue, 5% in the liver, 5% in the liver-spleen–right atrium, and 1% to 2% simultaneously in other organs (i.e., kidney, urinary bladder, bone, tongue, prostate). The latter are referred to as *multiple tumor, undeterminable primary.* In general, the biologic behavior of this neoplasm is highly aggressive, with most anatomic forms of the tumor infiltrating and metastasizing early in the disease. The exceptions are primary dermal and conjunctival or third eyelid HSAs, which have a low metastatic potential.

Clinical and Clinicopathologic Features

The owners' complaints and the clinical signs at presentation are usually related to the site of origin of the primary tumor; to the presence or absence of metastatic lesions; and to the development of spontaneous tumor rupture, coagulopathies, or cardiac arrhythmias. More than half of the dogs with HSA are evaluated because of acute collapse after spontaneous rupture of the primary tumor or a metastatic lesion. Some episodes of collapse may stem from ventricular arrhythmias, which are relatively common in dogs with splenic or cardiac HSA. In addition, dogs with splenic HSA are often seen because of abdominal distention secondary to tumor growth or hemoabdomen.

Dogs with cardiac HSA are usually presented for evaluation of right-sided congestive heart failure (caused by cardiac tamponade) or cardiac arrhythmias (see the chapters on cardiovascular system disorders for additional information). Dogs with cutaneous or subcutaneous neoplasms are usually evaluated because of a mass, which may be surrounded by hemorrhage. Greyhounds with intramuscular HSA typically present with a swollen and bruised rear limb; the tumor is frequently in the biceps femoris or quadriceps.

Two common problems in dogs with HSA, regardless of the primary location or stage, are anemia and spontaneous bleeding. The anemia is usually the result of intracavitary bleeding, microangiopathic hemolysis (MAHA), or both, whereas the spontaneous bleeding is usually caused by disseminated intravascular coagulation (DIC) or thrombocytopenia secondary to MAHA (see later discussion). HSA is so highly associated with clinical DIC (see Chapter 87) that when a dog with DIC of acute onset without an obvious primary cause is evaluated, HSA should be considered high on the list of differential diagnoses.

HSAs are usually associated with a wide variety of hematologic and hemostatic abnormalities. Hematologic abnormalities in dogs with HSA have been well characterized and include anemia; thrombocytopenia; the presence of nucleated red blood cells (RBCs), RBC fragments (schistocytes), and acanthocytes in the blood smear; and leukocytosis with neutrophilia, a left shift, and monocytosis. In addition, hemostatic abnormalities are also common in dogs with HSAs. However, these hematologic abnormalities are location dependent; for example, in our experience, anemia, thrombocytopenia, schistocytosis, and acanthocytosis are more common in dogs with splenic, right atrial, or visceral HSA than in dogs with subcutaneous or dermal HSA.

Most dogs with HSAs evaluated at the authors' clinics are anemic, and more than half have RBC fragmentation and acanthocytosis. The pretreatment hemostasis profiles are normal in less than 20% of the dogs; most dogs have thrombocytopenia. Approximately half of the hemostasis profiles may meet three or more criteria for diagnosis of DIC. Approximately 25% of these dogs can die as a result of their hemostatic abnormalities.

Diagnosis

HSAs can be diagnosed cytologically on the basis of the appearance of fine-needle aspirates (FNAs) or impression smears; however, the ability to identify these neoplastic cells in cytology samples may be impaired by blood contamination present, given this tumor's vascularity. When visible, the neoplastic cells are similar to those in other sarcomas in that they are spindle-shaped or polyhedral; however, they are quite large (40-50 μm), have large nuclei with a lacy chromatin pattern and one or more nucleoli, and a bluish gray, usually vacuolated cytoplasm (Fig. 81.1). Nucleated RBCs and acanthocytes/schistocytes can also be present in FNAs of HSAs, independently of the primary site. Although HSA cells are relatively easy to identify in tissue aspirates or impression smears, they are extremely difficult to identify in HSA-associated effusions. The probability of establishing a cytologic diagnosis of HSA after evaluating effusions is less than 25%. An additional problem with effusions is that they frequently contain reactive mesothelial cells that may resemble neoplastic cells, leading to a false-positive diagnosis of HSA.

In general, a presumptive clinical or cytologic diagnosis of HSA should be confirmed histopathologically, if feasible. Because of the large size of some splenic HSAs, however, multiple samples (from different morphologic areas) should be submitted in appropriate fixative, or ideally, the entire spleen should be submitted for the most thorough evaluation. Histochemically, HSA cells are positive for von Willebrand factor antigen in approximately 90% of the cases, and CD31, a novel marker, is positive in up to 100% of HSA cells. In practice, these are the two most routinely used histochemical stains that can be beneficial to help confirm a diagnosis of HSA.

Metastatic sites can be detected radiographically, ultrasonographically, or on computed tomography (CT). The staging diagnostics that should be considered for dogs with HSA include a complete blood count (CBC), serum biochemistry profile, hemostasis screen, urinalysis, thoracic radiographs, abdominal ultrasonography, and echocardiography. The latter is used to identify cardiac masses and determine the baseline fractional shortening before instituting doxorubicin-containing chemotherapy (see the section on treatment and prognosis). As mentioned earlier, concurrent splenic and right atrial masses can occur in dogs with HSA; in a recent study <10% of dogs initially diagnosed with splenic HSA had a right atrial mass on staging echocardiography, and 30% of dogs initially diagnosed with cardiac HSA had a splenic mass on staging ultrasonography (Boston et al., 2011). The number of dogs with concurrent right atrial masses on staging echocardiography may be falsely decreased, due to the fact that it can be more difficult to assess for cardiac masses in the absence of pericardial effusion; however, it does appear that concurrent cardiac HSA when splenic HSA is first diagnosed is less common.

Thoracic radiographs in dogs with metastatic HSA are typically characterized by the presence of interstitial or alveolar infiltrates, as opposed to the common "cannonball" metastatic lesions seen with other tumors. The radiographic pattern may be due to true metastases, DIC and intrapulmonary bleeding, or acute respiratory distress syndrome (ARDS).

Ultrasonography constitutes a reliable way to evaluate dogs with suspected or confirmed HSA for intraabdominal disease. Neoplastic lesions appear as nodules with variable echogenicity, ranging from anechoic to hyperechoic (Fig. 81.2). Hepatic metastatic lesions can often be identified using this imaging technique. However, the clinician should bear in mind that what appear to be metastatic nodules in the liver of a dog with a splenic mass may represent regenerative hyperplasia rather than true metastatic lesions. Contrast ultrasonography appears to enhance the operator's ability to detect hepatic metastatic nodules from HSA, but it is not easily available. Therefore we recommend using caution

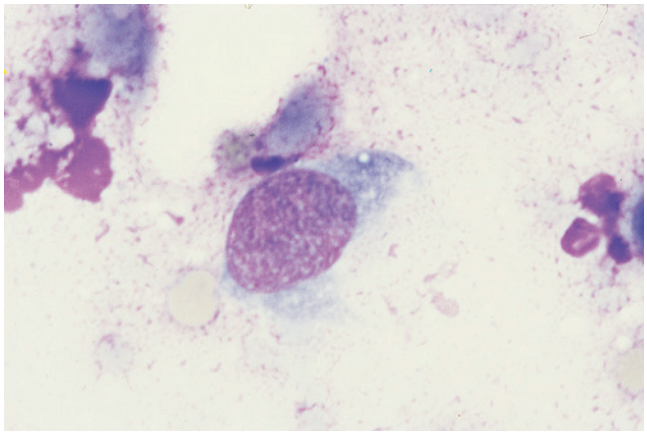


FIG 81.1
Cytologic features of canine hemangiosarcoma. Note the spindle-shaped cells, with a dark, vacuolated cytoplasm, and the fine nuclear chromatin pattern with prominent nucleolus (×1000).

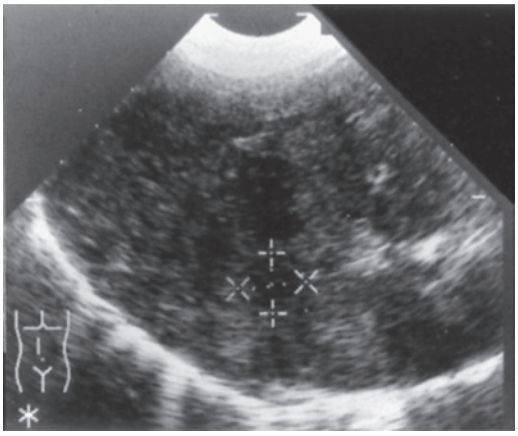


FIG 81.2
Ultrasonogram of an intraabdominal hemangiosarcoma.

when confirming hepatic metastasis only ultrasonographically, without the benefit of cytology or histopathology.

Overall, establishing a definitive diagnosis of HSA before surgical excision can be quite difficult, and for this reason, many clinicians will proceed with treatment (discussed later) without the benefit of a definitive diagnosis. Previous studies have reported the statistical likelihood of HSA in certain situations (mainly with splenic lesions), which can help clinicians discuss the probabilities with owners before consideration of surgery. If a dog presents with a splenic mass and a nontraumatic hemoabdomen, there is an approximately 50% to 75% possibility of a diagnosis of splenic HSA. However, a recent study has shown that, if only a splenic mass is present without a hemoabdomen, the possibility of HSA decreases to approximately 30% (meaning 70% of these lesions are benign). Extensive investigation into biomarkers of HSA (mainly splenic and cardiac) has been attempted; however, there is still no clear diagnostic test to differentiate a splenic or cardiac mass (unless cytologic analysis revealed enough neoplastic cells to determine the diagnosis) without full histopathology (and potentially the necessity for immunohistochemistry to confirm endothelial origin).

Treatment and Prognosis

Historically, the mainstay of treatment for dogs with HSA has been surgery, although the results have been poor. Survival times vary with the location and stage of the tumor, but in general (with the exception of dermal and conjunctival or third eyelid HSAs), they are quite short (approximately 20-60 days, with a 1-year survival rate of <10% after splenectomy alone). Results of treatment combining surgery and postoperative adjuvant chemotherapy with doxorubicin; doxorubicin and cyclophosphamide (AC protocol); and vincristine, doxorubicin, and cyclophosphamide (VAC protocol) are better than with surgery alone. Median survival times (MSTs) range from 4.5 to 8 months.

Clinical stage has been considered a negative prognostic factor for survival. The most routine staging system that is used in practice for dogs with splenic HSA is as follows:

- Stage I: disease confined to the spleen
- Stage II: ruptured splenic HSA
- Stage III: clinically detectable metastatic HSA; concurrent right atrial mass

Doxorubicin-based protocols are most commonly used in the adjuvant setting for HSA; we favor two typical protocols. As with most chemotherapy protocols, treatment choice depends on personal experience and preference. The first protocol, termed a *dose-intensified doxorubicin protocol* (see table on cancer chemotherapy protocols at the end of this chapter), involves 5 doses of doxorubicin delivered every 2 weeks (Sorenmo et al., 2004) and is quite suited for a general or referral practice. This protocol, when used in the adjuvant setting for splenic HSA, has been associated with an MST of 8.5 months for stage I disease, MST of 7 months for stage II disease, and MST of 3.5 months for stage III disease. The second protocol, termed the *VAC protocol*, involves a 21-day cycle repeated five or six times. In a previous study (Alvarez et al., 2013), the MST of dogs with stage III versus stage I/II HSA was compared in patients undergoing surgery and adjuvant VAC chemotherapy. Dogs with stage III disease had an MST of 6.5 months, and dogs with stage I/II HSA had an MST of 4.5 months (Figs. 81.3 and 81.4). In other words, dogs with metastatic disease did as well (or even better) than dogs without metastases. For this reason, in dogs with stage III disease, we generally discuss both the dose-intensified doxorubicin protocol and the VAC protocol; however, for stage I/II disease, one of us (KC) prefers the dose-intensified doxorubicin protocol. As discussed, dogs with visible metastatic disease at the time of diagnosis should not be denied treatment with this more aggressive chemotherapy protocol.

Neoadjuvant chemotherapy is also effective in dogs with soft tissue (e.g., subcutaneous, right atrial) HSA. Preoperative use of chemotherapy typically results in marked decrease in tumor size, thus making surgery easier. As discussed earlier, most dermal and conjunctival HSAs are cured by surgical excision and do not benefit from chemotherapy.

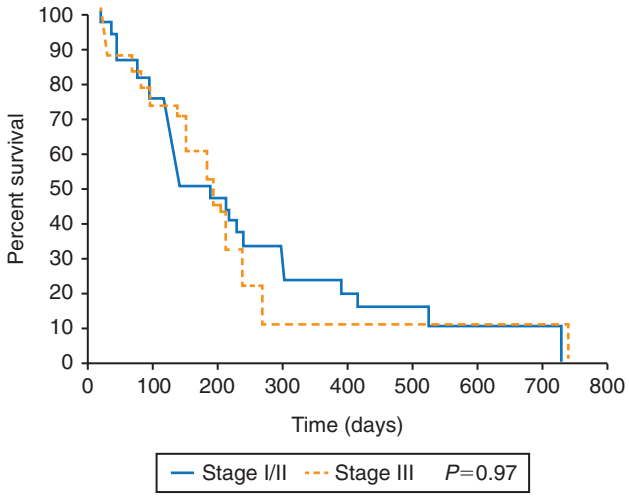


FIG 81.3
Survival times for dogs with stage III (195 days) and stage I/II HSAs (189 days) treated with VAC chemotherapy ($P = 0.97$).

There are two supplements that are also used to some degree in dogs with HSA. The first, Yunnan Baiyao, is a traditional Chinese herbal medicine that has been anecdotally reported to prolong survival time and help control bleeding in dogs with HSA. Additionally, more recently, in vitro effects of Yunnan Baiyao were investigated in canine HSA cells, and it was shown to cause dose and time-dependent HSA cell death through apoptosis (programmed cell death) (Wirth et al., 2016). The second, an extract from the common turkey tail mushroom (*Coriolous versicolor*), has been proposed to delay the progression of metastasis, affording a longer survival in dogs with HSA (Brown et al., 2012). This extract is found in the commercially available product, I'm-Yunity®, and additional investigation into this specific product is underway.

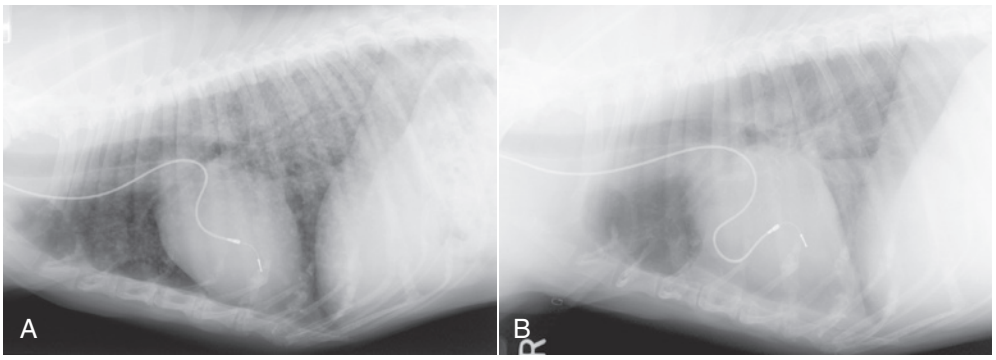


FIG 81.4
Thoracic radiographs of a 10-year-old, spayed female German Shepherd dog with pulmonary metastases from a primary splenic hemangiosarcoma before **(A)** and 9 weeks after initiating vincristine, doxorubicin, and cyclophosphamide chemotherapy **(B).** Notice the complete disappearance of the pulmonary nodules. The radiopaque line is the lead of a permanent pacemaker.

In summary, HSAs are usually diagnosed on the basis of historical, physical examination, and clinicopathologic findings, in conjunction with ultrasonographic and radiographic changes. A morphologic diagnosis can usually be made on the basis of cytologic findings, but histopathology may be necessary. Although surgery is the preferred treatment, survival times in such patients are short (except in dogs with dermal or conjunctival/third eyelid HSA), and for this reason, postoperative adjuvant chemotherapy using doxorubicin-based protocols is generally recommended, as it has been shown to prolong survival times in dogs with this malignancy.

OSTEOSARCOMA

Etiology and Epidemiology

Primary bone neoplasms are relatively common in dogs but rare in cats. Most primary bone tumors in dogs are malignant in that they usually cause death as a result of local infiltration (e.g., pathologic fractures or extreme pain leading to euthanasia) or metastasis (e.g., pulmonary metastases in osteosarcoma [OSA]). In cats, most primary bone neoplasms, although histologically malignant, can be cured by wide surgical excision (i.e., amputation). Neoplasms that metastasize to the bone are rare in dogs; some that occasionally metastasize to bones in dogs are transitional cell carcinoma of the urinary tract, OSA of the appendicular skeleton, mammary adenocarcinoma, and prostatic adenocarcinoma. Bone metastases are exceedingly rare in cats.

OSAs are the most common primary bone neoplasm in dogs. They can affect either the appendicular or axial skeletons, and they occur primarily in large- and giant-breed dogs and in Greyhounds; they are common in middle-aged to older dogs. In dogs weighing more than 40 kg, 95% of the tumors are appendicular (i.e., limbs), in contrast to dogs weighing less than 15 kg, where only 40% are appendicular. There is a distinct genetic predisposition to OSA in dogs; for example, in former racing Greyhounds, OSA is the most common cause of death (i.e., 25%), whereas OSAs are extremely rare in show Greyhounds in the United States. Due to the fact that canine OSA constitutes an excellent model for pediatric OSA, a large amount of research on the genetics of this tumor has been conducted in dogs (for a review, please see Rowell et al., 2011).

The biologic behavior of OSA is characterized by aggressive local infiltration of the surrounding tissues and rapid hematogenous dissemination (usually to the lungs). Although historically it was believed that OSAs of the axial skeleton had a low metastatic potential, it now appears that their metastatic rate is similar to that of the appendicular OSAs, with the exception of OSAs of the mandible, maxilla, or other calvarial locations, where the probability of metastases is lower (Selmic et al., 2014).

Clinical Features

Appendicular OSAs occur predominantly in the metaphyses of the distal radius, distal femur, and proximal humerus (i.e., *away from the elbow and toward the knee*), although other metaphyses can also be affected. OSA of the distal humerus or proximal radius is quite uncommon, so if an aggressive bone lesion is found in these locations, other diagnoses should also be considered. The location is also somewhat breed dependent; in Great Danes the most common site is the distal radius, whereas in Rottweilers and Greyhounds it is the distal femur. In Greyhounds, OSA of the femoral head or neck is a common cause of hip pain; therefore any Greyhound with hip pain should undergo radiographs (hip dysplasia leading to osteoarthritis is extremely uncommon in the breed). Owners seek veterinary care because of lameness or swelling of the affected limb. The pain and swelling can be acute in onset, leading to the presumptive diagnosis of a nonneoplastic orthopedic problem, and thus considerably delaying diagnosis and definitive therapy for the neoplasm while the dog is placed on nonsteroidal antiinflammatory drugs. A pathologic fracture at the time of diagnosis is

considered relatively rare and appears to be more common in Greyhounds, where approximately 15% of the patients present due to a pathologic fracture. Physical examination usually reveals a painful swelling in the affected area, with or without soft tissue involvement or pathologic fracture.

Diagnosis

Radiographically, OSAs exhibit a mixed lytic-proliferative pattern in the metaphyseal region of the affected bone (Fig. 81.5). Adjacent periosteal bone formation leads to the development of the so-called Codman triangle, which is composed of the cortex in the affected area and the periosteal proliferation. OSAs typically do not cross the articular space, but occasionally they can infiltrate adjacent bone (e.g., ulnar lysis resulting from an adjacent distal radial OSA). Because other primary bone neoplasms and some osteomyelitis lesions can mimic the radiographic features of OSAs, cytology or biopsy specimens of every lytic or lytic-proliferative bone lesion should be obtained before the owners decide on a specific treatment. An exception to this rule is an owner who has already decided that amputation is the initial treatment of choice for that lesion (i.e., the limb is amputated and the lesion submitted for histopathologic evaluation).



FIG 81.5
Radiographic appearance of an osteosarcoma in the distal tibia of a Greyhound; note the lytic and proliferative changes characteristic of this neoplasm **(A).** Radiographic appearance of a distal radial osteosarcoma with massive neoplastic new bone formation in a Mastiff **(B).**

Once a presumptive radiographic diagnosis has been established, and if the owners are contemplating treatment, thoracic radiographs or CT should be obtained to determine the extent of the disease. The authors generally obtain three radiographic views of the thorax and do not perform skeletal radiographic surveys (or radionuclide bone scan) unless there are clinical signs that warrant this investigation (i.e., lameness on a separate limb), as less than 10% of dogs with OSA have skeletal metastasis. Thoracic CT allows for detection of smaller nodules (Alexander et al., 2012), but to our knowledge, no correlations between dogs that had "negative" thoracic radiographs with pulmonary nodules on CT and survival have been established yet. Less than 10% of dogs with OSAs initially have radiographically detectable lung lesions; the presence of metastases is a strong negative prognostic factor.

When deemed necessary, the radiographic diagnosis can be confirmed before surgery (i.e., limb amputation or limb salvage) on the basis of the findings yielded either by FNA or by aspiration of the affected area using a bone marrow aspiration needle. In most cases, a blind percutaneous FNA can be performed with only manual restraint; if the operator cannot penetrate through the cortex, ultrasonographic guidance can help visualize a "window" through which the needle is inserted. OSA cells are usually round or oval; have distinct cytoplasmic borders; have a bright blue, granular cytoplasm; and have eccentric nuclei with or without nucleoli (Fig. 81.6). Osteoclast-like multinucleated giant cells are common, and there is frequently pink amorphous material (osteoid) in the background or in the cytoplasm of the osteoblasts. If the round cells cannot be convincingly identified as osteoblasts, most diagnostic laboratories can perform an alkaline phosphatase (ALP) cytochemical stain in unstained slides;

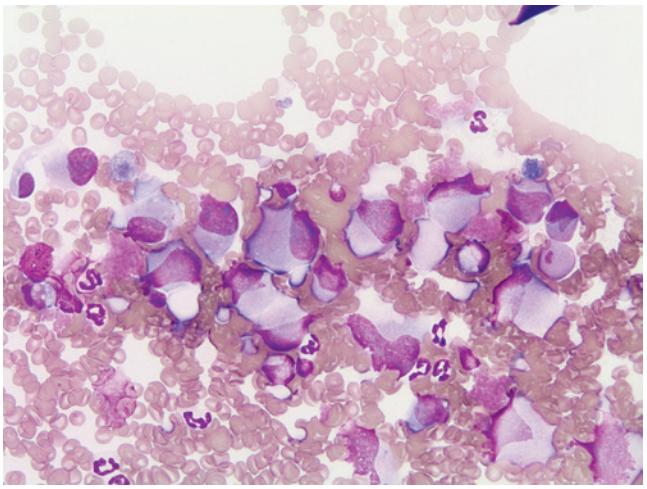


FIG 81.6
Characteristic cytologic features of osteosarcoma in a fine-needle aspirate of a lytic/proliferative lesion in the distal radius of a female Great Pyrenees. Note the round to oval eccentric nuclei with a fine chromatin pattern and prominent nucleoli, and the pink material (osteoid) in the cytoplasm of the neoplastic cells (×500).

osteoblasts are typically ALP positive. However, we have seen a fair number of histiocytic sarcomas that stain positive with ALP.

A preamputation diagnosis can also be made after histopathologic evaluation of core biopsy specimens from the affected areas. To obtain a bone biopsy, a 13- or 11-gauge Jamshidi bone marrow biopsy needle (Monoject, Covidien, Mansfield, MA) is used with the animal under general anesthesia, and a minimum of two (and preferably three) cores of tissue are obtained from both the center of the lesion and the area between affected and unaffected bone. Recently, a comparative assessment of the accuracy of cytologic and histopathologic biopsies on the diagnosis of canine bone lesions was performed, which revealed that the accuracy of cytology was similar to histopathology (approximately 80%), even in determination of tumor type. Typically, we recommend attempting to obtain a cytologic diagnosis (considering the use of ultrasound-guidance to increase potential yield), and only pursue bone biopsy if no cytologic diagnosis can be obtained and a diagnosis is required before consideration of treatment.

As long as the owners understand the biologic behavior of the neoplasm (i.e., the high likelihood of their dog dying of metastatic lung disease within 4-6 months of amputation if no chemotherapy is used) and as long as the clinical and radiographic features of the lesion are highly suggestive of OSA, the limb can be amputated in the absence of a histopathologic diagnosis. The amputated leg (or representative samples) and the regional lymph nodes should always be submitted for histopathologic evaluation. The presence of pulmonary or lymph node metastases, a high serum ALP activity, and the proximal humeral location are negative prognostic factors for survival in dogs with OSA.

Treatment and Prognosis

The standard of care for dogs with OSA is amputation and postoperative adjuvant single-agent or combination chemotherapy. The MST in dogs with appendicular OSA treated with amputation alone is approximately 4 to 6 months, whereas in dogs treated with amputation and cisplatin, carboplatin, doxorubicin, or combination chemotherapy the MST is 12 to 18 months; approximately 25% of the dogs live longer than 2 years. The dosages for chemotherapy in dogs with OSA are given in the table on cancer chemotherapy protocols at the end of this chapter and Box 81.1. The authors typically use carboplatin immediately after amputation (starting at the time of suture removal) for a total of six treatments.

An alternative therapeutic approach for dogs with distal radial or ulnar OSAs consists of sparing the affected limb. Instead of amputation, the affected bone is resected and an allograft from a cadaver or a prosthetic device is used to replace the neoplastic bone; novel biomaterials are also currently being investigated for this purpose. The dogs are also treated with chemotherapy and, in general, have almost normal limb function. Survival times in dogs treated with limb-sparing procedures are comparable with those in dogs that undergo amputation plus chemotherapy, with the added benefit to the owners of having a four-legged pet. The main complication is the development of osteomyelitis in the allograft, which occurs in up to 50% of patients; if that occurs, the limb frequently needs to be amputated. However, in patients with infected allografts that eventually undergo amputation, the survival times are significantly longer than in dogs that did not experience complications (Lascelles et al., 2005).

Recently, a novel form of irradiation (stereotactic radiation therapy) has been used for dogs with OSA. This approach allows for a high dose of radiation to be delivered to the primary tumor site, sparing the surrounding tissues of significant toxicity due to image guidance and stereotactic positioning, with the goal of affording dogs a similar survival time when compared with amputation or limb-sparing surgeries. The main complication in a relatively high percentage of dogs (up to 63%) undergoing this treatment is a pathologic fracture; in addition, skin necrosis appears to be common in Greyhounds undergoing this treatment. Pretreatment CT scans are being used to help predict which dogs may suffer a pathologic fracture, so that the best candidates for treatment can be chosen. These dogs should also be treated with postradiation chemotherapy, and bisphosphonates may be used to help strengthen the bone during the initial radiation series.

For owners who are not interested in limb amputation, limb-sparing surgeries, or stereotactic radiation therapy, more palliative intent treatments can be pursued, mainly to help with pain caused by the primary lesion. Another form of radiation therapy, termed *palliative radiation therapy*, can be used to help limit pain at the tumor site, and it is successful in approximately 75% of dogs for approximately 2 to 4

BOX 81.1

Chemotherapy Protocols and Palliative Treatment for Dogs With Osteosarcoma

Chemotherapy Protocols

1. Carboplatin: 300 mg/m^2, IV, q3-4 weeks for 4-6 doses
2. Doxorubicin: 30 mg/m^2, IV, q2 weeks, for 5 doses
3. Carboplatin: 300 mg/m^2, IV, on weeks 1 and 6, plus doxorubicin: 30 mg/m^2, IV, on weeks 3 and 9

Palliative Treatment

1. Zoledronate 0.1 mg/kg, IV, CRI in 0.9% saline, over 15 minutes, q3-4 weeks
2. Pamidronate: 1 mg/kg, IV, CRI in 0.9% saline, over 2 hours, q3-4 weeks
3. Tramadol: 3-5 mg/kg PO q8-12h
4. Deracoxib (Deramaxx): 1-2 mg/kg PO q24h*

CRI, Continuous rate infusion; *IV,* intravenous; *PO,* by mouth.
*Other nonsteroidal antiinflammatories are also effective.

months; the rate of pathologic fractures is approximately 40%. There is some information to suggest that adding chemotherapy to a course of palliative radiation therapy can enhance the analgesic effects and duration; however, doxorubicin should not be used in this setting because it acts as a radiation sensitizer and can cause severe local tissue reactions. Bisphosphonates (pamidronate 1 mg/kg, intravenous 2-hour constant rate infusion q3-4 weeks or zoledronate 0.1 mg/kg, intravenous 15-minute constant rate infusion q3-4 weeks) can be used concurrently with radiation therapy or as a sole therapy, and can improve pain in approximately 30% to 50% of dogs. Zoledronate, a newer generation bisphosphonate, is preferred by the author, as it has recently become less expensive and only requires a 15-minute infusion, in comparison to a 2-hour infusion necessary for pamidronate. Oral analgesics (see Box 81.1) are also used consistently in dogs that are not undergoing amputation or limb-sparing procedures.

Chemotherapy may modify the biologic behavior of the tumor, resulting in a higher prevalence of bone metastases and a lower prevalence of pulmonary metastases. Moreover, the doubling time (i.e., growth rate) of metastatic lesions appears to be longer than that in dogs that have not received chemotherapy, and there appear to be fewer metastatic nodules in treated than in untreated dogs. Therefore surgical removal of the metastatic nodules (i.e., metastasectomy) followed by additional chemotherapy may be recommended for a dog that has been treated with chemotherapy after amputation of the limb and in which one to two pulmonary metastatic lesions are detected (O'Brien et al., 1993). This is not recommended unless the dog has experienced a long relapse-free interval (>300 days), and the specific metastatic nodules have a long doubling time (>30 days).

Given the aggressive nature of OSA and its comparative value for pediatric OSA, there have been many attempts at novel medical therapy to help improve survival times of dogs with OSA. Recently, a multicenter, open label, prospective preclinical trial was conducted by the Comparative Oncology Trials Consortium (COTC) evaluating orally administered Rapamycin (Sirolomus) in the adjuvant setting for dogs with OSA. Dogs in this trial underwent amputation, received 4 doses of carboplatin, and were randomized to receive adjuvant Rapamycin or no additional treatment after finishing carboplatin chemotherapy. The results of this trial are not yet available; however, preliminary in vitro data suggest that Rapamycin can decrease the surviving tumor cell fraction in canine OSA cells. An additional ongoing COTC trial is currently evaluating immunotherapy using a recombinant, attenuated *Listeria monocytogenes* expressing chimeric human HER2/neu protein for dogs with OSA. Similar to the previous trial evaluating Rapamycin, dogs are undergoing amputation and receiving 4 doses of carboplatin, followed by 3 doses of the HER2/neu vaccine. In the first preliminary report of this study (Mason et al., 2016), dogs receiving this novel vaccine after amputation and carboplatin had significant longer survival times; however, only a small number of dogs was studied.

As discussed in previous paragraphs, the treatment of choice for OSAs in cats is limb amputation alone. Extremely long survival times (in excess of 2 years) are common in such cats. As discussed in Chapter 76, cisplatin is extremely toxic in cats and should therefore not be used in this species. If necessary, carboplatin or doxorubicin can be used instead.

MAST CELL TUMORS IN DOGS AND CATS

Not one of them is like another. Don't ask us why. Go ask your mother.
—From One Fish, Two Fish, Red Fish, Blue Fish, by Dr. Seuss

Mast cell tumors (MCTs) are among the most common skin tumors in dogs and are relatively common in cats. They originate from mast cells, which are intimately involved in the local control of vascular tone and which contain a large array of intracytoplasmic bioactive molecules, including heparin, histamine, leukotrienes, and several cytokines. Given their unpredictable biologic behavior, the term *mast cell tumor* is preferred to *mastocytoma* or *mast cell sarcoma.* Because of differences in the clinical and pathologic features of canine and feline MCTs, they are discussed separately.

MAST CELL TUMORS IN DOGS

Etiology and Epidemiology

MCTs constitute approximately 20% to 25% of the skin tumors seen by practicing veterinarians. Brachiocephalic breeds (Boxer, Boston Terrier, Bull Mastiff, English Bulldog) and Golden Retrievers are at high risk for MCTs. These tumors are also more common in middle-aged to older dogs (mean age, ≈8.5 years), and there is no gender-related predilection. MCTs have been found in sites of chronic inflammation or injury, such as burn scars.

Clinical and Pathologic Features

MCTs occur either as dermoepidermal masses (i.e., a superficial mass that moves with the skin) or subcutaneous/deep masses (i.e., the overlying skin moves freely over the tumor). Grossly, MCTs can mimic any primary or secondary skin lesion, including a macule, papule, nodule, tumor, or crust. Approximately 10% to 15% of all MCTs in dogs are clinically indistinguishable from the common subcutaneous lipomas. (Remember, a "lipoma"-feeling mass in the leg of a dog is almost always an MCT or a soft tissue sarcoma!) As a rule, an MCT cannot be definitively diagnosed until the lesion has been evaluated cytologically or histopathologically.

Most MCTs are solitary, although multifocal MCTs can occur. Regional lymphadenopathy caused by metastatic disease is also common in dogs with invasive MCTs or MCTs that have been present for a long period of time. Occasionally, splenomegaly or hepatomegaly is present in dogs with systemic dissemination.

Given the fact that mast cells produce a variety of bioactive (mainly vasoactive) substances, dogs with MCTs may be evaluated because of diffuse swelling (i.e., edema and inflammation around a primary tumor or its metastatic lesion), erythema, or bruising of the affected area. These episodes may be acute, and they may occur during or shortly after exercise or exposure to cold weather. Percutaneous FNA of an unexplained subcutaneous swelling in dogs should always be performed as part of the workup.

A "typical" MCT is a dermoepidermal, dome-shaped, alopecic, and erythematous lesion (Fig. 81.7). However, as discussed in previous paragraphs, MCTs rarely have a typical appearance. A clinical feature that may aid in the diagnosis of a MCT is the Darier sign, which is the erythema and wheal that form after the tumor is slightly traumatized (i.e., scraped, compressed, aspirated, etc.).

As discussed in Chapter 74, MCTs are easily diagnosed on cytology (see Fig. 74.8). Most dogs with MCTs have a normal, although eosinophilia (sometimes marked), basophilia, mastocythemia, neutrophilia, thrombocytosis, or anemia (or a combination of these) may be present. Serum biochemistry abnormalities are uncommon.

From a histopathologic standpoint, MCTs were traditionally classified using the Patnaik grading system into three categories: well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3). Several studies have shown that dogs with grade 1 tumors treated with surgery alone have longer survival times than identically treated dogs with grade 3 tumors, mainly because well-differentiated neoplasms are easier to resect and have a lower metastatic potential (i.e., most tumors in dogs with systemic mast cell disease are grade 3).

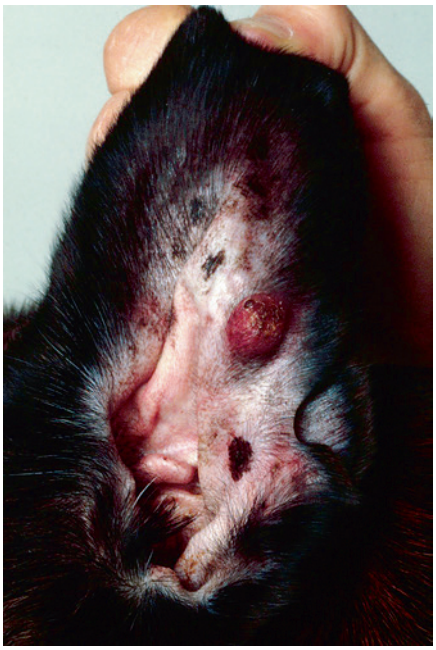


FIG 81.7
Dermoepidermal, dome-shaped lesion in the pinna of a Boxer. The cytologic diagnosis was mast cell tumor.

More recently, a group of pathologists proposed establishing a two-tier grading system for canine MCTs, using a low-grade and high-grade designation (Kiupel et al., 2011). A group of 28 pathologists from 16 institutions evaluated 95 MCTs from dogs treated by surgical resection alone. Interestingly, when grading the tumors using the original three-tier system, concordance among pathologists was approximately 60% to 65% for grades 1 and 2 tumors and 75% for grade 3 tumors. Using the newer two-tier grading system, there was a 98.6% consistency among six pathologists. Along with this, the MST for dogs with low-grade tumors was 23 months, compared with approximately 4 months for dogs with high-grade tumors. This newer grading scheme, overall, has been shown to decrease inter-pathologist variation as well as provide strong correlations with overall survival, MCT-associated mortality, and risk of metastasis. However, other authors have questioned whether this grading system correlates well with survival times (Stefanello et al., 2015).

In some cases, special stains may be required to identify the typical intracytoplasmic granules in poorly differentiated neoplasms. The mitotic index is of prognostic relevance in dogs with MCTs, so it should be provided by the pathologist (Romansik et al., 2007). In addition to the grading of the tumor, the pathologist should provide the clinician with information regarding the completeness of the excision. A dog with an incompletely excised MCT is rarely cured by the initial surgical procedure and requires either a second surgery, irradiation of the affected area, or chemotherapy.

Markers of proliferation, such as AgNOR (argyrophilic nucleolar organizing region) and Ki-67, have been used prognostically in some studies, and are now offered by several commercial laboratories. In these studies, high AgNOR and Ki-67 scores were associated with a shorter time to relapse and MSTs. We do not routinely use these stains to plan treatment of dogs with MCTs.

From a molecular standpoint, approximately 20% to 30% of canine MCTs have internal tandem duplications in exons 11 and 12 of c-kit; c-kit is the stem cell growth factor receptor, and its mutation results in immortalized clones that do not undergo apoptosis (Jones et al., 2004). Mutations in c-kit are more common in high-grade tumors and have been associated with decreased MST and disease-free interval (DFI), and a higher risk of local recurrence, metastasis, and MCT-related mortality.

Biologic Behavior

The biologic behavior of canine MCTs can be summed up in one word: unpredictable. Even though several criteria may help in establishing the biologic behavior of these neoplasms, they rarely apply to an individual dog (i.e., they may be meaningful from the statistical viewpoint; however, they are not always representative in a specific patient).

In general, solitary cutaneous MCTs that are termed low-grade (Kiupel) or grade 1 (Patnaik) have a low metastatic potential and low potential for systemic dissemination. However, the clinician may encounter a dog with several

dozen cutaneous MCTs, which on histopathologic evaluation are all considered low grade.

Grade 2 and 3 tumors have a higher metastatic potential and a higher potential for systemic dissemination than grade 1 MCTs. The newer Kiupel grading scheme helps clinicians determine how concerned to be about a specific MCT, which is especially helpful for MCTs with a grade 2 designation (under the Patnaik system), as some of these are categorized as low grade and some high grade. Grade 2, high-grade MCTs have a higher potential for metastasis and systemic dissemination than grade 2, low-grade MCTs. Metastases to the regional lymph nodes commonly occur (particularly in dogs with high-grade tumors), although occasionally a tumor "skips" the draining lymph node and metastasizes to the second or third regional node (e.g., a digital MCT in the rear limb metastasizing to the iliac or sublumbar node). Because nodal metastases can be present in normal-size lymph nodes, *every lymph node in the region of a MCT should be aspirated* before an aggressive surgery, regardless of whether it is enlarged or not. Pulmonary metastases are extremely rare. It also appears that MCTs in certain anatomic locations are more aggressive than tumors in other areas. For example, distal limb (e.g., toe), perineal, preputial, scrotal, inguinal, muzzle, and extracutaneous (e.g., oropharyngeal, intranasal) MCTs appear to have a higher metastatic potential than similarly graded tumors in other regions (e.g., trunk, neck).

Another biologic characteristic of canine MCTs is that they may become systemic, behaving like a hematopoietic malignancy (i.e., a lymphoma or leukemia). These dogs usually have a history of a high-grade or grade 3 cutaneous MCT that was excised, or a MCT in one of the locations described earlier. Most dogs with systemic mast cell disease (SMCD) are evaluated because of lethargy, anorexia, vomiting, and weight loss in association with splenomegaly, hepatomegaly, pallor, and (occasionally) detectable cutaneous masses. The CBC in affected dogs commonly reveals cytopenias, with or without circulating mast cells.

MCTs can release bioactive substances that may cause edema, erythema, or bruising of the affected area. Gastrointestinal tract ulceration may also occur as a result of hyperhistaminemia (≈80% of dogs euthanized because of advanced MCTs have gastroduodenal ulceration). Therefore any dog with an MCT should be considered to have an increased risk of gastroduodenal ulceration. Profuse intraoperative and postoperative bleeding and delayed wound healing occur in some dogs as a consequence of the bioactive substances released from mast cells.

A clinical presentation with a very distinctive biological behavior is the subcutaneous MCT (Thompson et al., 2011). Most dogs with subcutaneous MCT have a "lipoma"-feeling mass, usually in the leg (although other locations are possible). FNAs of these masses usually yield well-granulated mast cells, with no anisocytosis or mitotic figures. This clinical entity is very different than a "deep" dermal MCT, because most dogs with subcutaneous MCTs are cured by surgical excision alone, even when the tumor is incompletely excised.

Diagnosis

The evaluation of a dog with a suspected MCT should include FNA of the mass. MCTs are typically easy to diagnose cytologically. They consist of a monomorphic population of round cells with prominent intracytoplasmic purple granules; eosinophils are frequently present in the smear (see Fig. 74.8). In approximately one fourth to one third of MCTs, the granules do not stain with Diff-Quik; hence if agranular round cells are found in a dermal or subcutaneous mass resembling an MCT, the clinician should stain the slide with Giemsa or Wright stain to reveal the characteristic purple granules (see Fig. 74.13). A cytologic diagnosis of MCT allows the clinician to discuss treatment options with the owner and to plan therapeutic strategies (see the section on treatment and prognosis).

Although clinical pathologists frequently state the degree of differentiation of the cells in a cytologic specimen of an MCT, that scheme does not necessarily correlate with the histopathologic grading system. In other words, a cytologic diagnosis of a well-differentiated MCT does not necessarily imply that it will be a low-grade tumor when evaluated histopathologically (i.e., cytologic grading may not have the same prognostic implications as histopathologic grading). More recently, a variation of the Kiupel grading scheme was successfully applied to 152 cytologic specimens. Tumors were classified as high grade if the cells were poorly granulated or had at least two of four findings: mitotic figures, binucleated or multinucleated cells, nuclear pleomorphism, or >50% anisokaryosis. This cytologic grading scheme had 88% sensitivity and 94% specificity relative to histologic grading (Camus et al., 2016).

The clinical evaluation of a dog with a cytologically confirmed MCT should include careful palpation of the affected area and its draining lymph nodes; abdominal palpation, radiography, or ultrasonography to search for hepatosplenomegaly; a CBC, serum biochemistry profile, and urinalysis; and thoracic radiography if the neoplasm is in the cranial half of the body (i.e., to detect intrathoracic lymphadenopathy). Abdominal ultrasonography should be strongly considered in dogs with clinical negative prognostic factors, including an enlarged regional lymph node on physical examination, a MCT in any "high risk" location described earlier, an ulcerated MCT, history of rapid growth, known recurrence of a previous MCT, systemic signs that may indicate dissemination, or certain breeds. For example, in a recent study Shih Tzus and Rottweilers were reported to have a higher prevalence of high-grade MCTs (Mochizuki et al., 2017)

If lymphadenopathy, hepatomegaly, or splenomegaly is present, FNA of the enlarged lymph node or organ should be performed to detect mast cells (i.e., local neoplasm versus metastatic tumor versus SMCD); as discussed earlier, regional nodes should be aspirated, even if normal in size, before performing an aggressive surgery. Additionally, dogs with ultrasonographically normal liver and spleen can still have cytologic evidence of MCT metastasis, so aspirating these organs in dogs that have negative prognostic indicators (see previous discussion) is recommended.

Buffy coat smears to search for circulating mast cells are not clinically useful. Interestingly, circulating mast cells are more common in dogs with diseases other than MCTs; most dogs with mastocythemia have inflammatory disorders, regenerative anemia, tumors other than MCTs, or trauma. Circulating mast cells can frequently be recognized in the graphics of flow cytometry-based hematology analyzers (Fig. 81.8). Cytologic evaluation of a bone marrow aspirate may therefore be more beneficial for staging purposes, when deemed appropriate. On the basis of all these facts, the appropriate staging procedures in dogs with MCTs remain controversial. The authors do not use buffy coat smears or bone marrow aspirates routinely in dogs with MCT and a normal CBC; if cytopenias or leukoerythroblastic reactions are present, a bone marrow aspirate may be performed.

As a general rule, in dogs with solitary MCTs in a location amenable to wide surgical excision and no negative prognostic indicators, routine staging diagnostics (with the exception of regional lymph node aspiration) are not considered mandatory and can be performed postoperatively if there is indication of "aggressive" histopathology (i.e., high grade) (Table 81.1).

Treatment and Prognosis

As discussed previously, it is imperative to know whether the mass the clinician is preparing to excise is a MCT before surgery, because this information is useful when discussing treatment options with the family and when planning the treatment strategy. Dogs with MCT can be treated with surgery, radiotherapy, chemotherapy, molecular-targeted therapy, or a combination of these. However, the first two

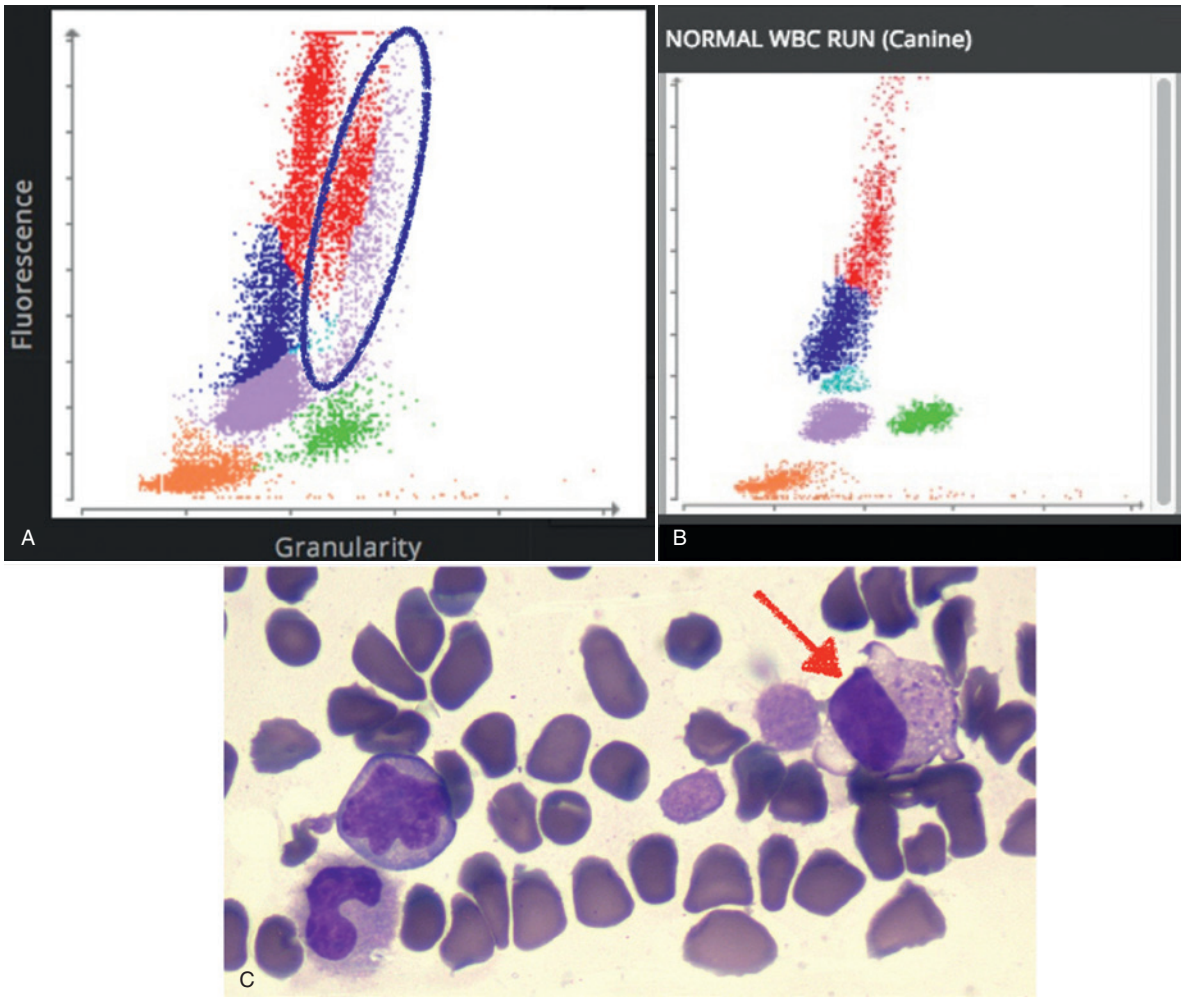


FIG 81.8
Leukocyte dotplots in a dog with systemic mast cell disease and mastocythemia **(A).** Note the second "peak" (*blue circle*) that represents the circulating mast cells, located to the right of the normal cells (the horizontal axis depicts granularity, so cells with inclusions are further to the right). **(B)** This image depicts a normal leukocyte graphic. **(C)** This image shows a circulating poorly granulated mast cell (Diff-Quick stain, ×1000). *Color code:* Purple, neutrophils; green, eosinophils; light blue, basophils; blue, lymphocytes; red, monocytes; orange, unlysed red blood cells.

treatment options are potentially curative, whereas chemotherapy or molecular-targeted therapy are generally only palliative. Treatment guidelines are provided in Table 81.2.

A solitary MCT in an area in which complete surgical excision is feasible, and in which the regional lymph node is free of metastasis, should be removed by aggressive *en bloc* resection (i.e., ideally with 2- to 3-cm margins around and one plane underneath the tumor). If a complete excision is obtained (according to the pathologist evaluating the specimen), and the tumor is a low-grade, grade 1 or 2 MCT, there is usually no need for further treatment (i.e., the dog is most likely cured). If the excision appears incomplete, the clinician can take one of three courses of action: (1) perform a second surgery in an attempt to excise the remaining tumor (the excised area should be submitted for histopathologic evaluation to assess the completeness of excision); (2) irradiate the surgical site (numerous protocols are available); or (3) administer a short course (3-6 months) of chemotherapy (discussed later). The three options appear to be equally effective, resulting in approximately an 80% probability of long-term survival.

A solitary MCT in an area in which surgical excision is difficult or impossible, or at a site where the cosmetic or functional results are unacceptable (e.g., prepuce, eyelid), can be successfully treated with radiotherapy. Approximately two thirds of dogs with a grade 1 or 2 localized MCT treated with radiotherapy alone are cured. Irradiation is also recommended for the management of tumors in high-risk areas. Intralesional injections of corticosteroids (triamcinolone, 1 mg intralesionally per centimeter of tumor diameter q2-3 weeks) can also successfully shrink the tumor (although it is usually only palliative). An alternative approach is to use neoadjuvant chemotherapy (i.e., chemotherapy before surgery). In these dogs a combination of vinblastine and prednisone (with or without lomustine) can be used to decrease the tumor size; then surgery is performed, followed by additional chemotherapy (discussed later).

Once metastatic or disseminated MCTs (or SMCD) develop, a cure is rarely obtained. The main exceptions are grade II, low-mitotic index MCT with confirmed metastasis to the regional lymph node, excised during surgery for the primary lesion, and treated with an aggressive course of postoperative chemotherapy. Treatment in other dogs consists of chemotherapy and supportive care, with a goal of palliating the neoplasm and its complications. There are multiple chemotherapy protocols that are widely used for dogs with MCTs, although four are used with relative frequency by the authors and are discussed here. We typically recommend

TABLE 81.1

Clinical Staging Scheme for Dogs With Mast Cell Tumors

STAGE	DESCRIPTION
I	One tumor confined to the dermis without regional lymph node involvement a. Without systemic signs b. With systemic signs
II	One tumor confined to the dermis with regional lymph node involvement a. Without systemic signs b. With systemic signs
III	Multiple dermal tumors or a large infiltrating tumor with or without regional lymph node involvement a. Without systemic signs b. With systemic signs
IV	Any tumor with distant metastases or recurrence with metastases a. Without systemic signs b. With systemic signs

TABLE 81.2

Treatment Guidelines for Dogs With Mast Cell Tumors

STAGE	GRADE	RECOMMENDED TREATMENT	FOLLOW-UP
I	1, 2	Surgical excision	Complete → observe Incomplete → second surgery or radiotherapy
I	3	Chemotherapy*	Continue chemotherapy
II	1, 2, 3	Surgical excision or radiotherapy	CCNU and prednisone (see below)*
III, IV	1, 2, 3	Chemotherapy*	Continue chemotherapy

Chemotherapy protocols for dogs with mast cell tumors:

1. Prednisone, 50 mg/m^2 by mouth (PO) q24h for 1 week; then 20-25 mg/m^2 PO q48h indefinitely plus lomustine (CCNU), 60 mg/m^2 PO q3 weeks
2. Prednisone, 50 mg/m^2 PO q24h for 1 week; then 20-25 mg/m^2 PO q48h indefinitely plus lomustine (CCNU), 60 mg/m^2 PO q6 weeks, alternating doses with vinblastine, 2 mg/m^2 IV q6 weeks (the dog receives lomustine, 3 weeks later vinblastine, 3 weeks later lomustine again, and so on)

*For more information, see table at the end of this chapter.

an alternating chemotherapy protocol including vinblastine, lomustine, and prednisone (see chemotherapy table on page 1337) in dogs with nonsurgical or disseminated MCTs. This has been associated with a 50% to 70% response rate and can afford improvement in quality of life for these patients. Lomustine or vinblastine can also be used as a single-agent therapy (in combination with prednisone); however, these are generally associated with a less favorable response rate (<40%). As described in a previous chapter, hepatotoxicity is a relatively frequent complication associated with lomustine administration, and when lomustine is combined with vinblastine, it allows administration of lomustine every 4 to 6 weeks instead of every 3 weeks, which may decrease the prevalence of clinically relevant hepatoxicity.

As stated earlier, dogs with grade 2, low-mitotic index MCTs with confirmed metastasis to the regional lymph node (and no distant metastases) that are treated with adequate local control (complete surgical excision or incomplete excision followed by radiotherapy) and an alternating protocol of vinblastine, lomustine, and prednisone can have prolonged survival times. In a study of 21 dogs receiving this treatment combination (the lymph node was removed at the time of surgery), the MST was 45 months (Lejeune et al., 2015). For that reason, aggressive therapy should still be discussed for dogs with MCTs that have confirmed regional lymph node metastasis, because if a low-mitotic index tumor is found, long-term survival is likely in most dogs.

Because a variable proportion of canine MCTs have c-kit mutations, small molecule tyrosine kinase inhibitors (TKIs) such as toceranib (Palladia [Zoetis, Madison, NJ], 2.5 mg/kg orally [PO], every other day) are effective in approximately 40% of canine MCTs and in up to 90% of MCTs with c-kit mutations (London et al., 2009; reviewed in London CA, 2013). Masitinib (Kinavet, AB Science, Short Hills, NJ) has also been shown to prolong the disease-free intervals in dogs with MCTs independently of the presence of c-kit mutations; however, it is no longer available in the United States. Adverse effects in dogs receiving small molecule TKI are mainly anorexia, vomiting, or diarrhea, and are dose dependent. These can be seen in up to 50% of dogs receiving TKI therapy.

MAST CELL TUMORS IN CATS

Etiology and Epidemiology

Although MCTs are relatively common in cats, they rarely result in the considerable clinical problems seen in dogs with this neoplasm. Most cats with MCTs are middle-aged or older (median, 10 years old), with apparently no gender-related predilection, although some purebred cats may be at higher risk of development (Siamese, Burmese, Russian Blue, Ragdoll) (Melville et al., 2015). Feline leukemia virus and feline immunodeficiency virus do not play a role in the development of this tumor.

As opposed to the dog in which most MCTs are cutaneous or subcutaneous, cats exhibit two main forms of feline MCTs: cutaneous MCT, splenic or visceral mast cell disease, and intestinal MCT. Although they may coexist in the same cat, most often these disease entities occur singularly.

Clinical and Pathologic Features

Visceral MCTs are most commonly seen in the spleen of cats, and involvement of the liver, abdominal lymph nodes, bone marrow, and peripheral blood are often found. Most affected cats initially have nonspecific signs such as anorexia and vomiting; abdominal distention caused by massive splenomegaly is a consistent feature. As in dogs, the hematologic abnormalities in cats with SMCD are extremely variable and include cytopenias, mastocythemia, basophilia, eosinophilia, or a combination of these; however, a high percentage of cats may have normal CBCs.

Intestinal MCTs are the third most common type of intestinal tumor in cats. Cats with intestinal MCTs are usually evaluated because of gastrointestinal signs such as anorexia, vomiting, or diarrhea. Abdominal masses are palpated in approximately one half of these cats. Most tumors involve the small intestine, where they can be solitary or multiple. Metastatic disease affecting the mesenteric lymph nodes, liver, spleen, and lungs is commonly found at the time of presentation. Multiple intestinal masses in cats are most commonly associated with lymphoma and with MCT, although both neoplasms can coexist. Gastrointestinal tract ulceration has also been documented in affected cats.

Cats with cutaneous MCTs usually initially have solitary or multiple, small (2-15 mm), white to pink dermoepidermal masses, primarily in the head and neck regions, although solitary dermoepidermal or subcutaneous masses also occur in other locations. It has been reported that, on the basis of the clinical, epidemiologic, and histologic features, MCTs in cats can be classified as either mast cell–type MCTs (common) or histiocytic-type MCTs (rare). Cats with mast cell–type MCTs are usually older than 4 years of age and have solitary dermal masses; Siamese cats may have a predilection. Cats with histiocytic-type MCTs are primarily younger Siamese cats, generally under the age of 4 years. Typically, such cats have multiple (miliary) subcutaneous masses that exhibit a benign biologic behavior. Some of these neoplasms appear to regress spontaneously. The subcutaneous MCTs commonly seen in dogs are extremely rare in cats. Unlike the situation in dogs, the histopathologic grade does not appear to correlate well with the biologic behavior of MCTs in cats. There also appears to be a specific syndrome where cats with multiple cutaneous MCTs can also have splenic mast cell disease, so careful abdominal palpation and/or abdominal imaging may be warranted in these cats. In these cats, cutaneous lesions can resolve with splenectomy alone.

Diagnosis and Treatment

The diagnostic approach to cats with MCT is similar to that in dogs. As in dogs, some mast cells in cats are poorly granulated and the granules may not be easily identified during a routine cytologic or histopathologic evaluation.

As a general rule, surgery is indicated for cats with a solitary cutaneous mass, for cats with two to five skin masses, and for cats with intestinal or splenic involvement. As discussed previously, cutaneous MCTs in cats are less aggressive than in dogs, and in most affected cats, removal of a solitary dermoepidermal MCT using a biopsy punch is curative; the same applies to cats with fewer than five dermoepidermal MCTs. Cats with splenic MCT can have prolonged survival times when undergoing splenectomy, even if metastatic disease is present at the time of treatment, with survival times over 1 to 2 years recently reported (Kraus et al., 2015). In the more recent study, there was no definitive benefit seen in cats that received chemotherapy following splenectomy; however, cats that did not undergo splenectomy had a significantly shorter survival than cats those who were splenectomized. If chemotherapy is pursued, the most common agents tend to be corticosteroids (prednisone, dexamethasone), alkylating agents (chlorambucil, lomustine), vinblastine, or TKIs. Cats with intestinal MCTs are generally treated with surgery and/or chemotherapy, and initial survival times were shown to be quite poor due to the presence of metastatic disease in many cats. However, recently, a larger study reported an overall MST of 1.5 years in cats treated with a variety of chemotherapy, surgery, or steroids alone, so more prolonged survivals may be possible even without surgery (Barrett et al., 2018).

We recommend using chlorambucil (20 mg/m^2, PO, q2 weeks) with or without dexamethasone (4-5 mg total dose, q1-2 weeks, PO or subcutaneously) after splenectomy or intestinal MCT removal in cats with systemic disease. In most cases, survival times of 1 to 2 years are common.

INJECTION SITE SARCOMAS IN CATS

An association between injections/vaccination and the development of sarcomas has been recognized in cats since the early 1990s, and epidemiologic studies have confirmed the association. In this syndrome, fibrosarcomas (FSAs) or other types of sarcomas develop in the subcutis or muscle in the interscapular region or the thigh, common sites of injection/vaccination. It is estimated that a sarcoma develops in 1 to 2 of 10,000 cats that receive an injection. Although the exact pathogenesis is still unclear, both the adjuvants and the local immune response against the antigens (i.e., inflammation) have been implicated as causative agents. A recent epidemiologic study reported that cats with injection site sarcoma (ISS) had a higher probability of having received long-acting corticosteroid injections in the interscapular region, whereas cats with rear limb ISS were significantly less likely to have received recombinant vaccines than inactivated vaccines (Shrivastav et al., 2012).

Despite changes in vaccination recommendations in 2001 to administer rabies vaccine in the right rear leg as distally as possible, the feline leukemia virus (FeLV) vaccine in the left rear leg as distally as possible, and the FVRCP±C vaccine in the right shoulder, a high proportion of tumors still develops in the interscapular region (Shaw et al., 2009). Current vaccination protocols for cats should be evaluated by general practitioners, so that safe vaccination practices are routinely used (see Recommended Reading for the most recent American Association of Feline Practitioners (AAFP) guidelines).

A rapidly growing soft tissue mass develops in the region weeks to months after vaccination or injection in cats with ISSs. A vaccine- or injection-associated inflammatory reaction may precede the development of this neoplasm. Therefore an ISS should be suspected in any cat with a superficial or deep mass in the interscapular or thigh regions, and every effort should be made to establish a diagnosis immediately. The current recommendation is to use the "3, 2, 1 Rule": worry if the mass persists for more than 3 months after vaccination, is larger than 2 cm in diameter, or grows 1 month after the injection.

Although FNA findings may provide a definitive answer, more often an incisional or needle biopsy is necessary because sarcomas do not consistently exfoliate cells (see Chapter 71). However, excisional biopsies are not recommended, as shorter survival times may be seen in cats that have undergone an excisional biopsy prior to definitive treatment.

Although most FSAs in dogs and cats have a low metastatic potential, ISSs are quite aggressive and should be treated accordingly. Although multiple studies are currently in progress, on the basis of the results of studies reported in the literature and on the findings in cats seen at the author's clinic, the rate of metastases of ISSs can be high (probably as high as 50%-70% in cats with recurrent tumors). Pulmonary metastatic lesions can be detected at presentation in up to 20% of cats with ISSs.

The treatment of choice for cats with ISS is *aggressive surgical excision* (see Chapter 75). In keeping with the maxim "cut it once, but cut it all," an *en bloc* resection (to include any biopsy tracts) should be performed immediately after the diagnosis is established, provided there is no metastatic disease (Phelps et al., 2011). Cats treated with aggressive surgery have significantly longer disease-free survival times than cats treated with conservative surgery (274 versus 66 days); also, cats with tumors in the limbs have significantly longer disease-free survival times than cats with tumors in the trunk (325 versus 66 days; Hershey et al., 2000). Cats that experience local recurrence after the first aggressive surgery have significantly shorter MSTs than those without recurrence (365 versus 1100 days [Romanelli et al., 2008] and 499 versus 1461 days [Phelps et al., 2011]); as expected, cats with metastases at presentation also have shorter MSTs than those without distant metastases (165 versus 930 days [Romanelli et al., 2008] and 388 versus 1528 days [Phelps et al., 2011]). Complete surgical excision of a relatively small ISS (i.e., <2 cm in diameter) is usually associated with long-term remissions and even cure. Although the role of postoperative adjuvant chemotherapy has not been thoroughly evaluated, cats with large or incompletely excised tumors may benefit from treatment with mitoxantrone and

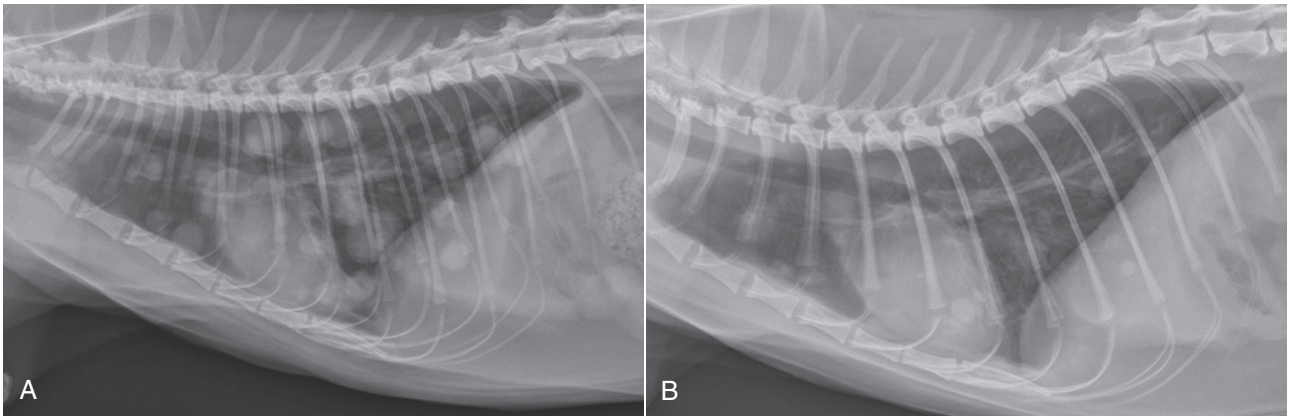


FIG 81.9
Left lateral thoracic radiographs in a cat with an injection site sarcoma and metastatic pulmonary disease before **(A)** and after doxorubicin/cyclophosphamide chemotherapy **(B).** Note marked reduction in the size of the pulmonary nodules.

cyclophosphamide, doxorubicin and cyclophosphamide, or carboplatin. One of the author's clinics has seen objective complete or partial responses in cats with nonresectable or metastatic ISS treated with doxorubicin/cyclophosphamide combinations (Fig. 81.9) or with carboplatin alone; some of these cats have been in remission for longer than 1 year. If metastatic disease is already present, chemotherapy is not usually effective.

In cats with nonresectable, high-grade ISS, the authors have seen objective responses to doxorubicin/cyclophosphamide or doxorubicin/lomustine chemotherapy, and neoadjuvant chemotherapy (i.e., chemotherapy to decrease the size of the mass, then surgery, then additional chemotherapy) has been used successfully in cats with high-grade ISS in the clinic. Small molecule TKIs are currently being investigated in cats with ISSs; however, initial studies have not shown overwhelming response rates.

Suggested Readings

Alvarez FJ, et al. Treatment of dogs with stage III hemangiosarcoma using the VAC protocol. *J Am Anim Hosp Assoc*. 2013;49(6):370.

Bertazzolo W, et al. Canine angiosarcoma: cytologic, histologic, and immunohistochemical correlations. *Vet Clin Pathol*. 2005;34:28.

Boston SE, et al. Concurrent splenic and right atrial mass at presentation in dogs with HSA: a retrospective study. *J Am Anim Hosp Assoc*. 2011;47:336.

Brown DC, et al. Single agent polysaccharopeptide delays metastases and improves survival in naturally occurring hemangiosarcoma. *Evid Based Complement Alternat Med*. 2012.

Ferrer L, et al. Immunohistochemical detection of CD31 antigen in normal and neoplastic canine endothelial cells. *J Comp Pathol*. 1995;112:319.

Hammer AS, et al. Efficacy and toxicity of VAC chemotherapy (vincristine, doxorubicin, and cyclophosphamide) in dogs with hemangiosarcoma. *J Vet Intern Med*. 1991a;5:16.

Lamerato-Kozicki AR, et al. Canine hemangiosarcoma originates from hematopoietic precursors with potential for endothelial differentiation. *Exp Hematol*. 2006;34:870.

Lana S, et al. Continuous low-dose oral chemotherapy for adjuvant therapy of splenic hemangiosarcoma in dogs. *J Vet Intern Med*. 2007;21:764.

Liptak JM, et al. Retroperitoneal sarcomas in dogs: 14 cases (1992-2002). *J Am Vet Med Assoc*. 2004;224:1471.

O'Brien RT. Improved detection of metastatic hepatic hemangiosarcoma nodules with contrast ultrasound in three dogs. *Vet Radiol Ultrasound*. 2007;48:146.

Ogilvie GK, et al. Surgery and doxorubicin in dogs with hemangiosarcoma. *J Vet Intern Med*. 1996;10:379.

Pirie CG, et al. Canine conjunctival hemangioma and hemangiosarcoma: a retrospective evaluation of 108 cases (1989-2004). *Vet Ophthalmol*. 2006;9:215.

Sorenmo KU, et al. Chemotherapy of canine hemangiosarcoma with doxorubicin and cyclophosphamide. *J Vet Intern Med*. 1993;7:370.

Sorenmo KU, et al. Efficacy and toxicity of a dose-intensified doxorubicin protocol in canine hemangiosarcoma. *J Vet Intern Med*. 2004;18:209.

Weisse C, et al. Survival times in dogs with right atrial hemangiosarcoma treated by means of surgical resection with or without adjuvant chemotherapy: 23 cases (1986-2000). *J Am Vet Med Assoc*. 2005;226:575.

Wirth KA, et al. In vitro effects of Yunnan Baiyao on canine hemangiosarcoma cell lines. *Vet Comp Oncol*. 2016;14:281.

Osteosarcoma

Alexander K, et al. A comparison of computed tomography, computed radiography, and film-screen radiography for the detection of canine pulmonary nodules. *Vet Radiol Ultrasound*. 2012;53:258.

Boston SE, et al. Evaluation of survival time in dogs with stage III osteosarcoma that undergo treatment: 90 cases (1985-2004). *J Am Vet Med Assoc*. 1905;228:2006.

Chun R, et al. Toxicity and efficacy of cisplatin and doxorubicin combination chemotherapy for the treatment of canine osteosarcoma. *J Am Anim Hosp Assoc*. 2005;41:382.

Fan TM, et al. Single-agent pamidronate for palliative therapy of canine appendicular osteosarcoma bone pain. *J Vet Intern Med*. 2007;21:431.

Gordon IK, et al. Evaluation of the mammalian target of rapamycin pathway and the effect of rapamycin on target expression and

cellular proliferation in osteosarcoma cells from dogs. *Am J Vet Res*. 2008;69:1079.
Hillers KR, et al. Incidence and prognostic importance of lymph node metastases in dogs with appendicular osteosarcoma: 228 cases (1986-2003). *J Am Vet Med Assoc*. 2005;226:1364.
LaRue SM, et al. Limb-sparing treatment for osteosarcoma in dogs. *J Am Vet Med Assoc*. 1734;195:1989.
Lascelles BD, et al. Improved survival associated with postoperative wound infection in dogs treated with limb-salvage surgery for osteosarcoma. *Ann Surg Oncol*. 2005;12:1073.
Mason NJ, et al. Immunotherapy with a HER2-targeting Listeria induces HER2-specific immunity and demonstrates potential therapeutic effects in a Phase I trial in canine osteosarcoma. *Clin Cancer Res*. 2016;22:4380.
McMahon M, et al. Adjuvant carboplatin and gemcitabine combination chemotherapy postamputation in canine appendicular osteosarcoma. *J Vet Intern Med*. 2011;25:511.
Moore AS, et al. Doxorubicin and BAY 12-9566 for the treatment of osteosarcoma in dogs: a randomized, double-blind, placebo-controlled study. *J Vet Intern Med*. 2007;21:783.
Mueller F, et al. Palliative radiotherapy with electrons of appendicular osteosarcoma in 54 dogs. *In Vivo*. 2005;19:713.
O'Brien MG, et al. Resection of pulmonary metastases in canine osteosarcoma: 36 cases. *Vet Surg*. 1993;22:105.
Rosenberger JA, Pablo NV, Crawford PC. Prevalence of and intrinsic risk factors for appendicular osteosarcoma in dogs: 179 cases (1996-2005). *J Am Vet Med Assoc*. 2007;231:1076.
Rowell JL, McCarthy DO, Alvarez CE. Dog models of naturally occurring cancer. *Trends Mol Med*. 2011;17:380.
Rubin JA, et al. Factors associated with pathological fractures in dogs with appendicular primary bone neoplasia: 84 cases (2007-2013). *J Am Vet Med Assoc*. 2015;247:917.
Sabattini S, et al. Comparative assessment of the accuracy of cytologic and histologic biopsies in the diagnosis of canine bone lesions. *J Vet Intern Med*. 2017;31:864.
Selmic LE, et al. Outcome and prognostic factors for osteosarcoma of the maxilla, mandible, or calvarium in dogs: 183 cases (1986-2012). *J Am Vet Med Assoc*. 2014;245:930.

Mast Cell Tumors

Barrett LE, et al. Outcome following treatment of feline gastrointestinal mast cell tumours. *Vet Comp Oncol*. 2018;16:188.
Camus MS, et al. Cytologic criteria for mast cell tumor grading in dogs with evaluation of clinical outcome. *Vet Pathol*. 2016;53:1117.
Carlsten KS, et al. Multicenter prospective trial of hypofractionated radiation treatment, toceranib, and prednisone for measurable canine mast cell tumors. *J Vet Intern Med*. 2012;26:135.
Evans BJ, et al. Treatment outcomes and prognostic factors of feline splenic mast cell tumors: a multi-institutional retrospective study of 64 cases. *Vet Comp Oncol*. 2018;16:20.
Hahn KA, et al. Masitinib is safe and effective for the treatment of canine mast cell tumors. *J Vet Intern Med*. 2008;22:1301.
Henry C, Herrera C. Mast cell tumors in cats: clinical update and possible new treatment avenues. *J Feline Med Surg*. 2013;15:41.
Hosoya K, et al. Adjuvant CCNU (lomustine) and prednisone chemotherapy for dogs with incompletely resected grade 2 mast cell tumors. *J Am Anim Hosp Assoc*. 2009;45:14.
Jones CL, et al. Detection of c-kit mutations in canine mast cell tumors using fluorescent polyacrylamide gel electrophoresis. *J Vet Diagn Invest*. 2004;16:95.
Kiupel M, et al. Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Vet Pathol*. 2011;48:147.
Kraus KA, et al. Outcome and prognostic indicators in cats undergoing splenectomy for splenic mast cell tumors. *J Am Anim Hosp Assoc*. 2015;51:231.
Lejeune A, et al. Aggressive local therapy combined with systemic chemotherapy provides long-term control in grade II stage 2 canine mast cell tumour: 21 cases (1999-2012). *Vet Comp Oncol*. 2015;13:267.
Lepri E, et al. Diagnostic and prognostic features of feline cutaneous mast cell tumours: a retrospective analysis of 40 cases. *Vet Res Commun*. 2003;27 Suppl 1:707.
London CA. Kinase dysfunction and kinase inhibitors. *Vet Dermatol*. 2013;24:181.
London CA, et al. Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision. *Clin Cancer Res*. 2009;15:3856.
Macy DW, et al. Mast cell tumor. In: Withrow SJ, et al, eds. *Clinical veterinary oncology*. Philadelphia: JB Lippincott; 1989.
McManus PM. Frequency and severity of mastocythemia in dogs with and without mast cell tumors: 120 cases (1995-1997). *J Am Vet Med Assoc*. 1999;215:355.
Melville K, et al. Feline cutaneous mast cell tumours: a UK-based study comparing signalment and histological features with long-term outcomes. *J Feline Med Surg*. 2015;17:486.
Mochizuki H, et al. Association of breed and histopathological grade in canine mast cell tumours. *Vet Comp Oncol*. 2017;15:829.
Molander-McCrary H, et al. Cutaneous mast cell tumors in cats: 32 cases (1991-1994). *J Am Anim Hosp Assoc*. 1998;34:281.
Pryer NK, et al. Proof of target for SU11654: inhibition of KIT phosphorylation in canine mast cell tumors. *Clin Cancer Res*. 2003;9:5729.
Romansik EM, et al. Mitotic index is predictive for survival for canine cutaneous mast cell tumors. *Vet Pathol*. 2007;44:335.
Séguin B, et al. Clinical outcome of dogs with grade-II mast cell tumors treated with surgery alone: 55 cases (1996-1999). *J Am Vet Med Assoc*. 2001;218:1120.
Sledge DG, et al. Canine cutaneous mast cell tumors: a combined clinical and pathologic approach to diagnosis, prognosis, and treatment selection. *Vet J*. 2016;215:43.
Stefanello D, et al. Comparison of 2- and 3-category histologic grading systems for predicting the presence of metastasis at the time of initial evaluation in dogs with cutaneous mast cell tumors: 386 cases (2009-2014). *J Am Vet Med Assoc*. 2015;246:765.
Thompson JJ, et al. Canine subcutaneous mast cell tumor: characterization and prognostic indices. *Vet Pathol*. 2011;48:156.
Webster JD, et al. Cellular proliferation in canine cutaneous mast cell tumors: associations with c-KIT and its role in prognostication. *Vet Pathol*. 2007;44:3.

Injection Site Sarcomas

Barber L, et al. Combined doxorubicin and cyclophosphamide chemotherapy for nonresectable feline fibrosarcoma. *J Am Anim Hosp Assoc*. 2000;36:416.
Hershey AE, et al. Prognosis for presumed feline vaccine-associated sarcoma after excision: 61 cases (1986-1996). *J Am Vet Med Assoc*. 2000;216:58.
Holtermann N, et al. The tyrosine kinase inhibitor toceranib in feline injection site sarcoma: efficacy and side effects. *Vet Comp Oncol*. 2017;15:632.
Kass PH, et al. Epidemiologic evidence for a causal relation between vaccination and fibrosarcoma tumorigenesis in cats. *J Am Vet Med Assoc*. 1993;203:396.

Lester S, et al. Vaccine-site associated sarcomas in cats: clinical experience and a laboratory review (1982-1993). *J Am Anim Hosp Assoc*. 1996;32:91.

Phelps HA, et al. Radical excision with five-centimeter margins for treatment of feline injection-site sarcomas: 91 cases (1998-2002). *J Am Vet Med Assoc*. 2011;239:97.

Romanelli G, et al. Analysis of prognostic factors associated with injection-site sarcomas in cats: 57 cases (2001-2007). *J Am Vet Med Assoc*. 2008;232:1193.

Scherk MA, et al. AAFP feline vaccination advisory panel report. *J Feline Med Surg*. 2013;15(785):2013.

Shaw SC, et al. Temporal changes in characteristics of injection-site sarcomas in cats: 392 cases (1990-2006). *J Am Vet Med Assoc*. 2009;234:376.

Shrivastav A, et al. Comparative vaccine-specific and other injectable-specific risks of injection-site sarcomas in cats. *J Am Vet Med Assoc*. 2012;241:595.

Wilcock B, et al. Feline postvaccinal sarcomas: 20 years later. *Can Vet J*. 2012;53:430.



Cancer Chemotherapy Protocols Commonly Used by the Authors

1. Lymphoma
   A. Induction of remission
      1. COP protocol (8-week duration)
         Cyclophosphamide: 50 mg/m^2 PO q48h for 8 weeks in dogs; 200-300 mg/m^2 PO q3 weeks in cats
         Vincristine: 0.5 mg/m^2 IV once per week for 8 weeks
         Prednisone: 40-50 mg/m^2 PO q24h for 1 week; then 20-25 mg/m^2 PO q48h for 7 weeks
      2. COAP protocol
         Cyclophosphamide: 50 mg/m^2 PO q48h or 300 mg/m^2 PO q3 weeks*
         Vincristine: 0.5 mg/m^2 IV once per week
         Cytosine arabinoside: 100 mg/m^2, IV or SC, divided q12h for 4 days
         Prednisone: 40-50 mg/m^2 PO q24h for 1 week; then 20-25 mg/m^2 PO q48h
         In cats, cytosine arabinoside is administered for only 2 days and the remaining three drugs (cyclophosphamide, vincristine, prednisone) are administered for 6 weeks rather than 8 weeks.
      3. CLOP protocol
         As in COP protocol but with the addition of L-asparaginase at a dosage of 10,000-20,000 IU/m^2 IM q4-6 weeks
      4. UW-25 protocol (This protocol uses no maintenance chemotherapy—for additional information please see text)
         Week 1: Vincristine: 0.5-0.75 mg/m^2 IV
         Prednisone: 40 mg/m^2 PO q24h
         Week 2: Cyclophosphamide: 200-250 mg/m^2, IV or PO
         Prednisone: 30 mg/m^2 PO q24h
         Week 3: Vincristine: 0.5-0.75 mg/m^2 IV
         Prednisone: 20 mg/m^2 PO q24h
         Week 4: Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV
         Prednisone: 10 mg/m^2 PO q24h
         Week 5: **No treatment—discontinue prednisone if CR**
         Week 6: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 7: Cyclophosphamide: 200-250 mg/m^2, IV or PO
         Week 8: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 9: Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV
         Week 10: **No treatment**
         Week 11: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 13: Cyclophosphamide: 200-250 mg/m^2, IV or PO
         Week 15: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 17: Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV
         Week 18: **No treatment**
         Week 19: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 21: Cyclophosphamide: 200-250 mg/m^2, IV or PO
         Week 23: Vincristine: 0.5-0.75 mg/m^2 IV
         Week 25: Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV
   B. Maintenance
      1. LMP protocol
         Chlorambucil: 20 mg/m^2 PO q2 weeks
         Prednisone: 20-25 mg/m^2 PO q48h
         Methotrexate: 2.5-5 mg/m^2 PO 2 or 3 times per week

Continued

Cancer Chemotherapy Protocols Commonly Used by the Authors—cont'd

2. CCNU/Prednisone protocol
   CCNU (lomustine): 60-70 mg/m^2 PO q3 weeks
   Prednisone: 20-25 mg/m^2 PO q48h
3. LAP protocol
   Chlorambucil: 20 mg/m^2 PO q2 weeks
   Prednisone: 20-25 mg/m^2 PO q48h
   Cytosine arabinoside (Cytosar): 200-400 mg/m^2 SC q2 weeks; alternating with chlorambucil
4. COP protocol used every other week for 6 cycles; then every third week for 6 cycles; then monthly thereafter

C. "Rescue"

DOGS

1. D-MAC protocol (14-day protocol; repeat continuously for 10-16 weeks)
   Dexamethasone: 0.5 mg/lb (1 mg/kg) PO or SC on days 1 and 8
   Actinomycin D (Cosmegen): 0.75 mg/m^2 IV push on day 1
   Cytosine arabinoside (Cytosar): 200-300 mg/m^2 IV drip over 4 hours or SC on day 1
   Melphalan (Alkeran): 20 mg/m^2 PO on day 8 (after 4 doses of melphalan, substitute chlorambucil at the same dose)
2. MOPP protocol (28-day protocol; repeat continuously until relapse)
   Mechlorethamine: 3 mg/m^2 IV on days 0, 7
   Vincristine: 0.7 mg/m^2 IV on days 0, 7
   Procarbazine: 50 mg/m^2 PO q24h for days 0-13
   Prednisone: 30-40 mg/m^2 PO q24h for days 0-13
3. L-asparaginase, CCNU, and prednisone
   CCNU (lomustine): 70 mg/m^2 PO q3 weeks
   L-asparaginase: 400 u/kg SC or IM q3 weeks
   Prednisone: 2 mg/kg PO q24h, taper when remission obtained
4. Dacarbazine: 800-1000 mg/m^2 q14-21 days
5. CCNU (lomustine): 60-80 mg/m^2 q21 days
6. Rabacfosadine: 0.82-1 mg/kg IV over 30 minutes q3 weeks

CATS

1. ACD protocol (21-day cycle)
   Doxorubicin: 1 mg/kg IV on day 1
   Cyclophosphamide: 200-300 mg/m^2 PO on day 10
   Dexamethasone: 4 mg/cat PO q1-2 weeks
2. AMD protocol
   Cytosine arabinoside: 100-200 mg/m^2/day IV CRI for 1-2 days
   Mitoxantrone: 4 mg/m^2 in IV CRI, mixed in the bag with the cytosine arabinoside
   Dexamethasone: 0.5-1 mg/lb (1-2 mg/kg) PO weekly; repeat q3 weeks
3. CCNU: 10 mg/cat q3-6 weeks

II. Acute lymphoid leukemia (ALL)
   COAP, CLOP, COP, or CHOP protocols

III. Chronic lymphocytic leukemia (CLL)
1. Chlorambucil: 20 mg/m^2 PO q2 weeks (with or without prednisone, 20 mg/m^2 PO q48h)
2. Cyclophosphamide: 50 mg/m^2 PO q48h, and prednisone: 20 mg/m^2 PO q48h

IV. Acute myelogenous leukemia
1. Cytosine arabinoside: 5-10 mg/m^2 SC q12h for 2-3 weeks; then on alternate weeks
2. Cytosine arabinoside: 100-200 mg/m^2 in IV CRI over 4 hours
   Mitoxantrone: 4-6 mg/m^2 in IV CRI over 4 hours; repeat every 3 weeks

V. Chronic myelogenous leukemia
1. Hydroxyurea (Hydrea): 50 mg/kg PO q24-48h until normal white blood count

VI. Multiple myeloma
1. Melphalan (Alkeran): 2-4 mg/m^2 PO q24h for 1 week; then q48h. Can also be given at 6-8 mg/m^2 PO for 5 days, repeating every 21 days
   Prednisone: 40-50 mg/m^2 PO q24h for 1 week, then 20 mg/m^2 PO q48h
2. As in III.2



Cancer Chemotherapy Protocols Commonly Used by the Authors—cont'd

VII. Mast cell tumors (nonresectable, systemic, or metastatic)
1. Prednisone: 40-50 mg/m^2 PO q24h for 1 week; then 20-25 mg/m^2 PO q48h
2. Lomustine (CCNU): 60 mg/m^2 PO q3 weeks (with or without prednisone as in 1)
3. LVP protocol
Vinblastine: 2 mg/m^2 IV q4-6 weeks alternating with
Lomustine (CCNU): 60 mg/m^2 PO q4-6 weeks
Prednisone: 20-25 mg/m^2 PO q48h
4. Toceranib (Palladia): 2.5 mg/kg, PO q48h
5. Masitinib (Kinavet): 10-12 mg/kg PO q24h

VIII. Soft tissue sarcomas—dogs
1. VAC protocol (21-day cycle)
Vincristine: 0.75 mg/m^2 IV on days 8 and 15
Doxorubicin: 30 mg/m^2 IV (or 1 mg/kg if < 10 kg) on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
Sulfa-trimethoprim: 15 mg/kg PO q12h

IX. Soft tissue sarcomas—cats
1. AC protocol (21-day cycle)
Doxorubicin: 1 mg/kg IV on day 1
Cyclophosphamide: 200-300 mg/m^2 on day 10
2. MiC protocol (21-day cycle)
Mitoxantrone: 4-6 mg/m^2 in IV drip over 4 hours on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
3. Carboplatin: 10 mg/kg IV q4 weeks

X. Osteosarcoma—dogs
1. Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV q2 weeks for 5 doses
2. Carboplatin: 300 mg/m^2 IV q3 weeks for 4-6 doses
3. Doxorubicin and carboplatin as before, alternating drugs q3 weeks for 2-3 doses each

XI. Carcinomas—dogs
1. FAC protocol
5-Fluorouracil: 150 mg/m^2 IV on days 8 and 15
Doxorubicin: 30 mg/m^2 (or 1 mg/kg if < 10 kg) IV on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
Sulfa-trimethoprim: 15 mg/kg PO q12h
2. Carboplatin: 300 mg/m^2 IV q3 weeks
3. Gemcitabine: 675 mg/m^2 IV CRI for 30 minutes, q2 weeks

XII. Carcinomas—cats
5-Fluorouracil is toxic in cats, producing severe, and often fatal, central nervous system signs. Cisplatin is also extremely toxic, causing acute pulmonary toxicity in this species.
1. Carboplatin: 10 mg/kg IV q4 weeks
2. AC protocol (21-day cycle)
Doxorubicin: 1 mg/kg IV on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
3. MiC protocol (21-day cycle)
Mitoxantrone: 4-6 mg/m^2 IV CRI over 4 hours on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
4. MiCO protocol (21-day cycle)
Mitoxantrone: 4-6 mg/m^2 IV CRI over 4 hours on day 1
Cyclophosphamide: 200-300 mg/m^2 PO on day 10
Vincristine: 0.5-0.6 mg/m^2 IV on days 8 and 15

XIII. Metronomic chemotherapy protocol
- Palladia (2.5 mg/kg, PO, Mon, Wed, Fri) plus
- Cyclophosphamide (10 mg/m^2, PO, Tue, Thu, Sat) or chlorambucil (2-4 mg/m^2, PO, Tue, Thu, Sat) plus
- A nonsteroidal antiinflammatory drug at therapeutic dosages plus
- Famotidine (0.5-1 mg/kg PO q24h)

CRI, Constant rate infusion; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *SC,* subcutaneously.
*The daily dose should be divided into two to four daily administrations. The duration of chemotherapy using this protocol varies.

PART THIRTEEN ▪ Hematology

C. Guillermo Couto

CHAPTER 82

Anemia



DEFINITION

Anemia is defined as a decrease in the red blood cell (RBC) mass. In practical terms, it can be defined as a decrease in the packed cell volume (PCV) or hematocrit (HCT), hemoglobin (Hb) concentration, or RBC count below the reference interval (RI) for the species. In the context of this chapter, PCV and HCT are used interchangeably. In special circumstances, anemia is diagnosed in a given patient with an HCT that has decreased over time, even though it may remain within reference values. For example, Greyhounds and other sighthounds (see Chapter 83) rarely have HCT values below 50%, so an anemic Greyhound may have an HCT within the RI for "generic" dogs. Because the RIs reflect the actual status in 95% of the feline and canine population, occasionally an abnormal value is actually normal for a particular animal, prompting a needless evaluation in search of other abnormalities. Remember that anemia rarely constitutes a primary diagnosis; therefore every effort should be made to identify its cause.

In a recent study of 1098 cats with anemia 633 of 1098 (57.7%) were classified as nonregenerative (NRA) and 465 of 1098 (42.3%) as regenerative (RA). The HCT was significantly lower in cats with RA compared with those with NRA ($P < 0.05$) (Furman et al., 2014).

CLINICAL AND CLINICOPATHOLOGIC EVALUATION

When interpreting the HCT, Hb concentration, or RBC count, the clinician should keep in mind that, in some situations, these values are above (e.g., sighthounds) or below (e.g., during puppyhood or pregnancy) the RI for the species. From a practical standpoint, when evaluating the erythroid series, the clinician does not need to assess all the values in the complete blood count (CBC) because several of them provide similar information. For example, the HCT, Hb concentration, and RBC count provide the same type of information—an increase in the number of RBCs usually results in an increased HCT and Hb concentration, and vice versa. Thus when evaluating the erythron in a CBC, the HCT is typically used as an indirect index of the RBC mass (or number).

The main clinical manifestations of anemia in dogs and cats include pale or icteric mucous membranes, lethargy, exercise intolerance, pica (mainly in cats), and decreased overall activity; in dogs, pica is mainly associated with pure red cell aplasia (PRCA, see later; Box 82.1). These clinical signs can be acute or chronic and vary in severity; the duration of the clinical signs may not reflect the mechanism of anemia. For example, acute clinical signs are common in cats with chronic anemia; most cats with chronic anemia compensate by shifting the oxyhemoglobin dissociation curve to the right, thus releasing oxygen to the tissues more readily. Therefore cats are clinically stable until their HCT is markedly decreased (i.e., <10% or so) and they develop acute clinical signs. Owners may also detect some of the adaptive changes to anemia, such as tachycardia or an increased precordial beat. Following are several important questions to ask the owner of an anemic cat or dog when taking a history:

- *Is the pet currently receiving any medication?* Certain drugs can cause hemolysis, gastrointestinal (GI) blood loss, or bone marrow hypoplasia.
- *Have the owners detected any blood loss or dark (tarry) stool?* GI tract bleeding from a tumor or a gastric ulcer frequently lead to iron deficiency anemia (IDA) in dogs.
- *Have the owners noticed any fleas?* Severe flea infestation can cause IDA.
- *Has the cat recently been tested for feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infections?* Retroviruses can cause bone marrow hypoplasia, myelodysplasia, or leukemias, leading to cytopenias.

BOX 82.1

Clinical Manifestations of Anemia in Cats and Dogs

History

- Breed (e.g., congenital enzymopathies, babesiosis in Pitbulls)
- Family history
- Exercise intolerance, syncopal episodes
- Pallor, jaundice
- Localized or generalized bleeding
- FeLV or FIV infection
- Vector-borne diseases (e.g., ehrlichiosis, anaplasmosis, babesiosis)
- Malnutrition, malabsorption
- Chronic inflammation, cancer
- Travel history

Physical Examination

- Pallor, jaundice, petechiae, ecchymoses
- Lymphadenopathy
- Hepatomegaly, splenomegaly
- Tachycardia, heart murmur, cardiomegaly, left ventricular hypertrophy
- Occult blood in the stool
- Hematuria, bilirubinuria

FeLV, Feline leukemia virus; *FIV,* feline immunodeficiency virus.

BOX 82.2

Drugs and Toxins That Can Cause Anemia in Cats and Dogs

Acetaminophen
Antiarrhythmics
Anticonvulsants
Antiinflammatories (nonsteroidal)
Barbiturates
Benzocaine
Chemotherapeutic agents
Chloramphenicol
Cimetidine
Gold salts
Griseofulvin
Levamisole
Methimazole
Methionine
Methylene blue
Metronidazole
Penicillins and cephalosporins
Phenothiazines
Propylthiouracil
Propylene glycol
Sulfa derivatives
Vitamin K
Zinc

- *Has the owner noticed any ticks on the dog?* Ehrlichiosis can cause bone marrow hypoplasia; babesiosis can cause hemolysis.
- *Has the dog been in a fight with a Pitbull? Babesia gibsoni* infection causes signs similar to those of immune-mediated hemolytic anemia, and it is transmitted by Pitbull bites.
- *Has the pet been vaccinated recently?* Modified live vaccines can cause bleeding as a result of platelet dysfunction or thrombocytopenia, or they may be associated with immune-mediated hemolysis.
- *Has the dog received any shots for mismating recently or has urinary incontinence?* Estrogen derivatives can cause bone marrow aplasia or hypoplasia.

In addition to these questions, a detailed travel and pharmacologic history should be obtained. Certain infectious diseases associated with anemia used to have a geographic distribution (e.g., babesiosis in the southeastern part of the United States); however, global warming and worldwide travel have extended the range of most of these infectious agents. In addition, dogs frequently travel throughout the United States; thus the geographic disease distribution is becoming less common. Some drugs and toxins that have been associated with anemia in cats and dogs are listed in Box 82.2; however, as a general rule, any drug can cause any cytopenias in a given patient (i.e., idiosyncratic reaction).

When evaluating a patient with pallor, first one must determine whether it is caused by hypoperfusion or anemia; that is, not every patient with pale mucous membranes is anemic. The simplest approach is to evaluate the HCT and capillary refill time (CRT). Dogs and cats with cardiovascular disease and hypoperfusion usually have normal HCT values and additional clinical signs, whereas symptomatic anemic dogs have low HCT; in addition, anemic dogs and cats almost always have hyperkinetic pulses. Dogs and cats with congestive heart failure can occasionally have dilutional anemia caused by intravascular fluid retention. The CRT may be difficult to evaluate in anemic patients because of the absence of contrast due to the pallor.

The clinician should also look for petechiae, ecchymoses, and evidence of deep bleeding in dogs and cats with pallor. These findings are suggestive of a platelet or clotting factor deficiency (as seen in animals with Evans syndrome, disseminated intravascular coagulation [DIC], or acute leukemias; see Chapter 87), resulting in blood loss anemia. Jaundice is common in dogs but rare in cats with hemolytic anemia; in these patients, the color of the gums is white on yellow, as opposed to white on pink, because the HCT is low. In our clinic, most dogs with jaundice have hemolysis, whereas most cats with jaundice have liver disease.

Particular attention should be paid to the lymphoreticular organs, such as the lymph nodes and spleen, because several disorders associated with anemia may also result in lymphadenopathy, hepatosplenomegaly, or both (Table 82.1). Abdominal radiographs in a dog with intravascular hemolysis may reveal metallic foreign bodies in the stomach, a potential source of zinc that frequently results in intra- and

TABLE 82.1

Disorders Commonly Associated With Anemia and Hepatomegaly, Splenomegaly, and/or Lymphadenopathy

DISORDER	FREQUENCY	SPECIES
Lymphoma	F	D, C
Mycoplasmosis	F	C > D
Acute leukemias	F	C, D
Ehrlichiosis, anaplasmosis, leishmaniasis	F*	D > C
Systemic mast cell disease	R	C > D
Bone marrow hypoplasia	R	C, D
Immune-mediated hemolytic anemia	F	D > C

C, Cat; *D*, dog; *F*, frequent; *R*, rare.
*Geographic variation.

extravascular hemolysis. Abdominal ultrasonography may reveal diffuse splenomegaly with a mottled texture in dogs with anemia caused by immune-mediated hemolysis or in those with lymphoma, leukemias, or malignant histiocytosis.

The degree of anemia may be helpful in establishing its cause. To this end, anemias are graded according to HCT level as follows:

	Dogs	Cats
Mild	30%-36%	20%-24%
Moderate	18%-29%	15%-19%
Severe	<18%	<14%

For example, if an anemic dog or cat has severe anemia, certain causes (e.g., bleeding, anemia of chronic disease [ACD], anemia of renal disease, IDA) can immediately be ruled out because none of those mechanisms is likely to result in such a severe decrease in the HCT; therefore the patient most likely has hemolysis or a bone marrow disorder (see later). The severity of the clinical signs also usually correlates with the pathogenesis of the anemia. For example, a dog or cat with severe anemia and mild to moderate clinical signs more likely has a chronic anemia (e.g., bone marrow disease); acute causes of severe anemia (e.g., hemolysis) result in clinical signs of marked severity because the adaptive compensatory changes have not yet occurred.

As part of the evaluation of a patient's PCV, the plasma should be examined for evidence of icterus (yellow), hemolysis (pink or red), or both (port wine–colored plasma), and the protein content should be determined with a refractometer. The microhematocrit tube should be carefully inspected for evidence of autoagglutination (see p. 1348), and a saline slide agglutination test should be performed (see later). A blood smear should be evaluated to detect morphologic changes that may point the clinician toward the cause of the anemia. Blood smear evaluation is a must, because it provides relevant clinicopathologic information in most patients with anemia.

A common issue that often comes up is whether a general practicing veterinarian should do CBCs in house or send them to a referral laboratory. The introduction of accurate, user-friendly, benchtop hematology analyzers has revolutionized the practice of small animal hematology. Currently, more than 75% of U.S. veterinary practices have their own analyzers. Most of these instruments are trouble-free and provide accurate results. However, when values are outside the RI or are flagged, the clinician or technician should always evaluate a blood smear from the patient in question. The blood smear constitutes the easiest, cheapest quality control for the instrument; yet, it is only evaluated by <5% of veterinarians.

New benchtop analyzers frequently provide a graphic depiction of the cell distribution (dot plot, histogram, or cytogram). Depending on the instrument, these dot plots provide clinically relevant information regarding cell size, distribution, presence of reticulocytes, left shift, nucleated RBCs, and other cell features. Representative dot plots of a normal dog and a normal cat are depicted in Fig. 82.1. The graphics provide powerful statistically relevant information. For example, with flow cytometry analyzers, the RBC graphs include approximately 80,000 erythrocytes, whereas the leukocyte graphs contain approximately 15,000 cells. For comparison, when we perform a manual leukocyte differential count, we evaluate 100 cells. Think about how long it would take us to evaluate 80,000 erythrocytes and 15,000 leukocytes in a blood smear under the microscope! As I like to say, "it's a numbers game."

Once it has been established that the patient is anemic, it should be determined whether the anemia is regenerative, nonregenerative, or due to IDA. This is accomplished by obtaining a reticulocyte count during a routine CBC (some of the in-house flow cytometry analyzers, such as the LaserCyte and ProCyteDx from IDEXX Laboratories, Westbrook, Maine, provide reticulocyte counts), obtaining a reticulocyte count from the reference laboratory, or simply evaluating a blood smear for the presence of polychromasia (Fig. 82.2). The RBC indices reported by impedance analyzers are extremely unreliable to determine regeneration; approximately 8% to 11% of dogs with regenerative anemia have the typical macrocytic hypochromic indices described in the literature; however, >70% have high red cell distribution width (RDW) and/or polychromasia (Hodges and Christopher, 2011).

Visual evaluation of the RBC dot plot allows easy classification of the anemias as regenerative, nonregenerative, or IDA (Fig. 82.3). This reflects the pathogenesis of the anemia, thereby dictating the most logical diagnostic and therapeutic approach (Box 82.3).

In brief, regenerative anemias always stem from extramedullar causes because the presence of reticulocytes or polychromatophilic RBCs (immature RBCs) in the circulation is a clear indication of a functional bone marrow; regenerative anemias can result *only* from hemolysis or blood loss.

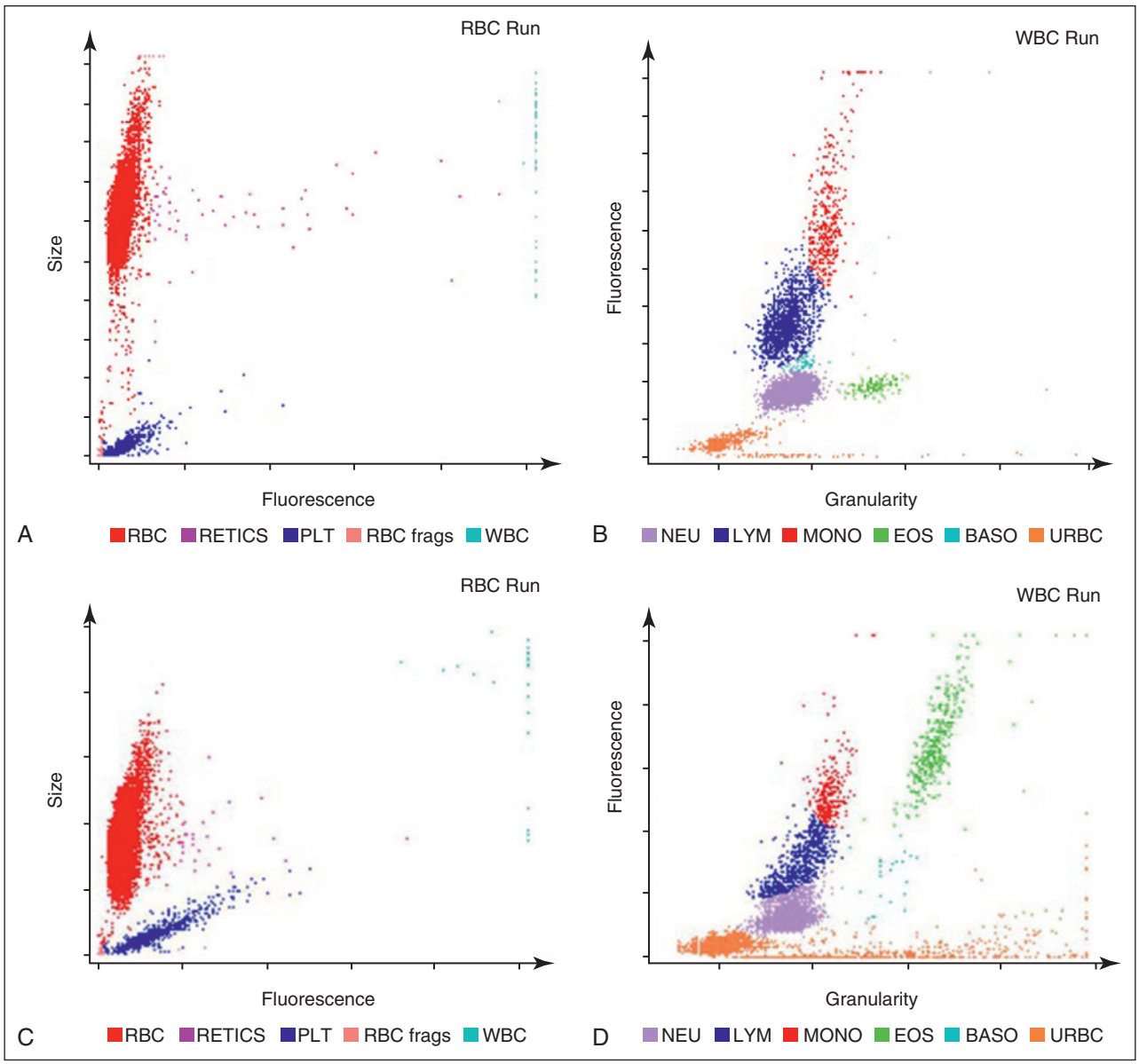


FIG 82.1
Dot plots of normal dog and cat. **(A)** and **(B)** Normal red blood cell (RBC) and white blood cell (WBC) dot plots in a normal dog. **(C)** and **(D)** Normal RBC and WBC dot plots in a normal cat. In the RBC graph, the *vertical axis* depicts size, and the *horizontal axis* shows fluorescence (RNA or DNA content). *Red dots* represent RBCs; *purple dots,* reticulocytes (RETICS); and *blue dots,* platelets (PLT). In the WBC dot plots, the vertical axis depicts fluorescence, a measure of nuclear size and complexity, whereas the horizontal axis depicts granularity (cytoplasmic complexity). *Lavender dots* represent neutrophils (NEU); *green dots,* eosinophils (EOS); *teal dots,* basophils (BASO); *blue dots,* lymphocytes (LYM); and *red dots,* monocytes (MONO). *Orange dots* are unlysed RBCs (URBC).

Nonregenerative anemias can be caused by bone marrow or extramarrow disorders, such as erythroid hypoproliferation, chronic inflammatory disease, and chronic kidney disease (CKD); obviously, anemias caused by acute hemorrhage or hemolysis are nonregenerative for the first 48 to 96 hours. Although IDA was traditionally classified as nonregenerative, most dogs with chronic blood loss leading to IDA display a mild to moderate degree of regeneration, and the RBC indices are different than in other nonregenerative anemias (i.e., they are microcytic and hypochromic; see later). Therefore I prefer to classify IDA in a separate category. Regenerative anemias are usually acute, whereas nonregenerative and IDAs are chronic.

During the initial clinical evaluation of an anemic patient, examination of the blood smear or dot plots usually suffices to determine whether the bone marrow is responding

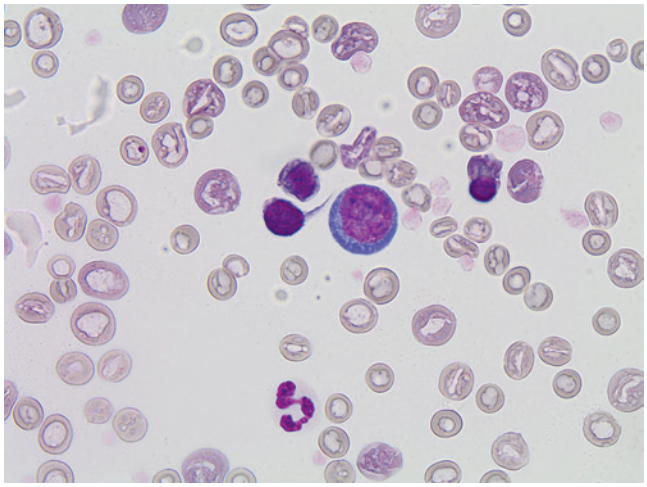


FIG 82.2
Strongly regenerative anemia in a dog depicting anisocytosis, polychromasia, and nucleated RBCs, including a large immature rubricyte *(middle)* (×1000).

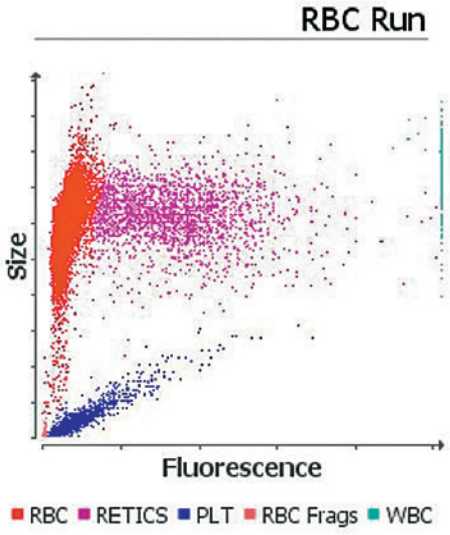


FIG 82.3
RBC dot plot of a dog with strongly regenerative anemia (reticulocyte count, 360,000/µL) due to immune mediated hemolysis. Note the large reticulocyte cloud in purple (RETICS). Fig. 82.1, *A*, depicts a normal canine RBC dot plot for comparison. *PLT,* Platelets.

appropriately to the anemia (i.e., whether the anemia is regenerative or not; see Figs. 82.2 and 82.3). Several pieces of information can be acquired during the examination of a good-quality, properly stained blood smear, including the RBC size and morphology, approximate numbers and morphology of white blood cells and platelets, and presence of autoagglutination, nucleated RBCs, hypochromasia (IDA), polychromasia (indicative of regeneration), and RBC parasites. Ideally, the clinician or technician should *always* perform this cursory evaluation of the blood smear; a blood sample should be submitted to a diagnostic laboratory for further analysis and evaluation by a clinical pathologist if

BOX 82.3

Pathogenetic Classification of Anemias

Regenerative

Blood loss (after 48-96 hours)
Hemolysis

Semiregenerative

IDA

Nonregenerative

ACD
ARD
Bone marrow disorder
Blood loss/hemolysis (first 48-96 hours)
Endocrine anemia

ACD, Anemia of chronic disease; *ARD,* anemia of renal disease; *IDA,* iron deficiency anemia.

the diagnosis is still uncertain after evaluating the blood smear. Some of the abnormalities detected during a careful examination of the blood smear and their clinical implications are summarized in Table 82.2. This evaluation should be conducted under an oil immersion lens in a monolayer field in which the erythrocytes are in a single layer and 50% of the cells are touching.

A CBC and reticulocyte count in an anemic patient provide more absolute data by which to assess the degree of regeneration. However, the information presented here must be used cautiously because the number of reticulocytes should increase proportionally to the decrease in the HCT. For example, a reticulocyte count of 120,000/µL (or ≈4%) represents an appropriate response for a dog with an HCT of 30% but not for one with an HCT of 10%.

With the advent of automated analyzers that provide reticulocyte counts, it has become apparent that up to 10% of dogs with normal HCT have a high reticulocyte count. We now know that excitement causes the release of reticulocytes from the spleen into systemic circulation; hence, an excited dog will likely have a higher reticulocyte count than a calm one. Approximately half of the dogs with a normal HCT and high reticulocyte count have catecholamine-related splenic release of reticulocytes. The other half are the most important ones: they are usually dogs with early immune-mediated hemolysis or with hemangiosarcoma (HSA); they are not yet sufficiently anemic, but they are regenerating. Therefore a blood smear should always be evaluated in a dog with reticulocytosis, regardless of the HCT.

Overall, normal dogs and cats with a normal HCT have less than 100,000 reticulocytes/µL and 50,000 reticulocytes/µL, respectively. Most dogs have between 10,000 and 60,000/µL. As noted, when evaluating dot plots from a LaserCyte or ProCyteDx (IDEXX), the presence of a large reticulocyte cloud is almost always indicative of regeneration (see Fig. 82.3); however, given that dogs with IDA frequently have reticulocytosis, the MCV and MCHC should also be evaluated.

TABLE 82.2

Interpretation of Morphologic RBC Abnormalities in Cats and Dogs

MORPHOLOGIC ABNORMALITY	COMMONLY ASSOCIATED DISORDERS
Macrocytosis	Regeneration, breed-related feature (Poodles); FeLV infection; dyserythropoiesis (bone marrow disease)
Microcytosis	Iron deficiency; breed-related characteristic (Akita, Shar Pei, Shiba Inu); portosystemic shunt or microvascular dysplasia; PRCA; polycythemia (erythrocytosis); inflammation
Hypochromasia	Iron deficiency
Polychromasia	Regeneration
Poikilocytosis	Regeneration; iron deficiency; hyposplenism
Schistocytosis (fragments)	Microangiopathy; hemangiosarcoma; DIC; hyposplenism
Spherocytosis	IHA; hemophagocytic malignant histiocytosis; babesiosis; zinc toxicity
Acanthocytosis (spur cells)	Hemangiosarcoma; lymphoma; other malignancies; liver disease; hyposplenism
Echinocytosis (burr cells)	Artifact; renal disease; pyruvate kinase deficiency anemia
Elliptocytosis	Congenital elliptocytosis (dogs)
Heinz bodies	Oxidative insult to RBCs
Howell-Jolly bodies	Regeneration; hyposplenism
Autoagglutination	IHA
Metarubricytosis	Breed-related characteristic (Schnauzer, Dachshund); extramedullary hematopoiesis; regeneration; lead toxicity; hemangiosarcoma
Leukopenia	See text.
Thrombocytopenia	See text.
Pancytopenia	Bone marrow disorder; hypersplenism

DIC, Disseminated intravascular coagulation; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *IHA,* immune hemolytic anemia; *PRCA,* pure red cell aplasia; *RBC,* red blood cell.
Modified from Couto CG et al.: Hematologic and oncologic emergencies. In Murtaugh R et al., editors: *Veterinary emergency and critical care medicine,* St Louis, 1992, Mosby.

Dogs with high reticulocyte counts and microcytosis/hypochromasia typically have IDA.

The following points generally hold true:

1. If the RBC indices are macrocytic and hypochromic, the anemia is most likely associated with the presence of high numbers of reticulocytes, which are larger and contain less Hb than mature RBCs. Therefore the anemia is likely regenerative. However, >85% of regenerative anemias are normocytic normochromic or normocytic hypochromic.
2. If the reticulocyte count is higher than 120,000/µL (or ≈4%) and the anemia is mild to moderate, the anemia is likely regenerative.
3. As part of the evaluation of a patient with regenerative anemia, it is beneficial to determine the serum or plasma protein concentration because blood loss usually results in hypoproteinemia and hemolysis does not. Other physical examination and clinicopathologic findings that help distinguish blood loss from hemolytic anemias are listed in Table 82.3.

MANAGEMENT OF THE ANEMIC PATIENT

The first basic principle of the management of anemic (or bleeding) patients is to collect all blood samples before instituting any therapy. Because the condition in most of these patients may constitute a true emergency at the time of presentation, samples often are not collected until the patient has been completely stabilized, resulting in treatment-induced changes in hematologic or serum biochemical values.

REGENERATIVE ANEMIAS

Blood Loss Anemia

Acute blood loss in otherwise normal dogs and cats results in reticulocytosis (regeneration) within 48 to 96 hours. Therefore animals evaluated shortly after a traumatic injury and severe blood loss usually have a nonregenerative anemia with a low to normal serum (plasma) protein concentration. The source of bleeding should be identified and the bleeding

TABLE 82.3

Criteria for Differentiating Blood Loss From Hemolytic Anemias

VARIABLE	BLOOD LOSS	HEMOLYSIS
Serum (plasma) protein concentration	Normal-low	Normal-high
Evidence of bleeding	Common	Rare
Icterus	No	Common
Hemoglobinemia	No	Common
Spherocytosis	No	Common
Hemosiderinuria	No	Yes
Autoagglutination	No	Occasional
Direct Coombs test	Negative	Usually positive (in IHA)
Splenomegaly	No	Common
RBC changes	No	Common (see Table 82.2)

IHA, Immune hemolytic anemia; *RBC,* red blood cell.
From Couto CG et al.: Hematologic and oncologic emergencies. In Murtaugh R et al., editors: *Veterinary emergency and critical care medicine,* St Louis, 1992, Mosby, p 359.

stopped; if the patient is bleeding as a result of a systemic hemostatic defect, it should be identified and specific treatment should be initiated (see Chapter 87). Aggressive intravenous (IV) fluid therapy with crystalloids or colloids or the transfusion of blood or blood components is often required in patients with anemia caused by acute blood loss (see p. 1355).

Hemolytic Anemia

In humans, the bone marrow is capable of undergoing hyperplasia until its production rate is increased approximately sixfold to eightfold; the same is probably true for dogs and cats. As a consequence, a considerable number of RBCs must be destroyed before anemia develops. As noted, some dogs and cats with a normal HCT have high numbers of circulating reticulocytes; if the serum bilirubin concentration is marginally increased, or if there is hemoglobinuria or bilirubinuria, hemolysis should be suspected in these patients. Regardless, a blood smear should be evaluated in every dog or cat with reticulocytosis to identify morphologic RBC changes, independently of whether the HCT is normal or low. As discussed earlier, the presence of reticulocytosis in dogs with normal HCT allows for early diagnosis of common diseases such as immune-mediated hemolysis and HSA.

As is the case in cats and dogs with blood loss anemia, patients with peracute hemolysis can be in a nonregenerative state at the time of presentation because the bone marrow has not yet been able to mount a regenerative response. In addition, in some dogs with immune-mediated hemolysis, the destruction of erythroid precursors in the bone marrow results in a lack of regeneration (PRCA; see later).

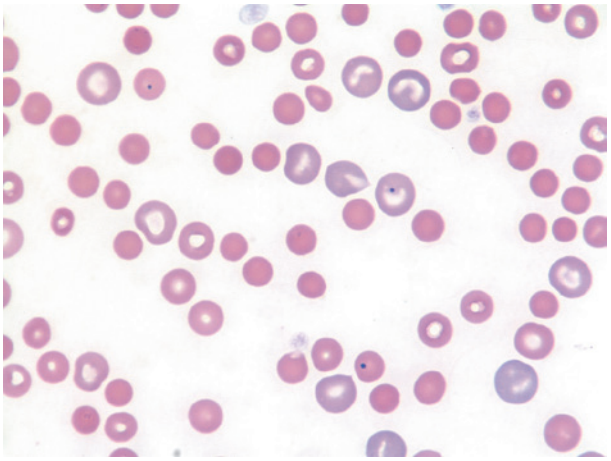


FIG 82.4
Abundant spherocytes in the blood smear of a dog with immune-mediated hemolytic anemia (IHA). Some erythrocytes and polychromatophilic erythrocytes contain Howell-Jolly bodies.

On the basis of their pathogenesis, hemolytic anemias can be classified as extravascular (i.e., the RBCs are destroyed by the mononuclear-phagocytic cells) or intravascular (i.e., the RBCs are lysed by antibody and complement, drugs, toxins, or by hitting fibrin strands). In addition, on the basis of the age of the animal at onset, anemias can be classified as congenital or acquired (Table 82.4). Most dogs and cats with hemolytic anemia seen at our clinic have acquired extravascular hemolysis.

In extravascular hemolysis, RBCs are phagocytosed by the mononuclear-phagocytic system (MPS) in the spleen, liver, and bone marrow. Stimuli that trigger RBC phagocytosis consist mainly of intracellular inclusions, such as RBC parasites or Heinz bodies and membrane coating with immunoglobulin G (IgG) or IgM (common in dogs). Congenital RBC enzymopathies can also precipitate extravascular hemolysis. Once abnormal RBCs are recognized, the MPS rapidly phagocytoses them, resulting in a decrease in the number of circulating RBCs and the generation of cells with specific morphologic changes (e.g., spherocytes). Anemia develops if the destruction of RBCs continues. Spherocytes are RBC "leftovers"; after a mononuclear-phagocytic cell takes "bites" off the cytoplasm and membrane, the membrane is resealed. The RBC then loses its redundant membrane and consequently its central pallor (Fig. 82.4). Spherocytes are characteristic of immune hemolytic anemia (IHA), although they can be seen in other disorders, such as *Babesia gibsoni* infection, zinc toxicity, or hemophagocytic malignant histiocytosis; they also appear in the recipient after transfusion of stored blood. Immune hemolysis is the most common cause of extravascular hemolytic anemia in dogs in our clinic. Drug-associated hemolysis (e.g., β-lactam antibiotics) and mycoplasmosis (formerly known as hemobartonellosis) are

TABLE 82.4

Causes of Hemolytic Anemia in Dogs and Cats

DISORDER	SPECIES	BREED
Congenital (Inherited?)		
Pyruvate kinase deficiency	D, C	*Dogs:* Basenji, Beagle, West Highland White Terrier, Cairn Terrier, Poodle, Dachshund, Chihuahua, Pug, Beagle, Labrador Retriever, American Eskimo *Cats:* Abyssinian, Somali, Bengal, Egyptian Mau, La Perm, Maine Coon cat, Norwegian Forest cat, Savannah, Siberian, Singapura, domestic short-haired cat
PFK deficiency	D	English Springer Spaniel, Cocker Spaniel, Whippet, Wachtelhund
Stomatocytosis	D	Alaskan Malamute, Miniature Schnauzer
Nonspherocytic hemolytic anemia	D	Poodle, Beagle
Acquired		
IHA	D > C	All
Neonatal isoerythrolysis	C	British breeds, Abyssinian, Somali (other type B cats)
Microangiopathic hemolytic anemia	D > C	All
Infectious		
Mycoplasmosis	C > D	All
Babesiosis	D > C	All (Pitbulls and *Babesia gibsoni*)
Cytauxzoonosis	C	All
Ehrlichiosis (uncommon)	D > C	All
Hypophosphatemia	D, C	All
Oxidants		
Acetaminophen	C	All
Phenothiazines	D, C	All
Benzocaine	C	All
Vitamin K	D, C	All
Methylene blue	C > D	All
Methionine	C	All
Propylene glycol	C	All
Zinc	D	All
Drugs That Can Cause Immune Hemolysis		
Sulfa drugs	D > C	Doberman, Labrador Retriever
Barbiturates	D	All
Penicillins and cephalosporins	D > C	All
Propylthiouracil	C	All
Methimazole	C	All
Antiarrhythmics (?)	D	All
Zinc	D	All

C, Cat; *D,* dog; *IHA,* immune hemolytic anemia; *PFK,* phosphofructokinase.
Modified from Couto CG et al.: Hematologic and oncologic emergencies. In Murtaugh R et al., editors: *Veterinary emergency and critical care medicine,* St Louis, 1992, Mosby, p 359.

the two most common causes in cats, although IHA is now more common in this species. Other causes of extravascular hemolytic anemia in dogs and cats are listed in Table 82.4.

Intravascular hemolysis can occur as a consequence of direct RBC lysis caused by antibodies that activate complement (e.g., immune-mediated hemolysis with a high concentration of IgG or IgM), infectious agents (e.g., *Babesia canis* infection), drugs or toxins (e.g., zinc in pennies minted after 1983, in pet carrier bolts, other hardware, and zinc oxide–containing ointments), metabolic imbalances (e.g., hypophosphatemia in dogs and cats with diabetes mellitus treated with insulin), or increased shearing of RBCs (e.g., microangiopathy, DIC). Intravascular hemolysis is considerably less common in dogs and cats than extravascular hemolysis, with the notable exception of DIC in dogs with HSA, zinc toxicity, and hypophosphatemia. Certain congenital enzymopathies (e.g., phosphofructokinase [PFK] deficiency) in dogs also result primarily in intravascular hemolysis.

Dogs with congenital (frequently familial) hemolytic anemias may have relatively prolonged clinical courses at the time of presentation, with the notable exception of English Springer Spaniels with PFK deficiency–associated hemolysis, in which acute hemolytic episodes occur after they hyperventilate during excitement (e.g., going to the veterinarian or field work) due to alkaline hemolysis.

Dogs and cats with acquired hemolytic anemias are usually evaluated because of acute clinical signs consisting of pallor, with or without icterus (in my experience, only approximately 50% of dogs and a much lower percentage of cats with hemolytic anemia are icteric); diffuse splenomegaly may be a prominent finding. If the patient has associated thrombocytopenia (e.g., Evans syndrome, DIC), petechiae and ecchymoses may be present. Clinical signs and physical examination findings associated with the primary disease can also be present in cases of secondary hemolytic anemias; however, as opposed to humans, they are extremely rare in dogs and cats.

In the evaluation of dogs or cats with hemolytic anemia, a careful examination of the blood smear is mandatory. Morphologic abnormalities pathognomonic for or highly suggestive of a particular cause are often detected with this method (see Table 82.2). In specific circumstances, capillary blood should also be evaluated. In dogs with *B. gibsoni* infection (mainly Pitbulls), the organism is rarely visualized in peripheral blood but is often obvious in capillary blood from the pinna (Fig. 82.5). We collect blood from the tip of the pinna after constricting it for a few seconds and applying alcohol to induce vasodilation. After puncturing the pinna with a 20-gauge needle, we collect a drop of seeping blood with a microhematocrit tube and use it to make a smear. In my experience, *B. gibsoni* organisms are easier to visualize when using Diff-Quik than Giemsa or Wright-Giemsa stain.

The sample should also be tested for autoagglutination by placing a large drop of anticoagulated blood on a glass slide at room temperature and at 4° C (Fig. 82.6). Autoagglutination occurs when large amounts of Ig are bound to the RBC so that the molecules tangle with molecules in adjoining

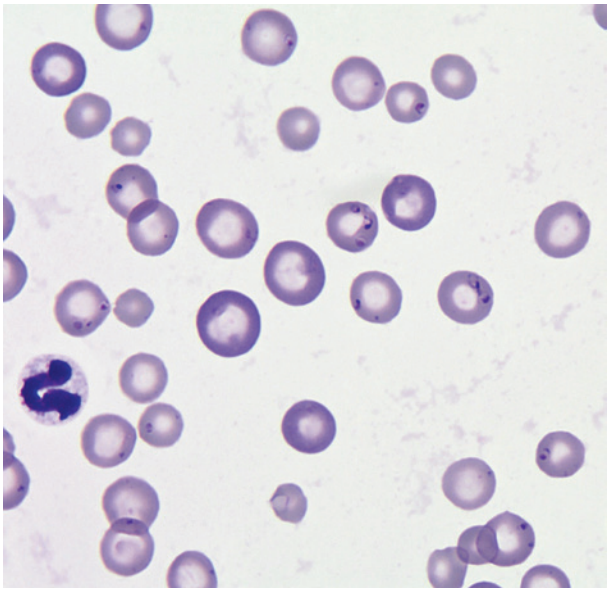


FIG 82.5
Large numbers of *B. gibsoni* in Diff-Quik stained capillary blood of a 7-year-old, female spayed Pitbull shortly after undergoing a splenectomy (×1000).

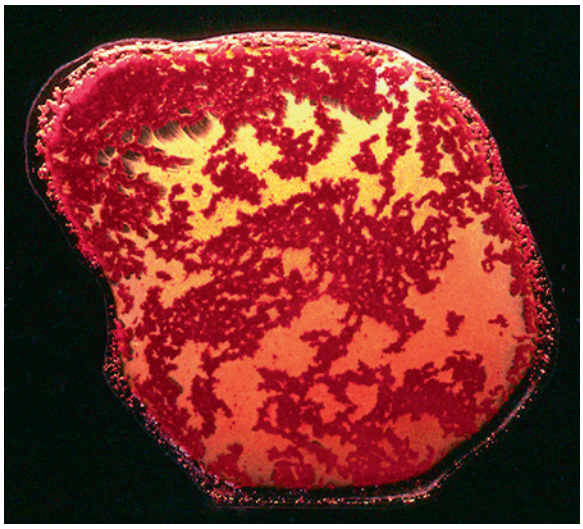


FIG 82.6
Marked saline autoagglutination in a dog with immune hemolytic anemia (IHA).

RBCs, and cause agglutination; it is sometimes referred to as Mother Nature's Coombs test (see later). It can be distinguished from rouleaux formation by adding saline solution, which disaggregates rouleaux; rouleaux formation is common in cats but rare in dogs. An easy way to do this is to place a drop of anticoagulated blood on a glass slide, adding a coverslip, and "shooting" saline solution underneath the coverslip (by capillarity) using a pipette.

A direct Coombs test to detect RBC-bound Ig should be performed in dogs and cats with suspected hemolysis and lack of autoagglutination (see later). As a general rule, the

presence of Ig coating on the RBCs indicates immune-mediated hemolysis. A positive Coombs test result should be interpreted with caution, however, because certain drugs and hemoparasites can induce the formation of antibodies that bind to the RBCs, thus causing secondary immune hemolysis (e.g., cats with mycoplasmosis or dogs with babesiosis). The administration of corticosteroids may also result in decreased binding of Ig molecules to the surface of the RBC thus resulting in false-negative results. Direct Coombs tests are usually not necessary in animals with autoagglutination because this phenomenon indicates the presence of Ig on the surface of the RBCs (i.e., biologic Coombs test). Cryoagglutination (i.e., the agglutination of RBCs if the blood sample is refrigerated for 6-8 hours) occurs in a large proportion of cats with mycoplasmosis and is usually associated with an IgM coating on the RBCs; also, more than 50% of cats with mycoplasmosis have a positive direct Coombs test.

If a causative agent cannot be identified (e.g., RBC parasite, drug, pennies in the stomach), the patient should be treated for primary or idiopathic IHA while further test results by, for example, serologic tests or polymerase chain reaction (PCR) assay for hemoparasites are pending. As noted, primary IHA is considerably more common in dogs than in cats; thus every effort should be made to identify a cause of hemolysis in cats, such as drugs or hemoparasites. For a more detailed discussion of IHA, please see the Immunology section.

Hemolytic anemias not associated with immune destruction of the RBCs are treated by removal of the cause (e.g., drug, infectious agent, gastric foreign body) and supportive therapy. Corticosteroids (see later) can be administered to suppress MPS activity while the causative agent is being eliminated, although this is not always beneficial. Doxycycline (10 mg/kg orally [PO] q24h for 21-42 days) usually results in the resolution of signs in dogs and cats with mycoplasmosis. In dogs with babesiosis, the treatment of choice depends on the specific organism (see Chapter 98).

Immune-mediated hemolytic anemia

IHA constitutes the most common form of hemolysis in dogs in most of the continental United States; this is not likely the case in areas endemic for vector borne diseases. Although two pathogenetic categories of hemolytic anemia are recognized—primary, or idiopathic, and secondary—most cases of IHA in dogs in our clinic are primary; that is, a cause cannot be found after exhaustive clinical and clinicopathologic evaluation. The immune-mediated destruction of RBCs can occur in association with drug administration (e.g., β-lactam antibiotics, barbiturates) or vaccination, but the latter has not been conclusively demonstrated. With the exception of the immune hemolysis secondary to hemoparasitism, IHA is rare in cats, although its prevalence is higher than in the past. The clinical course in dogs is typically acute, but peracute presentations are also common.

In IHA, the RBCs become coated mainly with IgG, which leads to the early removal of the coated cells by the MPS, generally in the spleen and liver. As a consequence, spherocytes are generated (see Fig. 82.4); therefore the presence of spherocytes in the blood smear of a dog with anemia is highly suggestive but not diagnostic of IHA. Spherocytes are difficult to identify in cats. Macroagglutination or microagglutination can also be detected in these patients (see Fig. 82.6).

The typical patient with IHA is a middle-aged, female, spayed Cocker Spaniel, Springer Spaniel, or small-breed dog, although there appears to be an increasing prevalence of IHA and other immune-mediated cytopenias in Golden Retrievers. Clinical signs in dogs with IHA include depression of acute (or peracute) onset, exercise intolerance, and pallor or jaundice, occasionally accompanied by vomiting or abdominal pain. Physical examination findings usually consist of pallor or jaundice, petechiae and ecchymoses if immune thrombocytopenia is also present, splenomegaly, and a heart murmur. As noted, jaundice can be absent in dogs with IHA. A subset of dogs with acute (or peracute) IHA with icterus and usually autoagglutination shows clinical deterioration within hours or days of admission because of multifocal thromboembolic disease or lack of response to conventional therapy. I treat these dogs more aggressively than the typical dog with IHA (see later).

Hematologic findings in dogs with IHA typically include strongly regenerative anemia, leukocytosis from neutrophilia with a left shift and monocytosis, increased numbers of nucleated RBCs, polychromasia, and spherocytosis. The serum (or plasma) protein concentration is usually normal to increased, and hemoglobinemia or bilirubinemia may be present (i.e., pink or yellow plasma). As noted, autoagglutination is prominent in some dogs. Thrombocytopenia is also present in dogs with Evans syndrome or DIC. Dogs with intravascular hemolysis frequently have hemoglobinuria (i.e., urine dipstick positive for blood and no RBCs in the sediment), and those with extravascular hemolysis have bilirubinuria.

The presence of polychromasia with autoagglutination and spherocytosis in a clinically ill dog with anemia of acute onset is almost pathognomonic of IHA, with the exception of Pitbulls with *B. gibsoni* infection that present with similar findings. In these cases, a direct Coombs test is usually not necessary to confirm the diagnosis. In dogs without some of these physical examination and hematologic findings, a direct Coombs test should be performed to detect Ig adsorbed to the RBC membrane. As noted, in Pitbulls, evaluation of capillary blood in a Diff-Quik–stained slide or PCR assay is mandatory to exclude *B. gibsoni* infection (see Fig. 82.5).

The direct Coombs test is negative in approximately 10% to 30% of dogs with IHA, although they still tend to respond to immunosuppressive therapy (see later). In these cases enough Ig or complement molecules may be bound to the RBC membrane to induce the MPS to stimulate phagocytosis but not enough to result in a positive Coombs test. In humans, hemolysis can occur with approximately 20 to 30 molecules of Ig bound to the RBC, whereas the direct Coombs test can only detect more than 200 to 300 molecules of Ig/cell. In some patients, prior administration of

exogenous corticosteroids may result in decreased antibody binding to the surface of the RBCs.

Immunosuppressive doses of corticosteroids (equivalent to 2-4 mg/kg of prednisone q12-24h) constitute the treatment of choice for primary IHA. Although dexamethasone can be used initially, it should not be used as maintenance therapy for prolonged periods because of its higher potential to cause GI tract ulceration or pancreatitis; in addition, if given on an alternate-day basis, it causes interference with the hypothalamic-pituitary-adrenal axis. In equivalent doses, dexamethasone does not appear to be more beneficial than prednisone in dogs. In cats with IHA, I use dexamethasone (4-5 mg/cat PO q1-2 wk) instead of prednisolone, with a high degree of success.

A high percentage of dogs treated with corticosteroids show a marked improvement within 24 to 96 hours (Fig. 82.7). Corticosteroids mainly act by three different mechanisms—they suppress MPS activity, decrease complement and antibody binding to the cells, and suppress Ig production. The first two effects are rapid in onset (hours), whereas the third effect is delayed (1-3 weeks). For additional information, see Chapters 72 and 73.

I have seen a high number of dogs with acute or peracute IHA generally associated with icterus and autoagglutination that undergo rapid deterioration and usually die of thromboembolism of the liver, lungs, or kidneys despite aggressive corticosteroid therapy (Fig. 82.8). In those patients, I use cyclophosphamide (Cytoxan), 200 to 300 mg/m^2 PO or IV in a single dose over a 5- to 10-minute period, or human IV immunoglobulin (IVIG), 0.5 g/kg as an IV infusion, in conjunction with a single IV dose of dexamethasone sodium phosphate (1-2 mg/kg). I also advocate the use of prophylactic heparin and/or aspirin therapy because dogs with hemolysis are at high risk for DIC and thrombosis. I use heparin therapy, 50 to 75 IU/kg subcutaneously (SC) q8h, and/or minidose aspirin, 0.5 mg/kg PO q24h. These dosages of heparin usually do not result in therapy-related prolongation of the activated clotting time (ACT) or activated partial

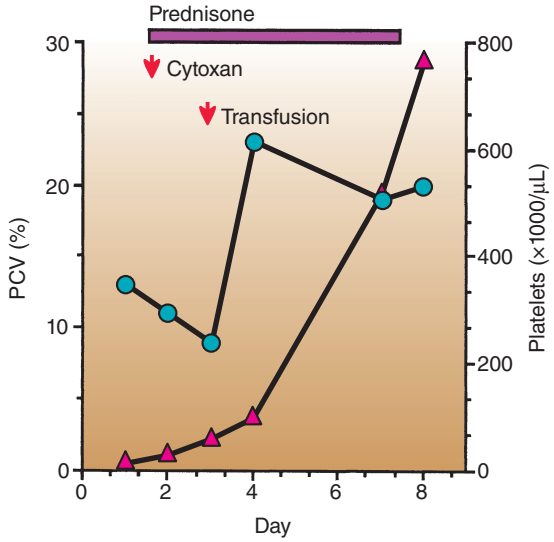


FIG 82.7
Response to treatment in a dog with immune hemolytic anemia (IHA) and immune-mediated thrombocytopenia (Evans syndrome). *PCV,* Packed cell volume; –•–, PCV; –Δ–, platelets; ↓, treatment administered.

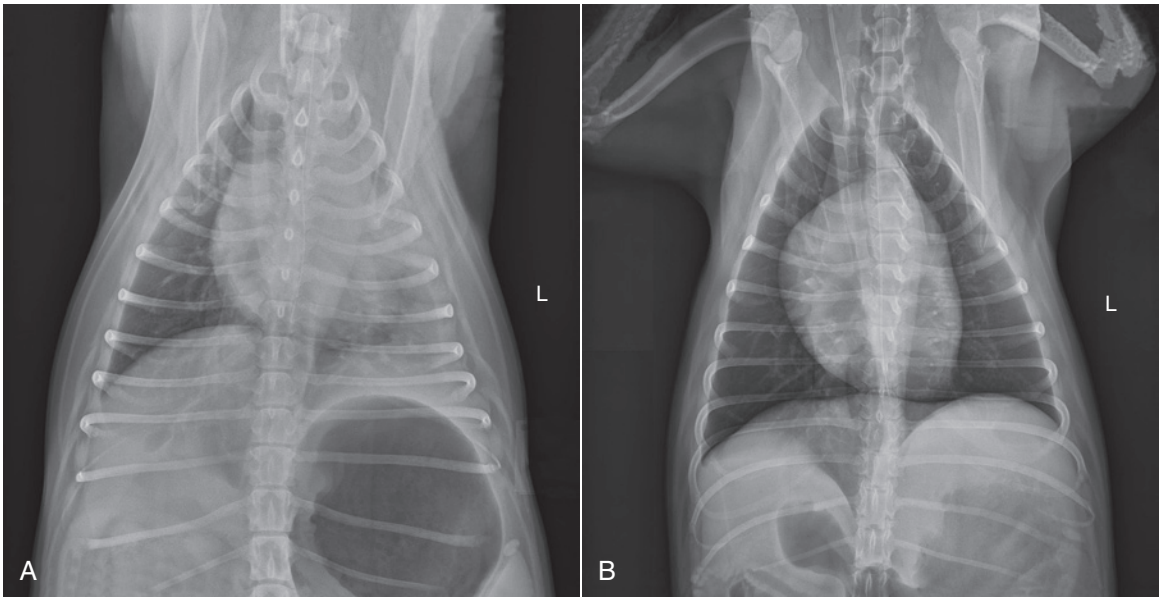


FIG 82.8
Thoracic radiographs before **(A)** and after anticoagulant therapy **(B)** in a mixed-breed dog with immune hemolytic anemia (IHA). Notice the almost complete consolidation of the left pulmonary field **(A)** and resolution 72 hours after treatment with heparin and aspirin **(B).**

thromboplastin time (aPTT), tests used routinely to monitor heparinization. The use of low-dose or minidose aspirin has been associated with lower mortality rates in dogs with IHA. Because dogs with IHA are at high risk for thromboembolic events, I refrain from placing central venous lines; thrombosis of the anterior vena cava commonly leads to severe pleural effusion in these dogs. Aggressive fluid therapy should be administered in conjunction with these treatments in an attempt to flush the microaggregates of agglutinated RBCs from the microcirculation. (*Note:* As a general rule, circulating blood does not clot.) In patients with severe anemia, the resultant hemodilution may be detrimental. If deemed necessary, oxygen therapy should also be used, but it is rarely beneficial unless the HCT or Hb can be increased.

As noted, I use human IV IgG (HIVIGG; 0.5-1 g/kg IV infusion, single dose) with a high degree of success in dogs with refractory IHA. This treatment is aimed at blocking the Fc receptors in the MPS with a foreign Ig, thus minimizing the phagocytosis of antibody-coated RBCs. This treatment appears to have other immunomodulatory effects as well. However, the product is moderately expensive (≈$700/dose for a 10-kg dog). This approach has had such a positive impact, however, that I frequently use it as first-line therapy in dogs with severe IHA.

Drugs used for the maintenance treatment of dogs with IHA include prednisone (1-2 mg/kg PO q48h) and azathioprine (50 mg/m^2 PO q24-48h), singly or in combination. Azathioprine is associated with few adverse effects, although close hematologic and serum biochemical monitoring is necessary because of its myelosuppressive and hepatotoxic potential; if myelosuppression or hepatotoxicity occurs, a dose reduction is necessary. Occasionally azathioprine must be discontinued in dogs with hepatotoxicity.

In cats, chlorambucil is an effective immunosuppressor with very low toxicity; I have used it successfully in cats with IHA, immune-mediated thrombocytopenia, or other cytopenias, 20 mg/m^2 PO q2wk. As noted, in cats I use dexamethasone (4-5 mg/cat PO q1wk) instead of prednisone or prednisolone. In general, dogs and cats with IHA require prolonged, often lifelong, immunosuppressive treatment. Whether an animal requires continuous treatment is determined by trial and error; decremental doses of the immunosuppressive drug(s) are administered for a given period (usually 2-3 weeks), at which time the patient is reevaluated clinically and hematologically. If the PCV has not decreased or has increased, and the patient is clinically stable or has shown improvement, the dose is reduced by 25% to 50%. This procedure is repeated until the drug is discontinued or the patient relapses. In the latter case, the dosage used previously that had beneficial effects is used again. In my experience, most dogs with IHA require lifelong treatment. Alternative treatments for dogs with refractory IHA include cyclosporine, mycophenolate, mofetil, and possibly splenectomy. For details, see Chapters 72 and 73.

Chlorambucil (20 mg/m^2 PO q2wk) appears to be the best induction and maintenance agent in cats with IHA refractory to corticosteroids or in those who develop corticosteroid-induced diabetes mellitus. In my experience, azathioprine causes pronounced myelosuppression in cats and should not be used.

One of the biggest dilemmas the clinician faces in the treatment of a dog with IHA is whether to administer a transfusion of blood or blood components. As a general rule, a transfusion should not be withheld if it represents a lifesaving procedure. However, because patients with IHA are already destroying their own antibody-coated RBCs, they may also be prone to destroying transfused RBCs, although this has not been scientifically proven. My recommendation is to administer a transfusion to any animal with IHA that is in dire need of RBCs (i.e., withholding a transfusion would result in the animal's death). I usually pretreat these patients with dexamethasone sodium phosphate (0.5-1 mg/kg IV), administer fluids through an additional IV catheter, and continue the heparin or aspirin therapy. Although cross-matching is indicated, time is usually of the essence; therefore non–cross-matched "universal" donor blood or packed RBCs are frequently administered.

Another issue pertaining to transfusion in dogs with IHA autoagglutination has to do with blood typing; if blood typing cards are used, the results will be false-positive for dog erythrocyte antigen (DEA) 1.1 (see later, "Transfusion Therapy"). Finally, no rule of thumb exists (e.g., PCV value, lack of response to oxygen therapy) regarding when to administer a transfusion. The clinician should use his or her best clinical judgment to determine when a transfusion of blood or blood components is necessary (e.g., does the patient exhibit tachypnea, dyspnea, or orthopnea?). If available, "universal donor" packed RBCs should be used instead of whole blood because they deliver a high oxygen-carrying capacity in a smaller volume; IHA is an isovolemic anemia.

NONREGENERATIVE ANEMIAS

With the exception of ACD, nonregenerative anemias do not appear to be clinically as common as regenerative forms in dogs, whereas the opposite is true in cats. Five forms of nonregenerative anemia are typically recognized in cats and dogs (see Box 82.3). Because IDA can be mildly to moderately regenerative, and the RBC indices are so different from those in other forms of nonregenerative anemia (microcytic, hypochromic versus normocytic, normochromic; see Boxes 82.3 and 82.4 and Tables 82.2 to 82.4) that it is easily identified as such, I prefer to classify it in a separate category. Anemia of endocrine disease is typically mild and usually is an incidental finding in dogs with hypothyroidism or hypoadrenocorticism (see Chapters 48 and 50). In general, most nonregenerative anemias and IDA in cats and dogs are chronic, thus allowing for physiologic adaptation to the decrease in the RBC mass. As a consequence, these types of anemias may be detected incidentally during the routine evaluation of a cat or dog, which to the owner is asymptomatic. In many cases (e.g., ACD), the anemia is mild, and clinical signs are absent. Although most nonregenerative anemias are chronic, two situations are commonly

BOX 82.4

Classification and Causes of Nonregenerative Anemia in Cats and Dogs

Anemia of chronic disease
Bone marrow disorders
- Bone marrow (or erythroid) aplasia-hypoplasia
- Myelophthisis
- Myelodysplastic syndromes
- Myelofibrosis
- Osteosclerosis, osteopetrosis

Anemia of renal disease
Acute blood loss or hemolysis (first 48-96 hours)
Anemia of endocrine disorders
- Hypoadrenocorticism
- Hypothyroidism

TABLE 82.5

Distinguishing Features of Anemia of Chronic Disease (ACD) and Iron Deficiency Anemia (IDA) in Dogs

PARAMETER	ACD	IDA
Serum iron concentration	↓	↓↓
Total iron-binding capacity	N	N↑
Percentage saturation	↓	↓↓
Bone marrow iron stores	↑	↓
Platelet count	N, ↓, ↑	↑, ↑↑
Fecal occult blood	N	±
Ferritin	N	↓

↓, Low; ↓↓, markedly low; ↑, high; ↑↑, markedly high; *N*, normal; ±, positive or negative.

encountered in which this form of anemia is acute—acute blood loss (first 48-96 hours) and peracute hemolysis. In these two cases, the bone marrow has not yet had time to mount a regenerative reticulocyte response, and the patients have severe clinical signs.

When evaluating dogs and cats with symptomatic nonregenerative anemias of acute onset, the clinician should try to answer the following questions:

- Has this patient had an acute blood loss or does it have hemolytic anemia and has not yet been able to mount a regenerative response (i.e., <48-96 hours have elapsed since the event)?
- Does this patient have chronic anemia but is now symptomatic because of intercurrent disease (e.g., heart failure, sepsis)?

Most clinical and clinicopathologic abnormalities in cats and dogs with nonregenerative anemia have been discussed. In general RBCs in dogs and cats with nonregenerative anemias are normocytic and normochromic; however, in cats with FeLV-related hypoproliferative anemias, RBCs are usually macrocytic and normochromic. As noted, in dogs and cats with IDA, the RBC indices are microcytic and hypochromic.

The clinical evaluation of a cat or dog with nonregenerative anemia differs radically from that of a patient with a regenerative form because the absence of regeneration reflects primary or secondary bone marrow abnormalities (e.g., bone marrow disorder, ACD). Therefore, after extramarrow causes have been ruled out by performing a physical examination and serum biochemical profile and urinalysis, a bone marrow aspiration or biopsy is typically indicated in these patients.

Anemia of Chronic Disease

ACD is the most common form of nonregenerative anemia in cats and dogs, but because it is mild it almost never results in clinical signs of anemia and the patients are usually evaluated as a consequence of their primary disorder (e.g., cancer, infection). ACD develops secondary to a variety of chronic inflammatory, degenerative, or neoplastic conditions. Although the term *anemia of chronic disease* implies a chronic onset, it has been established that cats can develop ACD in as little as 2 weeks. However, some of those cats were receiving fluid therapy that might have resulted in hemodilution (Ottenjan et al., 2006). In most cats with ACD, the PCV values range from approximately 18% to 25%, whereas in dogs they range from approximately 25% to 35%. Therefore ACD can usually be excluded in dogs with a PCV less than 20% and in cats with a PCV less than 17% to 18%. The RBC indices are normocytic and normochromic, and the CBC may also reflect the nature of the primary problem (e.g., leukocytosis, neutrophilia, monocytosis, hyperproteinemia resulting from a polyclonal gammopathy). Some cats with ACD have microcytic hypochromic RBC indices, a condition that mimics IDA.

Sustained inflammatory or neoplastic processes cause iron to be sequestered within the bone marrow MPS, and it is therefore not available to the erythroid precursors for normal erythropoiesis. This unavailability of iron is mainly mediated by hepcidin, lactoferrin, and other acute-phase reactants released from leukocytes during inflammation. In cats and dogs with ACD, the serum iron concentration and total iron-binding capacity (TIBC, or transferrin concentration) are usually decreased and the Hb saturation is low, but iron stores in the bone marrow are increased (Table 82.5). Although serum ferritin concentrations are the main feature that distinguishes ACD from IDA (i.e., high in ACD and low in IDA) in humans, the results of ferritin assays in dogs and cats with IDA and ACD are not as clear-cut. Therefore, to differentiate ACD from IDA conclusively, evaluation of bone marrow iron stores by Prussian blue staining is important. After a diagnosis of ACD has been confirmed, every effort should be made to identify the cause of the problem if it is not already evident.

Dogs and cats with ACD usually do not require specific or supportive therapy because treatment of the primary disorder causes the anemia to resolve. Although some have advocated the use of anabolic steroids in dogs and cats with ACD, these agents appear to be of little or no benefit. For a recent review of ACD I dogs and cats, please see Chikazawa and Dunning.

Bone Marrow Disorders

Neoplastic, hypoplastic, or dysplastic bone marrow disorders can result in anemia and other cytopenias. In these conditions, a so-called crowding out of the normal erythroid precursors by neoplastic or inflammatory cells (myelophthisis), paucity or absence of erythroid precursors (hypoplasia or aplasia, respectively), or maturation arrest of the erythroid precursors (dysplasia) occur. All these disorders, with the exception of PRCA (see the following section), typically affect more than one cell line, and the patients are bicytopenic or pancytopenic (see Chapter 86). In general, these disorders are chronic and the clinical signs are those of anemia (see p. 1340), with or without signs of the underlying disorder. Although some information regarding the pathogenesis of this type of anemia can be obtained by evaluating the clinical and hematologic data, a definitive diagnosis is usually made on the basis of the cytologic or histopathologic appearance of a bone marrow specimen and possibly by the results of serologic tests or PCR assay for the infectious agent (e.g., FeLV, FIV, *Ehrlichia canis*). Numerous "anemia panels" that combine serology and PCR for common infectious agents in both dogs and cats are offered by reference laboratories.

Bone marrow (or erythroid) aplasia-hypoplasia

Bone marrow aplasia-hypoplasia is characterized by aplasia or hypoplasia of all the bone marrow cell lines (bone marrow aplasia-hypoplasia or aplastic pancytopenia) or of selected cell lines, for example, erythroid precursors (RBC aplasia-hypoplasia or PRCA). This form of anemia (or combined cytopenias) can be caused by a variety of agents or disorders (see Chapter 86). The following discussion pertains to PRCA; some authors have referred to PRCA as the nonregenerative form of immune-mediated anemia. Pathologists prefer to use PRCA for patients in which there is aplasia-hypoplasia of all the RBC precursors. However, because the clinical and clinicopathologic findings are identical independently of where in the RBC series the maturation arrest occurs, I prefer to use PRCA.

Clinically, dogs and cats with PRCA are evaluated because of the clinical signs already discussed. Pica is common in dogs with PRCA. In contrast to ACD, in which the degree of anemia and thus the severity of the clinical signs is mild, cats and dogs with PRCA usually have a PCV of less than 15% and are usually symptomatic. Hematologically, severe (normocytic normochromic) nonregenerative anemia is usually the only abnormality; macrocytosis in the absence of reticulocytes is a consistent finding in cats with FeLV- or FIV-related aplastic anemia, and mild microcytosis can occasionally be present in dogs with PRCA. The large RBC volume in cats with retroviral infections is attributed to the erythroid dysplasia or dyserythropoiesis induced by the virus. Dogs with PRCA occasionally have circulating spherocytes, indicating an immune basis for the anemia. The direct Coombs test is also positive in more than 50% of these dogs, and their anemia responds to immunosuppressive therapy. Cats and dogs with bone marrow aplasia-hypoplasia are pancytopenic (see Chapter 86).

FeLV and FIV testing should be done in all cats with severe nonregenerative anemia, independently of their MCV. A bone marrow aspiration or biopsy specimen should also be obtained to rule out other bone marrow disorders.

The FeLV envelope protein p15E suppresses erythropoiesis in vitro and causes aplastic anemia in FeLV-infected cats. The anemia in these cats is usually chronic and severe—a PCV of 5% to 6% is relatively common—and despite supportive therapy, the condition of the patient deteriorates, leading the owners to request euthanasia. The supportive treatment of these cats includes whole blood or packed RBC transfusions, as needed; the interval between transfusions usually shortens with each transfusion until the cat needs transfusions weekly. Interferon administered orally may improve clinical signs, without resolution of the anemia, in some of these cats (see Chapter 96).

FeLV-negative cats with PRCA may have a positive direct Coombs test and frequently benefit from immunosuppressive doses of corticosteroids. I typically use 4 to 5 mg of dexamethasone/cat PO q1 to 2 weeks instead of the conventional prednisone or prednisolone daily or every other day. This steroid formulation is safe and effective, and I have not seen the development of secondary diabetes mellitus in the cats treated. The use of human recombinant erythropoietin (EPO; see later) does not appear to be indicated in these cats because their endogenous EPO activity is higher than that of normal cats. In addition, the long-term use of human recombinant EPO may lead to the development of anti-EPO antibodies and resultant refractory anemia.

Bone marrow aspirates in dogs and cats with PRCA reveal erythroid hypoplasia or hyperplasia of the early erythroid precursors and a maturation arrest at the rubricyte or metarubricyte stage. As noted, this poses an interesting situation because most clinical pathologists use PRCA only for the dogs and cats that have erythroid hypoplasia and IHA with delayed erythroid regeneration or nonregenerative form of immune-mediated anemia for those with erythroid hyperplasia and a maturation arrest. However, from a clinical standpoint, both situations behave the same way and respond to the same treatment, so I prefer to use PRCA for dogs and cats with either of these bone marrow cytologic findings.

The same treatment as that used during the maintenance phase of IHA is recommended for affected dogs (prednisone, 2-4 mg/kg PO q24-48h, and/or azathioprine, 50 mg/m^2 PO q24-48h). In cats, I have successfully used dexamethasone alone (as noted earlier) or in combination with chlorambucil, 20 mg/m^2 PO q2 weeks. Responses occur in approximately 70% to 80% of patients, but clinical and hematologic recovery may take 2 to 3 months; long-term (often lifelong) treatment is usually required. Supportive treatment and

transfusions of blood or packed RBCs are sometimes necessary. Because these patients are normovolemic, the latter is preferable. In addition, because transfusions may need to be administered on an ongoing basis, cross-matching is recommended before the administration of each transfusion. Of note, in dogs one of the mechanisms of adaptation to chronic hypoxia (e.g., anemia) is an increase in the intraerythrocytic 2,3-diphosphoglycerate (2,3-DPG) concentration, resulting in a lower oxygen affinity; that is, the delivery of oxygen to the tissues is facilitated. Because stored RBCs have lower concentrations of 2,3-DPG, the transfused cells have a higher affinity for oxygen. As a result, the transfusion of stored blood to a patient with chronic anemia may result in transient decompensation because approximately 24 hours is usually required for the transfused, stored RBCs to regain 50% of the normal 2,3-DPG concentration and become recharged.

Myelophthisis, myelodysplastic syndromes, myelofibrosis, and osteosclerosis-osteopetrosis

These disorders are discussed in Chapter 86.

Anemia of Renal Disease

The kidney is the main site of production of EPO, the principal stimulus of erythropoiesis. In addition, in dogs and cats with CKD, the life span of RBCs is considerably shorter and subclinical to clinical GI tract bleeding is present; high concentrations of parathyroid hormone may also suppress erythropoiesis. Consequently, anemia is common in these patients. The anemia is usually normocytic and normochromic, with few or no reticulocytes. HCT levels in dogs and cats with ARD are usually in the 20% to low 30% range, although HCT levels from 13% to 19% are common. Of note, the HCT in these patients is usually that low only after they have undergone intensive fluid therapy; on presentation, the anemia is not that severe because the patients are markedly dehydrated.

Improvement in renal function may result in marginal increases in the RBC mass. Anabolic steroids are rarely beneficial in improving the anemia in these patients. Human recombinant EPO has been used successfully to treat anemia in cats and dogs with chronic renal failure. A dose of 100 to 150 IU/kg SC, twice weekly, is administered until the HCT returns to a target value (usually 20%-25%); the interval between injections is then lengthened for maintenance therapy. The HCT usually returns to normal within 3 to 4 weeks of the initiation of treatment. Given the fact that this EPO is foreign to dogs and cats, an appropriate antibody response usually nullifies the beneficial effects of long-term therapy (6-8 weeks) in more than 50% of patients. Recently, darbepoetin was successfully used to treat anemia of renal disease in dogs (Fiocchi et al., 2017). In a study of 33 dogs with CKD and anemia, the median starting dosage and highest dosage of darbepoetin administered were 0.5 and 0.8 μg/kg SC once weekly, respectively. Response to treatment was defined as achieving a PCV ≥30% or an increase in PCV ≥10%. Twenty-eight of 33 dogs (85%) achieved a PCV ≥30%, and 22 of 33 (67%) dogs achieved an increase in PCV ≥10%; the median time to hematologic response was 29 days. No dog sustained a response at a dosing interval >q21 days. Potential adverse events included increased blood pressure requiring treatment ($n = 12$), seizures ($n = 5$), vomiting ($n = 3$), diarrhea ($n = 3$), and possible PRCA ($n = 2$) (Fiocchi et al., 2017).

Acute and Peracute Blood Loss or Hemolysis

After an acute episode of blood loss or hemolysis, the bone marrow takes approximately 48 to 96 hours to release enough reticulocytes to result in regeneration. Therefore blood loss and hemolytic anemias are nonregenerative during the initial phases of recovery.

In most dogs and cats with acute blood loss, profound bleeding is historically or clinically evident. If no obvious cause of bleeding is found, or if the patient is bleeding from multiple sites, the hemostatic system should be evaluated in search of a coagulopathy (see Chapter 87). Sites of internal bleeding should be evident after a complete physical examination is performed.

Once the bleeding has been stopped, the anemia typically resolves within days to weeks. The initial management of a bleeding episode should include supportive therapy and IV crystalloids or plasma expanders. If necessary, blood or packed RBCs or Hb solutions, if available, should be administered.

The management of dogs with peracute hemolysis was discussed earlier in the chapter.

Iron Deficiency Anemia

IDA is traditionally classified as nonregenerative, even though mild to moderate regeneration usually occurs. Moreover, as noted, the RBC indices in dogs and cats with IDA are microcytic and hypochromic, distinguishing it from other forms of anemia. When evaluating the CBC of a dog with microcytic hypochromic anemia, the clinician must remember that microcytosis occurs in some breeds (e.g., Akita, Shiba Inu, Shar Pei) and in dogs with other disorders, such as portosystemic shunts (see Table 82.2).

This form of anemia is well characterized in dogs with chronic blood loss. In cats, IDA has been well documented only in weanling kittens in whom iron supplementation results in rapid resolution of the clinical and hematologic abnormalities. IDA is extremely uncommon in adult cats; I have seen it primarily in association with chronic blood loss in cats with GI lymphoma. Given its rarity in cats, the following discussion of IDA pertains primarily to dogs.

Chronic blood loss leading to iron depletion is common in dogs with GI tract bleeding caused by neoplasia, gastric ulcers, or endoparasites (e.g., hookworms), and in those with a heavy flea infestation. Other causes of chronic blood loss, such as urogenital bleeding and iatrogenic bloodletting, are extremely rare. Recently, in a multicenter study of 688 dogs and 163 cats, the prevalence of anemia upon admission was 32%; the overall prevalence during the hospitalization period was 56% (Lynch et al., 2015). The RBC indices were not

reported in this study, so the prevalence of true IDA is unknown. The last recorded PCV was significantly lower than the admission PCV for both dogs (admission PCV, 42%; last recorded PCV, 34%, $P < 0.0001$) and cats (admission PCV, 31%; last recorded PCV, 26%, $P < 0.0001$). Patients that developed anemia had significantly more blood samples collected (nonanemic, 5 blood samples; anemic, 7 blood samples, $P < 0.0001$). Hospitalized cats were significantly more likely to develop anemia than dogs ($P < 0.0001$), but anemic dogs were significantly less likely to survive to discharge ($P = 0.0001$). Surgical patients were at higher risk of developing hospital-acquired anemia compared with medical patients (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.4-0.9; $P = 0.01$). Blood products were administered to 198 patients (158 dogs and 40 cats); packed RBCs were the most commonly administered product in 129 cases (100 dogs and 29 cats).

In my experience, the most common cause of symptomatic IDA in adult dogs that present for evaluation of signs associated with anemia is GI neoplasia.

Dogs with IDA are typically evaluated because of the signs of the anemia or because of GI tract signs such as diarrhea, melena, or hematochezia. Mild IDA is occasionally recognized during the routine evaluation of heavily parasitized dogs (mostly pups). Hematologically, most dogs with IDA have microcytic hypochromic indices, mild reticulocytosis, high RBC distribution width (RDW) with an occasional bimodal population of RBCs, thrombocytosis, low serum iron and TIBC (transferrin) concentrations, extremely low percentage of saturation (usually <10%), low serum ferritin concentration, and low iron stores in the bone marrow (see Box 82.5; Fig. 82.9). The typical tetrad of hematologic abnormalities in dogs with IDA is microcytosis, hypochromasia, mild regeneration, and thrombocytosis. "Anemia of the elderly," a progressive, age-related microcytic hypochromic anemia documented in people, was recently described in senior and geriatric dogs (Radakovich et al., 2017).

Because the most common cause of IDA in adult dogs is chronic GI tract bleeding, the stools should always be evaluated for occult blood with commercially available kits (see Chapter 27); if the results are negative, they should be evaluated again two or three times during a period when the animal is not eating canned dog food; myoglobin in canned dog food can rarely result in false-positive reactions. If occult blood is present in the stool, a GI tract neoplasm should be ruled out. Tumors commonly associated with IDA in dogs include GI stromal tumors (GISTs), leiomyomas and leiomyosarcomas, lymphomas, and carcinomas. In dogs with weight loss, IDA, positive fecal blood test results, and lack of clinical signs associated with the GI tract, the most likely diagnosis is a jejunal tumor (usually a GIST or leiomyosarcoma); I refer to these tumors as the silent GI neoplasms.

Another condition that can lead to IDA is chronic upper GI tract bleeding secondary to gastroduodenal ulceration, although most of these dogs have overt clinical signs associated with the GI tract (e.g., vomiting, hematemesis, weight loss). In pups or kittens with IDA, fecal flotation or a direct smear for hookworms and thorough physical examination to search for fleas are mandatory because these are the two most common causes of IDA in young dogs and cats.

IDA usually resolves within 6 to 8 weeks after the primary cause has been eliminated. Oral or intramuscular iron supplementation is usually not necessary to hasten the resolution of the hematologic abnormalities; a sound commercial diet usually achieves the same effect. As a general rule, if the cause can be eliminated, I do not use iron supplementation. The dietary iron requirement for adult dogs and cats is approximately 1.3 mg/kg/day.

BOX 82.5

Bone Marrow Disorders in Cats and Dogs

Marrow (or Erythroid) Aplasia-Hypoplasia

- FeLV (C)
- Immune-mediated disorders (D, C)
- Estrogen (D)
- Phenylbutazone (D)
- Other drugs (D, C)
- Idiopathic (D, C)

Myelophthisis

- Acute leukemias (D > C)
- Chronic leukemias (D > C)
- Multiple myeloma (D, C)
- Lymphoma (D, C)
- Systemic mast cell disease (C > D)
- Malignant histiocytosis (D > C)
- Metastatic carcinoma (rare D, C)
- Histoplasmosis (rare D, C)

Myelodysplastic Syndromes

- FeLV (C)
- FIV (C)
- Preleukemic syndrome (D, C)
- Idiopathic (D, C)

Myelofibrosis

- FeLV (C)
- Pyruvate kinase deficiency anemia (D)
- Idiopathic (D, C)

Osteosclerosis/Osteopetrosis

- FeLV (C)

C, Cat; *D,* dog; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus.

TRANSFUSION THERAPY

Veterinary transfusion medicine has made great strides in the past decade. Several commercial blood banks for pets are now available; most of them store blood components derived from processing units of whole blood or collected by apheresis. In a typical situation, a unit of whole blood is spun

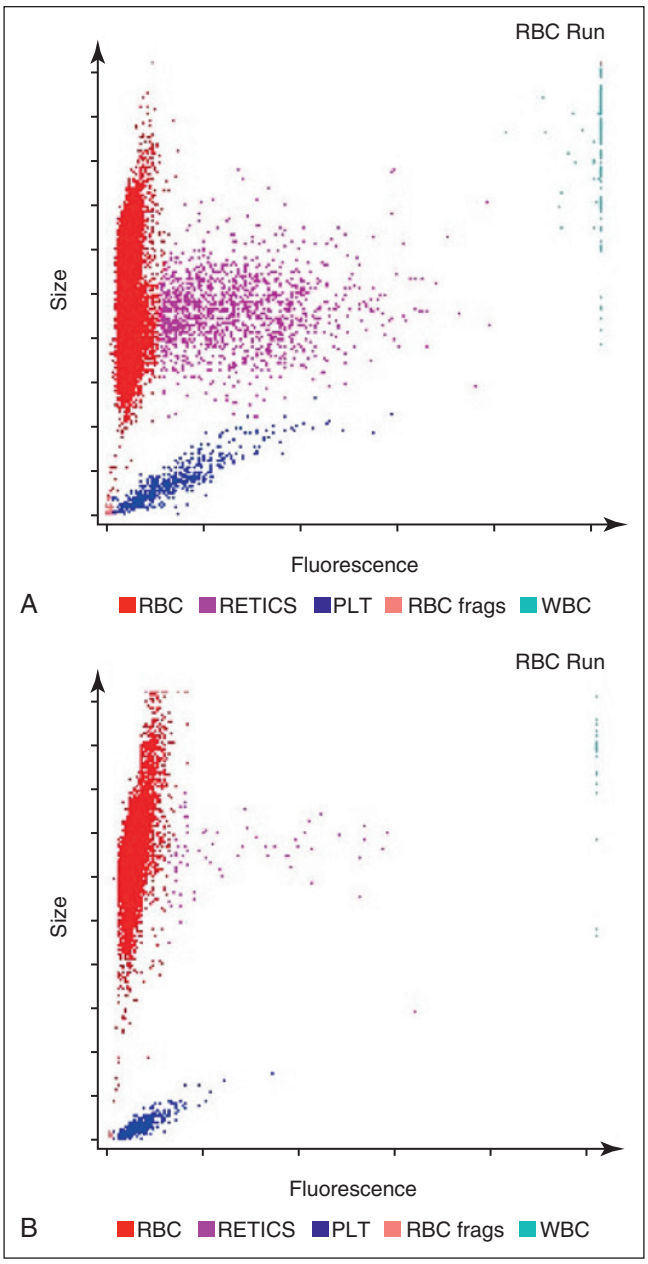


FIG 82.9
(A) Dot plots of a Greyhound with severe flea infestation and iron deficiency anemia (IDA) compared with a dot plot in a normal Greyhound. Note the RBC cloud lower in the vertical axis in **(A)** than in **(B)** indicating a low mean corpuscular volume, and the large reticulocyte cloud (RETICS) in *purple* **(A).** *PLT,* Platelets.

immediately after collection, and packed RBCs (pRBCs) and fresh-frozen plasma (FFP) stored at −20° C to −30° C are prepared. The pRBCs are preserved by adding a nutrient solution and can be stored for up to 5 weeks. After 1 year of storage at −20° C to −30° C, FFP is supposed to lose the labile clotting factors (V and VIII) and is referred to as stored plasma (SP) or frozen plasma (FP); however, we demonstrated that 5-year-old FP is still hemostatically active and can be used for transfusion (Urban et al., 2013). Some blood banks prepare platelet-rich plasma (PRP) or platelet concentrates by apheresis; a new platelet concentrate is now commercially available in the United states (Bodevet; http://www.bodevet.com). If FFP is allowed to warm up in a refrigerator, a sludge forms in the bottom of the bag when it reaches approximately 4° C to 6° C. That sludge can be separated by a short centrifugation, yielding cryoprecipitate (CRYO), a small volume rich in factor VIII, fibrinogen, and von Willebrand factor (vWF); the supernatant is termed *cryopoor plasma.*

The transfusion of whole blood or blood components (e.g., pRBCs, PRP, FFP, CRYO, or SP) is indicated in several clinical situations. Whole blood or pRBC transfusion is usually required to restore the oxygen-carrying capacity in patients with anemia. Whole blood may be used if the anemic patient is hypovolemic or if he or she needs clotting factors in addition to RBCs, whereas pRBCs are recommended for normovolemic dogs and cats with anemia (i.e., PRCA, ARD, hemolysis). Transfusion therapy should be used with caution in animals with IHA (see p. 1351) because a massive transfusion reaction may occur.

Clotting factor deficiencies (see Chapter 87) resulting in hemorrhage can be corrected through the administration of whole fresh blood if considerable blood loss has occurred or, ideally, FFP, FP, or SP. Cryoprecipitate contains a high concentration of factor VIII and vWF, so it is typically used in dogs with hemophilia A or von Willebrand disease. Cryopoor plasma is a good source of clotting factors (except for fibrinogen, factor VIII, and vWF) and albumin; therefore it is indicated in patients with common coagulopathies, such as rodenticide toxicity. PRP or platelet transfusions, if available, can be used in dogs and cats with severe thrombocytopenia resulting in spontaneous bleeding (Table 82.6). However, the platelet count of the recipient is rarely increased enough to halt bleeding. PRP and platelet transfusions are of little or no benefit in patients with peripheral platelet destruction (e.g., immune-mediated thrombocytopenia) because the platelets are removed from the circulation immediately after the transfusion. Transfusion with whole fresh blood, PRP, or FFP is also indicated for the management of patients with DIC (see Chapter 87).

Less frequently, plasma is prescribed to correct hypoalbuminemia. However, only rarely can relevant increases in the recipient's serum albumin concentration be achieved. Colloids or human albumin solutions are more effective for restoring plasma oncotic pressure.

BLOOD GROUPS

Several blood groups have been recognized in dogs; these include DEA 1.1 and 1.2 (formerly known as blood group A), DEA 3 through 8, and *Dal*; two new blood groups (*Kai1* and *Kai2*) were recently reported (Euler et al., 2016). We have stated repeatedly that dogs do not have naturally occurring antibodies against blood group antigens; therefore theoretically they can only acquire them after receiving a transfusion or after pregnancy. However, in a recent

TABLE 82.6

Practical Use of Blood Components

	WHOLE BLOOD	PRBCs	STORED PLASMA	FFP	CRYO	CRYOPOOR
Hypovolemic anemia	+++	++	–	–	–	–
Isovolemic anemia	+	+++	–	–	–	–
vWD	–	–	–	+++	++++	–
Hemophilia A	–	–	–	+++	++++	–
Hemophilia B	–	–	+++	++	–	++++
Rodenticide toxicity	–	–	+++	++	–	++++
Hypoalbuminemia	–	–	++	+	–	++++
Liver disease	–	–	++++	++	–	++++
Pancreatitis	–	–	++++	+++	–	++++
AT deficiency	–	–	++++	+++	–	++++
DIC	++	+	++	++++	–	++

AT, Antithrombin; *Cryo,* cryoprecipitate; *Cryopoor,* cryopoor plasma; *DIC,* disseminated intravascular coagulation; *FFP,* fresh-frozen plasma; *PRBCs,* packed red blood cells; *vWD,* von Willebrand disease.
– *to* ++++, Least indicated to best indicated.

report, 17% of dogs that had never received a transfusion were found to be incompatible by cross-matching (Odunayo et al., 2017). In addition, studies have reported a lack of association between pregnancy and the development of antibodies in dogs (Blais et al., 2009). Transfusion reactions can occur if blood positive for DEA 1.1, 1.2, or 7 is transfused, so donors should be negative for those antigens. However, clinically relevant acute hemolytic transfusion reactions are extremely rare in dogs. Transfusion of blood from a donor who has not been typed and has never been transfused to a recipient, independently of their blood type, is generally safe.

Blood groups in cats include A, B, AB, and *Mik*. Cats tested in the United States have almost exclusively been type A; the prevalence of type B cats varies greatly from geographic region to region and among breeds. Breeds in which 15% to 30% of the cats are type B include Abyssinian, Birman, Himalayan, Persian, Scottish Fold, and Somali; breeds in which more than 30% of cats are type B include the British Shorthair and Devon Rex. Because fatal transfusion reactions commonly occur in type B cats receiving type A blood, cats should always be cross-matched or typed before receiving a transfusion. In those cases, a type B cat should be used as a donor. Most type B cats seen in our clinic in the past 10 years have been domestic short-haired cats. Blood typing is also vital in cattery situations to prevent neonatal isoerythrolysis in type A or AB kittens born to type B queens.

CROSS-MATCHING AND BLOOD TYPING

Cross-matching is an alternative to blood typing in in-house donors or animals that have had prior transfusions, in cats, or in animals that will require multiple transfusions. Cross-matching detects many incompatibilities but does not guarantee complete compatibility. Major and minor cross-match kits are now commercially available for both dogs and cats (http://www.rapidvet.com/xmatch_info.html); this kit has recently been validated (ADD REFS PENDING). Blood compatible on cross-matching results in significantly higher post-transfusion HCTs in the recipient (Weltman et al., 2014).

Rapid, cage-side blood-typing cards for DEA 1.1 in dogs and for groups A and B in cats (RapidVet-H, DMS Laboratories, Flemington, NJ) and a gel-based system (DME VET Quick-Test DEA 1.1 and A+B, Alvedia, Limonest, France) have been validated and are now commercially available.

Interestingly, in some countries transfusing blood from dogs into cats appears to be a common emergency practice. However, the presence of strong antibodies against cat erythrocytes was recently demonstrated in dogs (Priolo et al., 2017); this procedure is strongly discouraged.

BLOOD ADMINISTRATION

Refrigerated blood may be warmed before or during administration, particularly in small dogs or cats; excessive heat should be avoided, however, because fibrinogen precipitation or autoagglutination may occur. However, warming up the blood before transfusion appears to have no effect on the recipient's core temperature, so it may not be necessary. The administration set should have a blood transfusion filter in place to remove clots and other particulate matter, such as platelet aggregates. The blood is usually administered via the cephalic, saphenous, or jugular veins. However, intraosseous infusion may be performed in small animals, neonates, or animals with poor peripheral circulation. To administer fluids or blood intraosseously, the skin over the femur is surgically prepared, and the skin and periosteum of the femoral

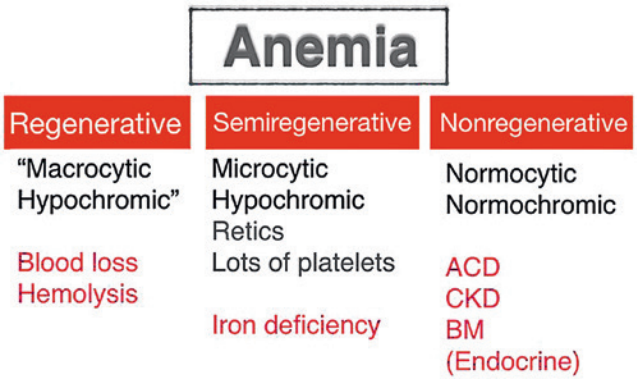


FIG 82.10
Pathogenetic classification of anemias.

trochanteric fossa are anesthetized with 1% lidocaine. A bone marrow needle (18 gauge) or intraosseus catheter is placed into the marrow cavity parallel to the shaft of the femur. Suction with a 10-mL syringe should yield marrow elements (fat, spicules, and blood), confirming correct placement of the needle. The blood is administered through a standard blood administration set.

The recommended rate of administration is variable but should not exceed 22 mL/kg/day (up to 20 mL/kg/h can be used in hypovolemic animals). Dogs and cats in heart failure may not tolerate a rate of more than 5 mL/kg/day. To prevent bacterial contamination, blood should not be exposed to room temperature during administration for longer than 4 to 6 hours; blood is considered to be contaminated if it has been at room temperature for more than 6 hours. If necessary, two smaller volumes of blood can be administered in succession. Blood should never be administered with lactated Ringer's solution because of the calcium chelation with citrate and consequent clot formation that may occur. Normal saline solution (0.9% NaCl) should be used instead. A simple rule of thumb to predict the increase in the recipient's HCT is to remember that 2.2 mL/kg (or 1 mL/lb) of transfused whole blood will raise the HCT by 1% if the donor has an HCT of approximately 40%. In cats, a unit of whole blood or pRBCs increases the recipients HCT by approximately 5% (i.e., from 10% to 15%).

COMPLICATIONS OF TRANSFUSION THERAPY

Transfusion-related complications can be divided into those that are immunologically mediated and those that are of nonimmunologic origin. Immune-mediated reactions include urticaria, hemolysis, and fever. Non–immune-mediated complications include fever or hemolysis resulting from the transfusion of improperly stored blood, circulatory overload, citrate intoxication, disease transmission, and the metabolic burden associated with the transfusion of aged blood. Signs of immediate immune-mediated hemolysis appear within minutes of the start of transfusion and include tremors, emesis, and fever; these are extremely rare in dogs but common in cats receiving incompatible blood products. Delayed hemolytic reactions are more common and are manifested primarily by an unexpected decline in the HCT after transfusion over days in association with hemoglobinemia, hemoglobinuria, and hyperbilirubinemia. Circulatory overload may be manifested by vomiting, dyspnea, or coughing. The syndrome of transfusion-associated lung injury (TRALI, a syndrome of peracute pulmonary disease associated with transfusion of blood components) was recently documented in dogs, although the prevalence is low (3.7%) (Thomovsky et al., 2014). Citrate intoxication occurs when the infusion rate is too fast or the liver cannot metabolize the citrate. Signs of citrate intoxication are related to hypocalcemia and include tremors and cardiac arrhythmias. If signs of a transfusion reaction are recognized, the transfusion must be slowed or halted.

Suggested Readings

Andrews GA, Penedo MCT. Red blood cell antigens and blood groups in the dog and cat. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. 6th ed. Ames, Iowa: Wiley-Blackwell; 2010:711.

Birkenheuer AJ, et al. Efficacy of combined atovaquone and azithromycin for therapy of chronic *Babesia gibsoni* (Asian genotype) infections in dogs. *J Vet Intern Med*. 2004;18:494.

Birkenheuer AJ, et al. Geographic distribution of babesiosis among dogs in the United States and association with dog bites: 150 cases (2000-2003). *J Am Vet Med Assoc*. 2005;227:942.

Birkenheuer AJ, et al. Serosurvey of anti-Babesia antibodies in stray dogs and American pit bull terriers and American Staffordshire terriers from North Carolina. *J Am Anim Hosp Assoc*. 2003;39:551.

Blais M-C, et al. Lack of evidence of pregnancy-induced alloantibodies in dogs. *J Vet Intern Med*. 2009;23:462.

Callan MB, et al. Canine red blood cell transfusion practice. *J Am Anim Hosp Assoc*. 1996;32:303.

Castellanos I, et al. Clinical use of blood products in cats: a retrospective study (1997-2000). *J Vet Intern Med*. 2004;18:529.

Chikazawa S, Dunning MD. A review of anaemia of inflammatory disease in dogs and cats. *J Small Animal Practice*. Blackwell Publishing Ltd. 2016;57(7):348–353.

Euler CC, et al. Survey of two new (Kai 1 and Kai 2) and other blood groups in dogs of North America. *J Vet Intern Med*. 15 ed. 2016;30(5):1642–1647.

Fiocchi EH, et al. The Use of Darbepoetin to Stimulate Erythropoiesis in the Treatment of Anemia of Chronic Kidney Disease in Dogs. *J Vet Intern Med*. Wiley/Blackwell (10.1111). 2017;31(2):476–485.

Furman E, et al. A retrospective study of 1,098 blood samples with anemia from adult cats: frequency, classification, and association with serum creatinine concentration. *J Vet Intern Med*. 2014;28(5):1391–1397.

Giger U, et al. Transfusion of type-A and type-B blood to cats. *J Am Vet Med Assoc*. 1991;198:411.

Giger U. Hereditary erythrocyte enzyme abnormalities. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. 6th ed. Ames, Iowa: Wiley-Blackwell; 2010:179.

Grahn RA, et al. Erythrocyte pyruvate kinase deficiency mutation identified in multiple breeds of domestic cats. *BMC Vet Res*. 2012;8:207.

Gurnee CM, Drobatz KJ. Zinc intoxication in dogs: 19 cases (1991-2003). *J Am Vet Med Assoc*. 2007;230:1174.

Harkin KR, et al. Erythrocyte-bound immunoglobulin isotypes in dogs with immune-mediated hemolytic anemia: 54 cases (2001-2010). *J Am Vet Med Assoc*. 2012;241:227.

Hiratzka JL, Licari LG, Peters LK. Incidence of hospital-acquired anemia in hospitalized dogs and cats. *J Am Vet Med Assoc*. 2018;252(5):560–564.

Hodges J, Christopher MM. Diagnostic accuracy of using erythrocyte indices and polychromasia to identify regenerative anemia in dogs. *J Am Vet Med Assoc*. 2011;238(11):1452–1458.

Lynch AM, et al. Hospital-acquired Anemia in Critically Ill Dogs and Cats: A Multi-Institutional Study. *J Vet Intern Med*. 2015; 17(30):141.

Mayank S, et al. Comparison of five blood-typing methods for the feline AB blood group system. *Am J Vet Res*. 2011;72:203.

Mayank S, et al. Comparison of gel column, card, and cartridge techniques for dog erythrocyte antigen 1.1 blood typing. *Am J Vet Res*. 2012;73:213.

Odunayo A, et al. Incidence of incompatible crossmatch results in dogs admitted to a veterinary teaching hospital with no history of prior red blood cell transfusion. *J Am Vet Med Assoc*. 2017;250(3):303–308.

Ottenjan M, et al. Characterization of anemia of inflammatory disease in cats with abscesses, pyothorax, or fat necrosis. *J Vet Intern Med*. 2006;20:1143.

Priolo V, et al. Naturally occurring antibodies in cats against dog erythrocyte antigens and vice versa. *J Feline Med Surg*. 2017;27:1098612X17727232.

Radakovich LB, et al. Hematology and biochemistry of aging-evidence of "anemia of the elderly" in old dogs. *Vet Clin Pathol*. 2017;13:1.

Spurlock NK, Prittie JE. A review of current indications, adverse effects, and administration recommendations for intravenous immunoglobulin. *J Vet Emerg Crit Care*. 2011;21:471.

Swann JW, Skelly BJ. Systematic review of evidence relating to the treatment of immune-mediated hemolytic anemia in dogs. *J Vet Intern Med*. 2013;27:1.

Tasker S, et al. Coombs', haemoplasma and retrovirus testing in feline anaemia. *J Small Anim Pract*. 2010;51:192.

Thomovsky EJ, Bach J. Incidence of acute lung injury in dogs receiving transfusions. *J Am Vet Med Assoc*. 2014;244(2):170–174.

Urban R, et al. Hemostatic activity of canine frozen plasma for transfusion using thromboelastography. *J Vet Intern Med*. 2013;27:964.

Weinkle TK, et al. Evaluation of prognostic factors, survival rates, and treatment protocols for immune-mediated hemolytic anemia in dogs: 151 cases (1993-2002). *J Am Vet Med Assoc*. 2005;226: 1869.

Weltman JG, Fletcher DJ, Rogers C. Influence of cross-match on posttransfusion packed cell volume in feline packed red blood cell transfusion. *J Vet Emerg Crit Care*. 2014;24(4):429–436.

CHAPTER 83

Clinical Pathology in Greyhounds and Other Sighthounds



Since the early 1990s, more than 250,000 retired racing Greyhounds (RRGs) have been placed in adoptive homes, and this number continues to increase each year. Practicing veterinarians are facing an increasing number of Greyhounds for routine wellness examinations and medical and surgical ailments. Consequently, they must be aware of the unique hematologic and biochemical idiosyncrasies characteristic of the breed (Zaldívar-López et al., 2011a).

The Greyhounds' history as racing sighthounds has resulted in a unique physiology that distinguishes them from other breeds. Greyhounds have larger muscle mass than most breeds; high hematocrit (HCT); lengthened carpal, tarsal, metacarpal, and metatarsal bones; and a keen sense of sight. These adaptations, among others, have likely contributed to the unique hematologic and biochemical characteristics in Greyhounds compared with non-Greyhound breeds, which have been well documented over the last 50 years. Results of routine clinical pathology tests in RRGs frequently lie outside the reference ranges for dogs. Some of the hematologic peculiarities in Greyhounds have also been described in other sighthounds. This chapter reviews clinicopathologic features specific to Greyhound dogs; these may also apply to other sighthound breeds. We recently reported hematology and chemistry reference intervals (RIs) for Deerhounds (please see Sheerer et al., 2013).

HEMATOLOGY

Although many clinicopathologic differences between Greyhounds and other breeds have been investigated, most of the research has focused on differences in hematologic values in the breed. Hematologic RIs for the breed have been published (Campora et al., 2011).

ERYTHROCYTES

Previous studies have reported that Greyhounds have a higher HCT value and hemoglobin (Hb) concentration when compared with non-Greyhound dogs. Traditionally, high HCT, Hb, and red blood cell (RBC) values have been considered an adaptation to exercise, under selective breeding for superior track performance, resulting in dogs with higher total oxygen-carrying capacity; however, numerous studies are being done to further investigate the underlying factors influencing these hematologic features in Greyhounds. The macrocytosis historically reported in Greyhounds does not appear to be reproducible with current instruments.

Pretraining Greyhounds between 9 and 10 months of age were found to already have higher HCT, Hb, and RBC values, and a tendency toward higher MCV when compared with non–breed-specific reference ranges (Shiel et al., 2007a). The selective breeding for speed in this breed is likely the cause of altered Hb function and properties because of the imperative need for an adequate oxygen supply at the tissue level under extreme conditions—that is, during the race (Zaldívar-López et al., 2011b). Greyhounds have lower Hb P_{50} values (the partial pressure of oxygen at which 50% of the Hb is saturated) than non-Greyhounds. The oxyhemoglobin dissociation curve is left-shifted; thus the Greyhound's Hb has a higher affinity for oxygen than non-Greyhounds, despite similar concentrations of RBC 2,3-diphosphoglycerate (2,3-DPG; Sullivan et al., 1994). Therefore the high Hb and HCT in Greyhounds may be a compensatory change secondary to decreased oxygen delivery to the tissues (low P_{50}), as seen in humans with high-affinity hemoglobinopathies. We recently documented that Greyhound Hb has a few unique amino acid mutations relevant to the oxygen affinity properties, changing the position of the globin chains and "hoarding" oxygen (Bhatt et al., 2011). Unpublished molecular genetics studies of Greyhound Hb have confirmed this fact.

Excited or apprehensive Greyhounds frequently have a high HCT and reticulocyte count. We demonstrated that, immediately after a race, the HCT and reticulocyte count increase proportionally for a brief period of time (60-90 minutes) (Horvath et al., 2014). This likely represents splenic release of reticulocytes in response to catecholamines.

Interestingly, the dog erythrocyte antigen (DEA) distribution is different in Greyhounds than in other breeds. In a recent study, only 13.3% of RRGs had DEA 1.1 antigen in

contrast with 60.6% in all other breeds combined; 2.9% had DEA 1.2 antigen (versus 0 in other breeds). Almost two thirds (63.4%) of the Greyhounds were considered universal donors in contrast with 18.2% in the other breeds (Iazbik et al., 2010). In contrast, approximately 50% of Galgos Españoles (Spanish Greyhounds) are positive for DEA 1.1 antigen.

LEUKOCYTES

Previous studies reported lower mean white blood cell (WBC) counts in Greyhounds compared with other breeds. As noted, adult Greyhound RIs have been established for total WBC, neutrophil, and lymphocyte counts (Campora et al., 2011). In most Greyhounds, eosinophils lack the typical orange/pink granules when using Wright-Giemsa or rapid hematology stains. These atypical eosinophils may be mistaken for toxic neutrophils on a routine blood smear stained with Diff-Quik, leading to an unnecessary search for a source of infection (Iazbik et al., 2005). These gray eosinophils also occur in some other sighthound breeds, such as Whippets, Scottish Deerhounds, and Italian Greyhounds but are uncommon in Galgos Españoles.

PLATELETS

Greyhounds have lower platelet concentrations (PLT) than dogs of other breeds (Zaldívar-López et al., 2011a). The stem cell competition model of hematopoiesis has been proposed as a possible mechanism for the low platelet count observed in Greyhounds, suggesting that bipotential stem cells within the bone marrow are programmed to become megakaryocytes or erythrocyte precursors.

Other proposed mechanisms for low platelet counts in Greyhounds include splenic or pulmonary sequestration or a chronic, low-grade, immune-mediated process leading to decreased platelet life span. Anecdotally, platelets tend to clump more in Greyhounds than in other breeds, behaving more like feline platelets. Therefore in-depth investigation of a potential underlying cause of thrombocytopenia is not necessary in healthy Greyhounds with moderate decreases in platelet count (<100,000/μL).

HEMOSTASIS

The main function of the hemostatic system is to keep the blood flowing within the cardiovascular system. The term *Greyhound bleeder* was proposed to describe dogs that tend to bleed spontaneously following minor trauma or after a simple surgical procedure (Lara-Garcia et al., 2008). Severe postoperative bleeding 1 to 4 days after limb amputation for osteosarcoma or trauma has also been reported in Greyhounds, often resulting in the need for blood component therapy during the postoperative period. Historically, Greyhounds with spontaneous bleeding have had normal platelet counts for the breed, von Willebrand factor (vWF) concentration, one-stage prothrombin time (OSPT), and activated partial thromboplastin time (aPTT) at the time of postoperative hemorrhage, making common bleeding disorders such as thrombocytopenia and clotting factor or vWF deficiencies unlikely causes of the bleeding.

When using the PFA-100 (platelet function analyzer; Dade Behring, West Sacramento, CA) to investigate primary hemostasis, healthy Greyhounds had shorter mean closure times (CTs)—the time required for a platelet plug to form in the capillary aperture and halt blood flow—than the non-Greyhound group; however, CT ranges were similar to reported values for other dog breeds (Couto et al., 2006). Surprisingly, the lower platelet counts observed in the breed were not associated with prolongation of the CT; the shorter CTs in Greyhounds are likely explained by the higher PCV, and thus viscosity, in the breed. A higher PCV and whole blood viscosity lead to peripheral platelet distribution and consequent increased interaction with the blood vessel surface. Shorter CTs in the breed may be an adaptive platelet response to accommodate higher shear in Greyhounds because Greyhounds also have significantly higher arterial blood pressure and aortic velocity than non-Greyhounds.

Thromboelastography (TEG) allows for the evaluation of blood coagulation via assessment of the speed and strength of clot formation. TEG is dependent on the function of the primary and secondary hemostatic systems and fibrinolysis, all of which can be affected by certain illnesses, environmental conditions, and pharmacologic agents. It was found that Greyhounds have slower clot kinetics and weaker clot strength when compared with non-Greyhounds (Vilar et al., 2008).

Mechanisms of postoperative bleeding have been investigated in retired racers; it was found that approximately one in four Greyhounds has moderate to severe bleeding 36 to 48 hours after routine gonadectomy (Lara-Garcia et al., 2008). Numerous parameters were used to evaluate primary and secondary hemostasis preoperatively—platelet count (PLT), OSPT, aPTT, platelet function using the PFA-100, fibrinogen (FIB), D-dimer, plasminogen, antiplasmin (AP), antithrombin (AT) levels, vWF concentration (vWF Ag), vWF collagen binding assay (vWF CBA), and factor XIII assay. Hemostasis assays were repeated in RRGs that developed bleeding complications at the time of the event, and in an age- and sex-matched control group of RRGs that underwent the same surgical procedures at the same time and did not bleed. Results from this study suggest that excessive postoperative bleeding in RRGs is not attributable to a primary or secondary hemostatic defect but may be related to altered fibrinolysis; the bleeders had lower AP levels than nonbleeders preoperatively, suggesting activated fibrinolysis and a hypocoagulable state.

CLINICAL CHEMISTRY

Several studies reported differences in specific serum biochemical values in Greyhounds when compared with those of the general canine population. Veterinarians working with Greyhounds must consider these breed-specific differences when interpreting serum chemistry profiles because

interpretation based on standard canine reference ranges may lead to misdiagnoses. These differences have been confirmed in a recent study with a large number of healthy animals, in which even narrower and therefore more breed-specific RIs were established for Greyhound biochemistry parameters (Dunlop et al., 2011).

CREATININE/SDMA

Creatinine concentrations are significantly higher in Greyhounds than in non-Greyhounds (1.6 and 1.03 mg/dL, respectively; Feeman et al., 2003). Greyhounds have considerable muscle mass and predictably have higher body stores of phosphocreatine, which may result in higher serum creatinine concentrations. Greyhounds have a higher glomerular filtration rate (GFR) than non-Greyhounds (Drost et al., 2006). Therefore the most likely cause of high serum creatinine concentrations in Greyhounds is the large muscle mass. These differences in serum urea and creatinine concentrations were recently confirmed using a large number of Greyhounds, and the study indicated even narrower RIs (11.34-26.18 and 1.12-1.98 mg/dL, respectively; Dunlop et al., 2011). Actively racing Greyhounds usually have blood urea nitrogen values above the RI for dogs, primarily because of a raw meat–based diet.

Simmetric dimethylarginine (SDMA) is an amino acid metabolite excreted exclusively by glomerular filtration (Braf et al., 2014). Shortly after this test became available recently, we noticed that results were frequently above the RI (0-14 µg/dL) in a high proportion of Greyhounds. After several studies, it is clear that the RIs for SDMA should be higher in Greyhounds; a recent study proposes using 19.9 µg/dL as the upper limit of the RI for Greyhounds) (Liffman et al., in press); this should prevent overdiagnosing renal disease in this breed.

LIVER ENZYMES

Dunlop et al. (2011) reported narrower RIs for liver enzyme levels in Greyhounds, finding higher alanine aminotransferase (ALT) activity compared with the generic canine RI. The mechanism of this change is yet to be determined.

SERUM ELECTROLYTES AND ACID-BASE BALANCE

Serum concentrations of sodium, chloride, and bicarbonate are higher in Greyhounds than in non-Greyhounds, and serum calcium (and ionized calcium), magnesium, and potassium concentrations are lower (Zaldívar-López et al., 2011a). The same study also found that Greyhounds have higher serum glucose concentrations when using a Nova analyzer (Nova Analytical Systems, Niagara Falls, NY) but lower glucose concentrations than the non-Greyhounds when using a Roche Hitachi 911 analyzer (GMI, Ramsey, MN).

Venous and arterial blood gas results in Greyhounds are presented in Table 83.1. Greyhounds have significantly higher pH, partial pressure of oxygen (P_{O_2}), oxygen saturation (S_{O_2}), oxyhemoglobin (O_2Hb), total Hb (tHb), oxygen content (O_2Ct), and oxygen capacity (O_2Cap), and significantly lower deoxyhemoglobin (HHb) and P_{50} values when compared with non-Greyhounds (Zaldívar-López et al., 2011b). These findings support the fact that this breed is able to carry a higher concentration of total oxygen in the blood. As noted, this breed also has a lower P_{50} and therefore high oxygen affinity. Current studies on hemoglobin-based oxygen carriers have revealed that in certain tissues, a high-affinity oxygen carrier is beneficial, delivering oxygen to the tissues that need it most, which would be of benefit during strenuous exercise. Although counterintuitive to traditional wisdom, these mechanisms could explain the benefits of having a high-affinity Hb.

TABLE 83.1

Venous Cooximetry and Blood Gas Reference Intervals*

PARAMETER	REFERENCE INTERVAL	
	GREYHOUNDS	NON-GREYHOUNDS
P_{O_2} (mm Hg)	36.3-84.3	34.6-69.6
P_{CO_2} (mm Hg)	25.6-39.9	24.7-44.4
S_{O_2} (%)	78.6-99.8	54.4-99.8
tHb (g/dL)	18.1-25.0	15.0-21.3
O_2Hb (%)	75.6-97.4	54.7-96.1
COHb (%)	0.9-3.9	0.4-4.5
MetHb (%)	0.0-2.2	0.1-2.8
HHb (%)	0.4-21.2	2.7-40.0
P_{50} (mm Hg)	26.0-28.4	21.4-38.4
O_2Ct (mL/dL)	19.7-32.0	13.3-24.6
O_2Cap (mL/dL)	23.8-34.1	20.2-28.5

COHb, Carboxyhemoglobin; *HHb,* deoxyhemoglobin; *MetHb,* methemoglobin; *O_2Cap,* oxygen capacity; *O_2Ct,* oxygen content; *O_2Hb,* oxyhemoglobin; *P_{CO_2},* partial pressure of carbon dioxide; *P_{O_2},* partial pressure of oxygen; *S_{O_2},* oxygen saturation; *tHb,* total hemoglobin.

*$n = 57$. These were established by our group (Zaldívar-López et al., 2011b) using the STP CCX Analyzer (Nova Biomedical, Waltham, MA).

PROTEIN

Recently published Greyhound-specific reference ranges for total protein, albumin, and globulin are 5.2 to 6.7, 2.7 to 3.7, and 2.2 to 3.3 g/dL, respectively (Dunlop et al., 2011). Thus Greyhounds have lower plasma, serum protein, and globulin concentrations.

The hypoglobulinemia in Greyhounds using serum protein electrophoresis has been investigated further (SPE; Fayos et al., 2005). The concentrations of total protein, total globulin, and α_1-, α_2-, β_1-, and β_2-globulins were significantly lower and the albumin-to-globulin ratio (A/G) was significantly higher in Greyhounds than in non-Greyhounds. No significant difference was found in albumin or γ-globulin concentrations. Possible mechanisms include chronic plasma

volume expansion associated with chronic conditioning and training; however, this mechanism does not explain why only some protein fractions are affected or why they persist after Greyhounds retired from racing. It has been recently reported that mean serum immunoglobulin A (IgA) and IgM concentrations in Greyhounds are lower than in non-Greyhounds, which may contribute to the low β-globulin concentrations in Greyhounds (Clemente et al., 2010).

The concentration of acute-phase proteins in Greyhounds has been evaluated (Couto et al., 2009). Serum concentrations of C-reactive protein (CRP), haptoglobin (Hp), acid-soluble glycoprotein (ASG), ceruloplasmin (CP), and serum amyloid A (SAA) were measured and compared between a group of healthy RRGs and age- and gender-matched healthy non-Greyhound controls. The concentrations of Hp, determined by colorimetric and immunoturbidimetric methods, and ASG were significantly lower in Greyhounds than in non-Greyhounds. CRP and CP concentrations were not significantly different between groups, and SAA concentrations were below the detection limit in all dogs. Because Hp and ASG migrate in the α-globulin fraction, results from this study may explain the low α-globulin concentrations in Greyhounds.

THYROID HORMONES

Greyhounds, Whippets, Salukis, Scottish Deerhounds, Sloughis, and other sighthound breeds have basal total T_4 (tT_4) concentrations below non–breed-specific reference ranges. Free T_4 (fT_4) concentrations can also be low, although not to the same extent as tT_4. However, thyroid-stimulating hormone (TSH) concentrations are normal; in Greyhounds, they are in the lower quartile of the RI (Shiel et al., 2007b, 2010). Highly variable triiodothyronine (T_3) concentrations have been reported; however, fT_3 concentrations in Greyhounds are usually below non–breed-specific reference ranges. No increase in the tT_4 concentration after the administration of exogenous TSH has also been described in Greyhounds (Gaughan and Bruyette, 2001). Shiel et al. (2007b) investigated thyroid hormone concentration in pretraining Greyhounds. Young pretraining Greyhounds had lower tT_4 and fT_4 concentrations and a tendency toward higher total T_3 concentrations when compared with non–breed-specific reference ranges.

A recent study by Shiel et al. (2010) retrospectively assessed the use of serum thyroid hormone concentrations by veterinarians to diagnose hypothyroidism in 398 sighthounds, including Greyhounds (n = 347) and other sighthounds such as Borzois (n = 22), Salukis (n = 11), Irish Wolfhounds (n = 14), and Scottish Deerhounds (n = 4). A cross-sectional study was also performed to assess serum thyroid hormone concentrations in healthy Salukis. Practitioners who had submitted blood samples for thyroid hormone testing had diagnosed hypothyroidism in 286 of 398 (71.9%) sighthounds on the basis of low serum concentrations of tT_4 or tT_3 alone. Seventeen sighthounds (4.3%) also had low fT_4 or fT_3 concentrations, and 30 sighthounds (7.5%) were diagnosed with hypothyroidism despite the fact that all measured thyroid hormone concentrations were within their respective reference limits. Only 65 sighthounds (16.3%) had additional abnormalities suggestive of hypothyroidism (high serum TSH concentration or positive thyroglobulin autoantibody [TGAA]). In addition, when compared with standard (non–breed-specific) reference limits, 154 of 282 Salukis (54.6%) had tT_4 values, and 67 of 216 Salukis (31%) had fT_4 values below reference limits. These findings support the fact that other sighthound breeds also have low serum tT_4 concentrations.

CARDIAC TROPONINS AND PRO-B NATRIURETIC PEPTIDE

Previously documented cardiovascular findings in healthy Greyhounds included a higher heart weight–to–body weight ratio, higher left ventricular free wall thickness, functional murmurs with no detectable structural or physiologic abnormalities, and higher vertebral heart scores (VHSs) than non-Greyhounds. Cardiac troponin I (cTnI) is a polypeptide found specifically in cardiac muscle. Serum concentrations of cTnI have been used as diagnostic and prognostic indicators of heart disease, including cardiac infarction in humans and cardiomyopathy in dogs. Greyhounds have significantly higher serum cTnI concentrations compared with non-Greyhounds; however, no significant differences in serum cTnI were noted between Greyhounds and Boxers with and without arrhythmogenic right ventricular cardiomyopathy (ARVC; LaVecchio et al., 2009). Interestingly, several Greyhounds in our study had cTnI concentrations within or above the range of Boxers with ARVC. Greyhounds with a heart murmur, high VHS, and high cTnI level could be incorrectly diagnosed with myocardial disease; thus until a more precise reference range is established, caution should be used when interpreting serum cTnI concentrations in Greyhounds with suspected cardiac disease.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker whose plasma concentration is high in some dogs with cardiopulmonary disease. NT-proBNP is a diagnostic tool that can be used to help determine if a patient has congestive heart failure. Greyhounds have functional heart murmurs, relative cardiomegaly, and high serum cTnI concentration.

We prospectively evaluated healthy client-owned dogs including RRGs and non-Greyhounds and found that plasmaNT-proBNPconcentration in Greyhounds was significantly higher than in non-Greyhound control dogs (946 versus 632 pmol/L; $P < 0.005$); 46% of Greyhounds had NT-proBNP > 1000 pmol/L.

Again, using generic RIs for dogs will result in classifying numerous Greyhounds as having heart disease when running these assays.

Renin, Angiotensin, Aldosterone

Given that Greyhounds have unique cardiovascular features, including the fact that they have well-documented white coat hypertension, we evaluated the RAAS in 20 Greyhounds and 20 age- and weight-matched non-Greyhound dogs (Martinez

et al., 2017). The serum angiotensin-converting enzyme (ACE) activity was determined by fluorometric assay. All other RAAS hormones were determined by radioimmunoassay. Symmetric dimethylarginine (SDMA) was measured by immunoassay. Measurements were compared with blood pressure and urine albumin concentration.

Serum creatinine (1.5±0.2 versus 1.0±0.1 mg/dL, $P < 0.001$), sodium (149, range 147-152 versus 148, range 146-150 mEq/L, $P = 0.017$), and SDMA (16.1±2.9 versus 12.2±1.8 µg/dL, $P < 0.001$) concentrations were significantly higher in Greyhounds than in non-Greyhounds. Plasma renin activity (0.69, range 0.10-1.93 versus 0.65, range 0.27-2.93 ng/mL/h, $P = 0.60$) and ACE activity (4.5, range 2.1-8.5 versus 4.6, range 2.1-11.4 activity/mL; $P = 0.77$) were similar between groups and did not correlate with higher systolic pressures and albuminuria in Greyhounds. Plasma aldosterone concentration was significantly lower in Greyhounds versus non-Greyhounds (11, range 11-52 versus 15, range 11-56 pg/mL, respectively; $P = 0.002$). The lower aldosterone concentration in Greyhounds is likely an appropriate physiologic response to higher serum sodium concentration and blood pressure, suggesting that angiotensin II effects in the renal tubule predominate over those of aldosterone.

Cobalamine, Folate, and Homocysteine

Two decades ago, we made the observation that most normal RRGs had lower serum cobalamine concentreations than non-Greyhound dogs (Fig. 83.1). Recently, Grützner et al. (2012) documented that Greyhounds are the breed with the highest probability of having hypocobalaminemia. In subsequent studies, we evaluated the serum concentration of homocysteine, because in humans hypocobalaminemia and hypofolatemia have been associated with hyperhomocysteinemia. High serum homocysteine concentrations frequently result in cardiovascular disease and in thrombosis (Heilman et al., 2016). Hyperhomocysteinemia was identified in 41% of the 423 serum samples; however, it was significantly more common in Greyhounds with hypocobalaminemia and hypofolatemia (92%) than in those with normal concentrations of cobalamine and folate (61%, $P = 0.0806$). Serum homocysteine concentrations were significantly higher in healthy Greyhounds than in those with diarrhea or thrombosis; however, there were no differences in folate or cobalamine concentrations among these three groups.

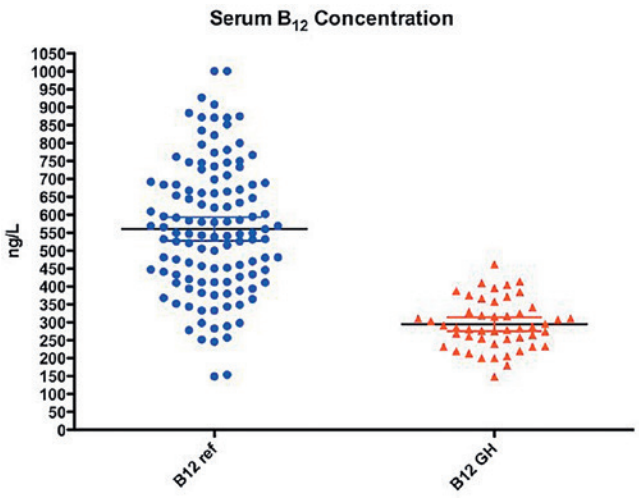


FIG 83.1
Serum cobalamin concentrations in Greyhounds and non-Greyhound dogs.

The low cobalamin and folate concentrations commonly seen in the breed should be taken into consideration when interpreting "diarrhea panels," because hypocobalaminemia and hypofolatemia are typically associated with several enteropathies, leading to unnecessary additional diagnostics in Greyhounds with diarrhea.

CLINICAL PATHOLOGY IN GREYHOUNDS: THE AUTHOR'S EXPERIENCE

Because of the well-known clinicopathologic peculiarities of this breed, the establishment of Greyhound-specific RIs has been of great interest to me for a long time. Several studies have been done involving different physiologic parameters (hematology, chemistry, coagulation, and blood gases) to help characterize these differences and establish RIs valid and specific for the breed.

The dogs used for the generation of these RIs are from two different populations. The first group is from the Greyhound Spay-Neuter-Dental Clinic at The Ohio State University for third- or fourth-year veterinary students in which Greyhounds from an adoption group (Greyhound Adoption of Ohio, Chagrin Falls, OH; www.greyhoundadoptionofoh.org) are spayed or neutered before being placed in adoptive homes. This program has a current animal use protocol (IACUC). Samples were collected over a 5-year span. The second group is the Greyhound blood donor population, which is a homogeneous population of healthy RRGs. Animals from both groups were considered healthy based on a normal physical examination and negative serology for *Ehrlichia canis, Anaplasma phagocytophilum, Borrelia burgdorferi,* and *Dirofilaria immitis* (Canine SNAP 4Dx Test, IDEXX Laboratories, Westbrook, ME).

Jugular or cephalic venous samples were collected in tubes containing sodium EDTA (for complete blood count [CBC]) and sodium citrate (for hemostasis assays), and without anticoagulant (for biochemical profiles). All CBC and hemostasis samples were analyzed within 4 hours of collection; the nonanticoagulated blood was immediately centrifuged and the serum was analyzed within 4 hours of sample collection. Samples for CBC were evaluated with LaserCyte or ProCyte Dx (IDEXX Laboratories) using the appropriate software settings. Samples with flags were not reevaluated because of a lack of additional blood samples. In a subset of dogs, CBCs were evaluated using a Cell-Dyn 3500 (Abbott Diagnostics, Santa Clara, CA). Differential WBC counts were performed manually by the staff at the Clinical

Pathology Laboratory at OSU, and plasma protein concentrations were obtained using a refractometer. The results obtained from the three hematology analyzers (CD-3500, LaserCyte, and ProCyte) are shown in Table 83.2.

The serum biochemistry profiles were determined using a COBAS c501 analyzer (Roche Diagnostics, Indianapolis; Table 83.3). For the conventional hemostasis assays (OSPT, aPTT, and FIB concentration), we used two different analyzers, the ACL 200 Coagulation Analyzer (Instrumentation Laboratory, Lexington, MA) and Stago Compact Analyzer (Diagnostica Stago, Parsippany, NJ). RIs are shown in Table 83.4.

Proposed RIs are summarized in Tables 83.1 through 83.4.



TABLE 83.2

Hematology Reference Intervals in Greyhounds*

PARAMETER	REFERENCE INTERVAL INSTRUMENTS FOR GREYHOUNDS			OTHER REFERENCE INTERVALS†	
	CD-3500	LASERCYTE	PROCYTE	GREYHOUND: ADVIA 120 AND ADVIA 2120	DOG: ADVIA 120
Total leukocytes ($\times10^9$/L)	3.3-7.5 (4.1-15.2)	4.4-10.8 (5.5-16.9)	3.6-6.9 (5.1-16.7)	3.38-8.51	5.84-20.26
Lymphocytes ($\times10^9$/L)	0.4-2.2 (1-4.6)	0.2-2.5 (0.5-4.9)	0.8-2.2 (1.1-5.1)	0.57-2.50	2.04-4.66
Neutrophils ($\times10^9$/L)	2.1-6.1 (4.1-15.2)	2.6-7.4 (2.0-12.0)	2.1-5.2 (2.9-11.6)	2.21-6.48	4.27-9.06
Monocytes ($\times10^9$/L)	0.0-0.5 (0-1.2)	0.3-1.1 (0.3-2.0)	0.1-0.3 (0.2-1.1)	0.01-0.75	0.24-2.04
Eosinophils ($\times10^9$/L)	0.0-0.6 (0-1.3)	0.0-1.1 (0.1-1.5)	0.0-1.0 (0.2-1.2)	0.00-0.31	0.1-1.2
Basophils ($\times10^9$/L)	0.0-0.0 (NA)	(0.00-0.01)	0.0-0.1 (0.0-0.1)	ND	ND
HCT (%)	46.9-62.5 (36-54)	42.7-61.5 (37-55)	51.5-71.0 (37.3-61.7)	50.0-68.0	42.0-62.0
Hb (g/dL)	16.3-22.0 (11.9-18.4)	15.1-20.4 (12.0-18.0)	17.4-24.1 (13.1-20.5)	16.9-22.8	13.7-20.3
RBC ($\times10^{12}$/L)	6.7-9.3 (4.9-8.2)	6.0-9.4 (5.5-8.0)	7.4-10.2 (5.6-8.8)	6.67-9.22	5.68-9.08
Reticulocytes ($\times10^9$/L)	ND	17.2-45.7 (14.7-17.9)	10.0-97.7 (6.6-100.7)	ND	ND
MCV (fL)	66.4-72.0 (64-75)	66.0-78.9 (60.0-77.0)	63.0-76.1 (61.6-73.5)	69.68-79.67	62.7-74.56
MCHC (g/dL)	34.1-36.0 (32.9-35.2)	29.4-38.2 (30.0-37.5)	33.1-35.1 (32.0-37.9)	ND	ND
MCH (pg)	ND	20.9-28.6 (18.5-30.0)	21.5-26.2 (21.2-25.9)	ND	ND
RDW (%)	14.2-17.2 (13.4-17.0)	14.7-15.9 (14.7-17.9)	16.0-22.2 (13.6-21.7)	ND	ND
Platelet count ($\times10^9$/L)	135.4-235.3 (106-424)	117.0-295.0 (175-500)	112.0-204.7 (148-484)	144.5-309.0	173.1-496.5
MPV (fL)	ND	6.9-11.8 (NA)	8.6-11.9 (8.7-13.2)	ND	ND

NA, Not available; *ND,* not done; *RDW,* red blood cell distribution width.

*These were determined at The Ohio State University using three different instruments: CD-3500 Analyzer (Abbott Diagnostics, Santa Clara, CA) with manual differential cell count; LaserCyte Analyzer (IDEXX Laboratories, Westbrook, ME); and ProCyteDx Analyzer (IDEXX). Instrument generic reference intervals are shown in parentheses. Additional columns correspond to published reference intervals for Greyhounds (Campora et al., 2011) and for dogs (Bauer N et al.: Reference intervals and method optimization for variables reflecting hypocoagulatory and hypercoagulatory states in dogs using the STA Compact automated analyzer, *J Vet Diagn Invest* 21:803, 2009).

†ADVIA 120 and ADVIA 2120, Siemens Medical Solutions USA, Malvern, Pa.

From Zaldívar-López S et al.: Clinical pathology of Greyhounds and other sighthounds, *Vet Clin Pathol* 40:414, 2011a.

TABLE 83.3

Reference Intervals for Serum Chemistry Profiles in Greyhounds (n = 100) Using the COBAS c501 Analyzer*

PARAMETER	REFERENCE INTERVAL GREYHOUNDS	OSU
BUN (mg/dL)	11-21	5-20
Creatinine (mg/dL)	1.0-1.7	0.6-1.6
Phosphorus (mg/dL)	2.3-5.3	3.2-8.1
Total calcium (mg/dL)	9.4-11.4	9.3-11.6
Sodium (mEq/L)	144.0-156.0	143-153
Potassium (mEq/L)	3.5-4.4	4.2-5.4
Chloride (mEq/L)	107.7-118.8	109-120
Anion gap	9.0-19.9	15-25
Osmolality	285.1-310.0	285-304
Bicarbonate (mmol/L)	20.0-31.3	16-25
ALT (IU/L)	28.0-81.9	10-55
AST (IU/L)	24.0-57.0	12-40
ALP (IU/L)	19.0-90.0	15-120
ALPCAP (IU/L)	0.05-31.0	0-6
CK (IU/L)	76.0-254.0	50-400
Cholesterol (mg/dL)	91.0-210.3	80-315
Bilirubin (mg/dL)	0.07-0.3	0.1-0.4
Total protein (g/dL)	4.8-6.3	5.1-7.1
Albumin (g/dL)	2.9-3.9	2.9-4.2
Globulin (g/dL)	1.7-3.0	2.2-2.9
A/G ratio	1.0-2.2	0.8-2.2
Glucose (mg/dL)	77.1-121.0	77-126

ALP, Alkaline phosphatase; *ALPCAP,* steroid isoenzyme of ALP; *ALT,* alanine aminotransferase; *AST,* aspartate transaminase; *BUN,* blood urea nitrogen; *CK,* creatine kinase.
*Roche Diagnostics, Indianapolis.
From Zaldívar-López S et al.: Clinical pathology of Greyhounds and other sighthounds, *Vet Clin Pathol* 40:414, 2011a.

TABLE 83.4

Reference Intervals for Hemostasis Profiles*

PARAMETER	ACL 200 (n = 88)†	STAGO COMPACT (n = 62)‡	OSU
OSPT (sec)	6.2-7.6	6.9-8.3	6-7.5
APTT (sec)	11.2-18.1	9.7-12.1	9-21
Fibrinogen (mg/dL)	83.0-190.4	88.7-180.1	100-384

*Determined at The Ohio State University (OSU) in Greyhounds using an ACL 200 Coagulation Analyzer (Instrumentation Laboratory, Lexington, MA) and Stago STA Compact CT (Diagnostica Stago, Parsippany, NJ).
†3.8% sodium citrate concentration tubes.
‡3.2% sodium citrate concentration tubes.
From Zaldívar-López S et al.: Clinical pathology of Greyhounds and other sighthounds, *Vet Clin Pathol* 40:414, 2011a.

CONCLUSIONS

Greyhounds have hematologic and serum biochemical values that frequently lie outside the reference ranges established for non-Greyhounds, suggesting differences in many aspects of their physiology. For these reasons, the establishment of breed- or group-specific (e.g., sighthounds) reference ranges is essential for the correct diagnosis and subsequent treatment of medical disorders based on clinicopathologic abnormalities. As the number of RRG adoptions increases in the United States, veterinarians will be faced with the challenge of interpreting laboratory parameters in light of the hematologic idiosyncrasies of the breed. Although the sample size in these studies is not as large as recommended for the creation of RIs, approximate intervals have been provided that will benefit clinicians by providing a better understanding of the hematologic and biochemical differences between Greyhounds and non-Greyhounds, thus helping avoid misdiagnoses based on wrong RIs for these sighthound breeds.

Suggested Readings

Bhatt VS, et al. Structure of Greyhound hemoglobin: origin of high oxygen affinity. *Acta Crystallogr D Biol Crystallogr*. 2011;67:395.

Braff J, et al. Relationship between serum symmetric dimethylarginine concentration and glomerular filtration rate in cats. *J Vet Intern Med*. 2014;28(6):1699.

Campora C, et al. Determination of haematological reference intervals in healthy adult greyhounds. *J Small Anim Pract*. 2011;52:301.

Clemente M, et al. Serum concentrations of IgG, IgA, and IgM in retired racing Greyhounds. *Vet Clin Pathol*. 2010;39:436.

Couto CG, et al. Acute phase protein concentrations in retired racing Greyhounds. *Vet Clin Pathol*. 2009;38:219.

Couto CG, et al. Evaluation of platelet aggregation using a point-of-care instrument in retired racing Greyhounds. *J Vet Intern Med*. 2006;20:365.

Couto KM, et al. Plasma N-terminal pro-B-type natriuretic peptide concentration in healthy retired racing Greyhounds. *Vet Clin Pathol*. 2015;44(3):405.

Drost WT, et al. Comparison of glomerular filtration rate between greyhounds and non-Greyhounds. *J Vet Intern Med*. 2006;20:544.

Dunlop MM, et al. Determination of serum biochemistry reference intervals in a large sample of adult greyhounds. *J Small Anim Pract*. 2011;52:4.

Fayos M, et al. Serum protein electrophoresis in retired racing Greyhounds. *Vet Clin Pathol*. 2005;34:397.

Feeman WE, et al. Serum creatinine concentrations in retired racing Greyhounds. *Vet Clin Pathol*. 2003;32:40.

Gaughan KR, Bruyette DS. Thyroid function testing in Greyhounds. *Am J Vet Res*. 2001;62:1130.

Grützner N, et al. Evaluation of serum cobalamin concentrations in dogs of 164 dog breeds (2006-2010). *J Vet Diagn Invest*. 2012.

Heilmann RM, et al. Hyperhomocysteinemia in Greyhounds and its Association with Hypofolatemia and Other Clinicopathologic Variables. *J Vet Intern Med*. 2016;31(1):109.

Horvath SJ, et al. Effects of racing on reticulocyte concentrations in Greyhounds. *Vet Clin Pathol*. 2014;43(1):15.

Iazbik MC, et al. Prevalence of dog erythrocyte antigens in retired racing Greyhounds. *Vet Clin Pathol*. 2010;39:433.

Iazbik MC, Couto CG. Morphologic characterization of specific granules in Greyhound eosinophils. *Vet Clin Pathol*. 2005;34:140.

Lara-Garcia A, et al. Postoperative bleeding in retired racing greyhounds. *J Vet Intern Med*. 2008;22:525.

LaVecchio D, et al. Serum cardiac troponin I concentration in retired racing greyhounds. *J Vet Intern Med*. 2009;23:87.

Liffman R, et al. Establishment of reference intervals for serum symmetric dimethylarginine in adult non-racing Greyhounds. *Vet Clin Pathol*. 2018;18:263.

Martinez J, et al. The renin-angiotensin-aldosterone system in Greyhounds and non-Greyhound dogs. *J Vet Intern Med*. 2017;31:988.

Sheerer KN, et al. Haematological and biochemical values in North American Scottish deerhounds. *J Small Anim Pract*. 2013;54(7):354.

Shiel RE, et al. Assessment of criteria used by veterinary practitioners to diagnose hypothyroidism in sighthounds and investigation of serum thyroid hormone concentrations in healthy Salukis. *J Am Vet Med Assoc*. 2010;236:302.

Shiel RE, et al. Hematologic values in young pretraining healthy Greyhounds. *Vet Clin Pathol*. 2007a;36:274.

Shiel RE, et al. Thyroid hormone concentrations in young, healthy, pretraining greyhounds. *Vet Rec*. 2007b;161:616.

Sullivan PS, et al. Platelet concentration and hemoglobin function in greyhounds. *J Am Vet Med Assoc*. 1994;205:838.

Vilar P, et al. Thromboelastographic tracings in retired racing greyhounds and in non-greyhound dogs. *J Vet Intern Med*. 2008;22:374.

Zaldívar-López S, et al. Blood gas analysis and cooximetry in retired racing Greyhounds. *J Vet Emerg Crit Care (San Antonio)*. 2011b;21:24.

Zaldívar-López S, et al. Clinical pathology of Greyhounds and other sighthounds. *Vet Clin Pathol*. 2011a;40:414.

CHAPTER 84

Erythrocytosis



DEFINITION AND CLASSIFICATION

Erythrocytosis is defined as an increase in the circulating red blood cell (RBC) mass and is manifested hematologically as an increase in the packed cell volume (PCV) or hematocrit (HCT) above the reference interval (RI). Because determination of the RBC mass in a clinical setting is cumbersome and impractical, a diagnosis of erythrocytosis is typically made on the basis of the high HCT, not an increased RBC mass. Certain dog breeds, such as most sighthounds, have HCT values above the RI for the species; this also occurs in dogs that live at high altitudes. For example, normal actively racing or retired racing Greyhounds can have an HCT as high as 70%. An increase in the RBC numbers may lead to severe hemorheologic alterations, resulting in clinical signs secondary to hyperviscosity. Although the term *polycythemia* is commonly used to refer to this hematologic abnormality, it is incorrect because the term actually means an increase in the numbers of all circulating cells ("poly" means multiple).

On the basis of its pathogenesis, erythrocytosis can be classified as relative or absolute (Box 84.1). The term *relative erythrocytosis* refers to hemoconcentration (i.e., dehydration) and is characterized by an increased PCV, usually in association with an increased serum or plasma protein concentration; in dogs and cats with relative erythrocytosis, the RBC mass is normal. Dogs with hemorrhagic gastroenteritis (HGE) frequently have relative erythrocytosis associated with normal serum or plasma protein concentration; the reason for the lack of increase in the protein concentration is unknown, but the erythrocytosis resolves with appropriate fluid therapy. In absolute or true erythrocytosis, the RBC mass is increased; it can be classified as primary or secondary depending on the pathogenesis and serum erythropoietin (Epo) concentration or activity.

Primary erythrocytosis (polycythemia rubra vera [PRV]) results from an autonomous, Epo-independent proliferation of RBC precursors in the bone marrow and is considered a myeloproliferative disease. As a consequence, most dogs and cats with PRV have low to nondetectable serum Epo concentrations. Recently, JAK2 mutations were identified in a dog with PRV (Beurlet et al., 2011); this mutation is common in humans with PRV. In a recent study, the clinical and hematologic features of 18 cats with primary erythrocytosis were reviewed (Darcy et al., 2018).

Secondary erythrocytosis results from increased orthotopic (produced by the kidneys) or heterotopic (produced in sites other than the kidneys) Epo production. Orthotopic (physiologically appropriate) Epo production occurs in response to tissue hypoxia, such as that occurring at a high altitude and in the settings of chronic cardiopulmonary disease, right-to-left cardiovascular shunts, and carboxyhemoglobinemia. Tumor-associated erythrocytosis (heterotopic or orthotopic Epo production) has been observed in humans with a wide variety of neoplasms, in dogs with renal masses, and in dogs with spindle cell sarcomas (e.g., nasal fibrosarcoma, schwannoma, cecal gastrointestinal stromal tumor). In a recent retrospective study we conducted, 15/29 (51%) of dogs with renal lymphoma had erythrocytosis. Hormonal stimuli may also trigger erythrocytosis in animals with normal tissue oxygenation, such as in dogs with hyperadrenocorticism and cats with hyperthyroidism. At the author's clinic, secondary erythrocytosis is more common in dogs, and PRV is more common in cats. However, erythrocytosis is rare in both species. Interestingly, although infiltrative renal diseases (e.g., lymphoma, feline infectious peritonitis) are common in cats, they rarely result in secondary erythrocytosis. Recently a cat with a renal adenocarcinoma and secondary erythrocytosis was reported.

Clinical and Clinicopathologic Findings

The clinical signs may occur acutely and consist primarily of functional abnormalities of the central nervous system (e.g., behavioral, motor, or sensory changes; seizures). In cats, signs of a transverse myelopathy are common; in the retrospective study of 18 cats with erythrocytosis, the most common clinical signs were seizures and mentation changes (Darcy et al., ePub ahead of print). A common manifestation of erythrocytosis in dogs is paroxysmal sneezing, likely caused by increased blood viscosity in the nasal mucosa.

BOX 84.1

Classification and Causes of Erythrocytosis in Cats and Dogs

Relative Erythrocytosis (Pseudoerythrocytosis)

Hemoconcentration

Absolute Erythrocytosis

Primary

PRV

Secondary

Appropriate (i.e., secondary to decreased tissue oxygenation)
- Pulmonary disease
- Right-to-left cardiovascular shunts
- High altitude
- Hemoglobinopathies?

Inappropriate (normal tissue oxygenation)
- Hyperadrenocorticism
- Hyperthyroidism
- Renal masses
- Neoplasms in other areas

PRV, Polycythemia rubra vera; *?,* not well documented in cats or dogs.

Cardiopulmonary signs may occasionally be present. Although the erythrocytosis usually develops gradually, most affected animals do not exhibit clinical signs until the RBCs have reached a critical mass or the PCV has reached a certain percentage. A PCV of 70% to 80% is relatively common in cats and dogs with absolute erythrocytosis. Physical examination and historical findings in dogs and cats with erythrocytosis may also include bright red mucous membranes (plethora), erythema, differential cyanosis, polyuria, polydipsia, splenomegaly, renal masses, and a neoplasm elsewhere.

Hematologic abnormalities are usually limited to the erythrocytosis and reticulocytosis (in light of a high HCT), although thrombocytosis may be present in cats and dogs with PRV. Microcytosis caused by relative iron deficiency (i.e., the erythron is extremely active and is relatively iron deficient) is common in dogs with erythrocytosis.

Diagnosis and Treatment

Relative erythrocytosis (i.e., dehydration) should be ruled out first. This is done primarily on the basis of the serum (or plasma) protein concentration, which is typically high in dogs and cats with this form of erythrocytosis. However, in certain circumstances, such as HGE, dogs may have a high HCT but a relatively normal serum protein concentration. Radioisotopic RBC mass determinations are commonly performed in humans with erythrocytosis, but this test is usually not done in small animals.

The initial approach used in small animals with absolute erythrocytosis is to decrease the blood viscosity by reducing the number of circulating RBCs. This can be accomplished by performing therapeutic phlebotomies, in which a certain volume of blood (≈20 mL/kg) is collected from a central vein through a blood collection set. In cats, a 19-gauge butterfly catheter coupled to a 60-mL syringe containing 500 to 600 U of heparin diluted in 3 to 5 mL of saline solution is typically used to collect blood from the jugular vein under chemical restraint; we use sevoflurane inhalant anesthesia. Interestingly, leeches have been used in a cat with PRV (Nett et al., 2001). Gradual phlebotomy (5 mL/kg, repeated as needed) is recommended for dogs and cats with right-to-left shunts and erythrocytosis because an increased RBC mass appears to be the body's way of enhancing oxygen delivery to the tissues, thereby compensating for the chronic hypoxemia in these animals. Because sudden decreases in blood volume can result in marked hypotension, a peripheral vein catheter can be used to administer an equivalent volume of saline solution at the same time that blood is being collected. However, collapsing episodes during or immediately after phlebotomy are extremely rare. As a result of its high viscosity in patients with erythrocytosis, it may be extremely difficult to obtain blood through a relatively small (e.g., 19-gauge) catheter.

Once the patient's condition has been stabilized, the cause of the erythrocytosis should be sought (Fig. 84.1). The following approach is recommended. The patient's cardiopulmonary status should first be evaluated by auscultation, precordial palpation, thoracic radiography, or echocardiography (see Chapters 1 and 2). An arterial blood sample should be obtained for blood gas analysis to rule out hypoxemia and pulse oximetry used to evaluate oxygenation. In some animals with erythrocytosis, the blood viscosity is so high that the blood gas analyzer, which is usually flow-dependent, cannot generate results; in this case, a therapeutic phlebotomy should be performed before a sample is resubmitted for testing (i.e., the partial pressure of oxygen, P_{O_2}, does not change after therapeutic phlebotomy). If the P_{O_2} is normal, excretory abdominal ultrasonography or computed tomography should be performed to determine whether masses or infiltrative lesions are present in the kidneys. If no such lesions are found, the patient most likely does not have renal secondary erythrocytosis, so a search for an extrarenal neoplasm should be conducted. Determination of serum Epo activity is not currently available for dogs and cats. In my experience, bone marrow evaluation of cats and dogs with erythrocytosis is unrewarding; in most cases the only abnormality is a decreased myeloid-to-erythroid ratio as a result of erythroid hyperplasia.

If PRV is diagnosed, hydroxyurea (30 mg/kg PO q24h) is administered for 7 to 10 days, after which the dosage can be gradually decreased or the dosing interval gradually lengthened to fulfill the patient's needs. Phlebotomy should be repeated as dictated by the patient's clinical signs. If the final diagnosis is secondary erythrocytosis, the primary disorder should be treated (e.g., surgery for a renal mass). The hydroxyurea protocol can also be used successfully in dogs with right-to-left shunts and secondary erythrocytosis (Moore and Stepien, 2001).

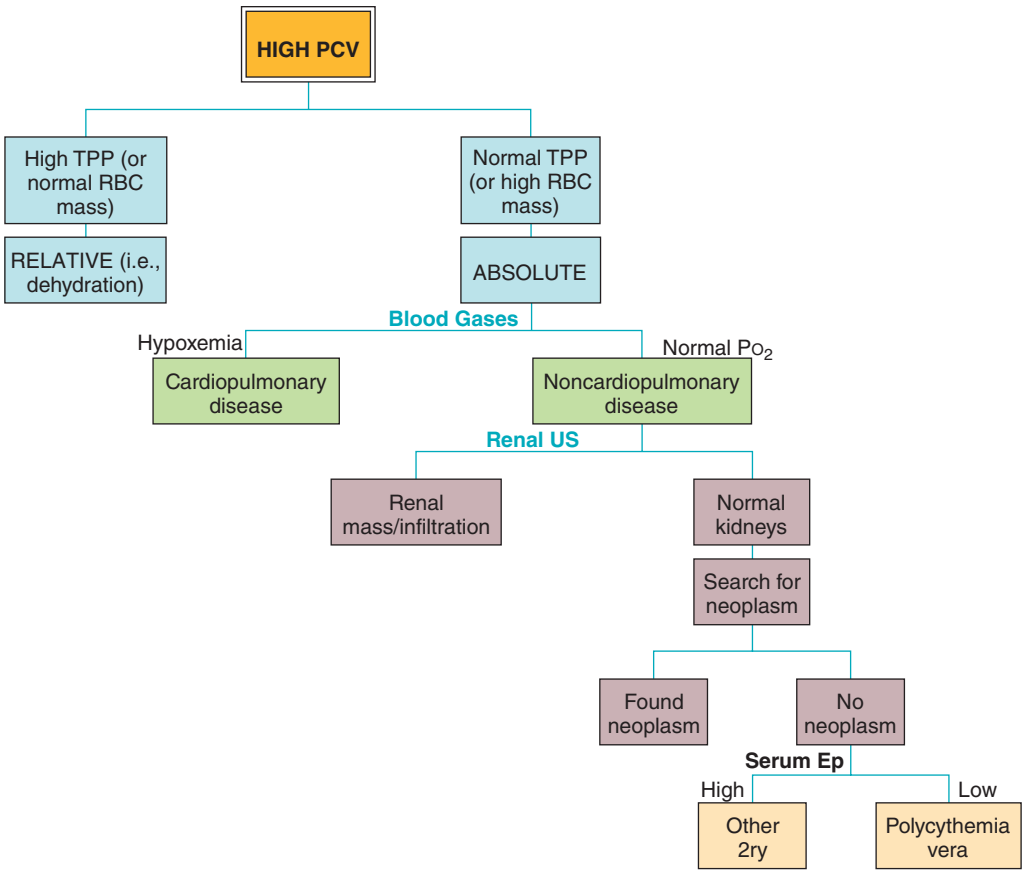


FIG 84.1
Diagnostic approach to the dog or cat with erythrocytosis. *Ep,* Erythropoietin; *PCV,* packed cell volume; *RBC,* red blood cell; *TPP,* total plasma protein; *US,* ultrasonography; *2ry,* secondary.

Most dogs and cats with PRV have extremely long survival times (>2 years) if treated with hydroxyurea, with or without a phlebotomy. Because this drug is potentially myelosuppressive, complete blood counts should be performed every 4 to 8 weeks and the dose adjusted according to the neutrophil count (see Chapter 75). The prognosis in dogs and cats with secondary erythrocytosis depends on the nature of the primary disease.

Suggested Readings

Beurlet S, et al. Identification of JAK2 mutations in canine primary polycythemia. *Exp Hematol*. 2011;39:542.

Campbell KL. Diagnosis and management of polycythemia in dogs. *Compend Cont Educ*. 1990;12:443.

Cook SM, et al. Serum erythropoietin concentrations measured by radioimmunoassay in normal, polycythemic, and anemic dogs and cats. *J Vet Intern Med*. 1994;8:18.

Darcy H, et al. Feline primary erythrocytosis: a multicentre case series of 18 cats. *J Fel Med Surg*. 2018;20:1192.

Durno AS, et al. Polycythemia and inappropriate erythropoietin concentrations in two dogs with renal T-cell lymphoma. *J Amer Anim Hosp Assoc*. 2011;47:122.

Hasler AH, et al. Serum erythropoietin values in polycythemic cats. *J Am Anim Hosp Assoc*. 1996;32:294.

Moore KW, Stepien RL. Hydroxyurea for treatment of polycythemia secondary to right-to-left shunting patent ductus arteriosus in 4 dogs. *J Vet Intern Med*. 2001;15:418.

Nett CS, et al. Leeching as initial treatment in a cat with polycythaemia vera. *J Small Anim Pract*. 2001;42:554.

Noh S, et al. Renal-adenocarcinoma-associated erythrocytosis in a cat. *Hemoglobin*. 2012;11:12.

Peterson ME, et al. Diagnosis and treatment of polycythemia. In: Kirk RW, eds. *Current veterinary therapy VIII*. Philadelphia: WB Saunders; 1983.

Randolph JF, et al. Erythrocytosis and polycythemia. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. 6th ed. Ames, Iowa: Wiley-Blackwell; 2010:162.

Sato K, et al. Secondary erythrocytosis associated with high plasma erythropoietin concentrations in a dog with cecal leiomyosarcoma. *J Am Vet Med Assoc*. 2002;220:486.

Van Vonderen IK, et al. Polyuria and polydipsia and disturbed vasopressin release in 2 dogs with secondary polycythemia. *J Vet Intern Med*. 1997;11:300.

Yamauchi A, et al. Secondary erythrocytosis associated with schwannoma in a dog. *J Vet Med Sci*. 2004;66:1605.

CHAPTER 85

Leukopenia and Leukocytosis



GENERAL CONSIDERATIONS

The leukogram, evaluated as part of the complete blood count (CBC), includes a quantification of the total number of white blood cells (WBCs) and the differential WBC count; ideally, it should also include morphologic leukocyte evaluation. Although a specific disorder is rarely diagnosed on the basis of the leukogram, the information obtained may be useful in limiting the number of differential diagnoses or in predicting the severity of the disease and its prognosis. In addition, sequential leukograms are helpful in monitoring a patient's response to therapy.

According to standard laboratory techniques, all nucleated cells are counted during a WBC count, including nucleated red blood cells (nRBCs). Differential leukograms determined by particle counters used at human referral laboratories are typically not valid for cats and dogs. New veterinary benchtop analyzers provide reliable WBC total and differential counts. The ProCyte Dx provides a five-part differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and includes flags for nRBCs and left shift or toxic neutrophils, whereas the impedance-based analyzers provide a three- or five-part differential count. As a general rule, when a benchtop hematology analyzer yields values outside the reference interval (RI) or the values are flagged, the clinician or a technician should carefully examine the graphics (see Figs. 79.6, 80.4, 80.6, 82.1, 82.3, and 82.9) and a blood smear.

Leukocytosis occurs if the WBC count exceeds the upper limit of the RI for the species; leukopenia occurs if the WBC count is below the RI. In some breeds of dogs (e.g., Belgian Tervuren, Greyhound), the WBC and neutrophil counts are frequently below the RI for the species, thus resulting in an erroneous diagnosis of leukopenia and neutropenia in an otherwise healthy dog. This should be kept in mind in dogs undergoing chemotherapy (see Chapters 75 and 76) because treatment delays based on a low WBC or neutrophil count (normal for the breed) have a detrimental effect on the patient's well being.

A differential WBC count may be reported in relative (percentages) or absolute numbers (number of cells per microliter). However, the absolute leukocyte numbers, not the percentages, should always be evaluated because the latter may be misleading, particularly if the WBC count is very high or very low. For example, a total WBC count of 3000 cells/μL (or 3×10^9/L) and a differential WBC count of 90% lymphocytes and 10% neutrophils can lead to one of the following two conclusions:

1. Based on the percentages alone, the dog has lymphocytosis and neutropenia; in this situation, the clinician may erroneously focus on the lymphocytosis rather than the neutropenia.
2. Based on the absolute numbers, the dog has severe neutropenia (300 cells/μL) with a normal lymphocyte count (i.e., 2700 cells/μL).

The latter obviously reflects the actual clinical situation. The clinician should then concentrate on determining the cause of the neutropenia and ignore the normal lymphocyte count.

NORMAL LEUKOCYTE MORPHOLOGY AND PHYSIOLOGY

From a morphologic standpoint, leukocytes can be classified as polymorphonuclear or mononuclear. Polymorphonuclear cells include the neutrophils, eosinophils, and basophils; the mononuclear cells include the monocytes and lymphocytes. Their basic morphologic and physiologic characteristics are outside the scope of this chapter.

The following morphologic changes have important clinical implications and should thus be recognized:

1. Neutrophils may become toxic in response to injury (Fig. 85.1); toxic neutrophils display characteristic cytoplasmic changes, including basophilia or granulation, vacuolation,

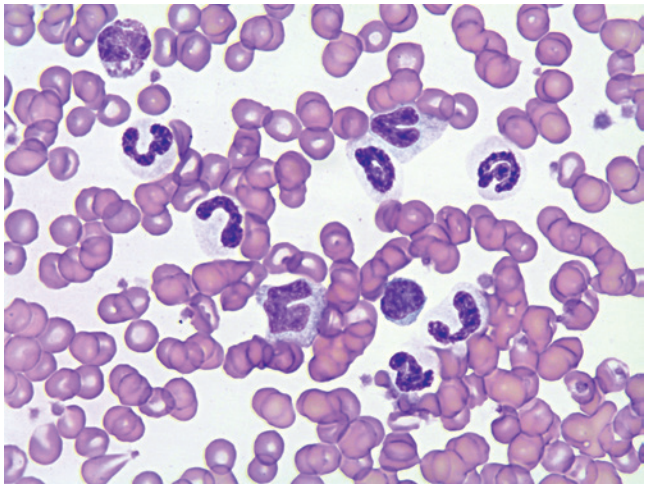


FIG 85.1
Left shift and toxic changes in a dog with an intraabdominal abscess (Diff-Quik stain; ×1000).

and Döhle bodies (small, bluish cytoplasmic inclusions that consist of aggregates of endoplasmic reticulum). This change occurs in the bone marrow and indicates that the neutrophils are "losing the battle" against the offending agent.

2. Giant neutrophils, bands, and metamyelocytes are large polyploidal cells that may result from skipped cell division; they represent yet another manifestation of systemic inflammation and are more common in cats than dogs.

Other neutrophil morphologic abnormalities recognized during a careful examination of blood smears include the Pelger-Huët anomaly (cats and dogs) and Chédiak-Higashi syndrome (cats). The Pelger-Huët anomaly occurs when the nucleus of polymorphonuclear leukocytes fails to divide, but the nuclear chromatin and cytoplasm maturation is complete (i.e., the nucleus has a band-like appearance, with mature clumped chromatin). Cats and dogs with this anomaly typically have profound "left shifts" in the absence of clinical signs. On careful examination of the smear, however, the cells in the left shift are mature cells with nuclear hyposegmentation and not immature neutrophils. This anomaly may be acquired or inherited (autosomal dominant) and is usually considered of minimal clinical relevance. We have seen it primarily in Australian Cattle dogs and in dogs undergoing chemotherapy.

Chédiak-Higashi syndrome, a lethal autosomal recessive condition of Persian cats with smoke-colored haircoats and yellow eyes, is characterized by enlarged neutrophilic and eosinophilic granules in association with partial albinism, photophobia, increased susceptibility to infections, bleeding tendencies, and abnormal melanocytes.

Nuclear hypersegmentation (i.e., four or more distinct nuclear lobes) may result from a prolonged neutrophil transit time (old neutrophils). It occurs in dogs with hyperadrenocorticism, cats and dogs receiving corticosteroid therapy, and cats and dogs with chronic inflammatory disorders.

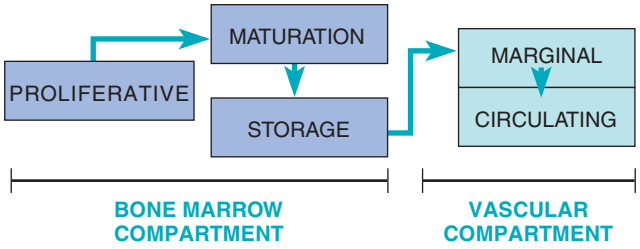


FIG 85.2
Theoretical neutrophil compartments in bone marrow and blood.

A basic review of neutrophil physiology follows. Three theoretical physiologic neutrophil compartments exist in the bone marrow (Fig. 85.2). The proliferative compartment is composed of dividing cells (myeloblasts, progranulocytes, and myelocytes); myeloblasts take approximately 48 to 60 hours to mature into metamyelocytes. The maturation compartment consists of metamyelocytes and band neutrophils; the transit time through this compartment is 46 to 70 hours. The storage compartment is composed of mature neutrophils; the transit time in this compartment is approximately 50 hours, and it contains an estimated 5-day supply of neutrophils. Mature neutrophils leave the bone marrow by a random process that involves changes in cell deformability and adhesiveness.

Two neutrophil pools are present in the vascular compartment (see Fig. 85.2). The marginal neutrophil pool (MNP) consists of neutrophils that are adhered to the vascular endothelium (and are thus not counted during a CBC). The circulating neutrophil pool (CNP) consists of the neutrophils circulating in the blood (i.e., the cells counted during a differential WBC count). The total blood neutrophil pool is composed of the MNP plus the CNP. In dogs the CNP is approximately equal in size to that of the MNP. However, in cats the MNP is approximately two to three times the size of the CNP. The neutrophil has an average blood transit time of approximately 6 to 8 hours in dogs and 10 to 12 hours in cats, with all blood neutrophils replaced every 2 to 2.5 days. Once the neutrophils leave the blood vessel (by diapedesis), they normally do not return to the circulation and are lost in the lungs, gut, other tissues, urine, or saliva.

LEUKOCYTE CHANGES IN DISEASE

Because the lower limit for the reference range for basophil and monocyte counts is 0, basopenia and monocytopenia are not discussed.

NEUTROPENIA

Neutropenia is defined as an absolute decrease in the number of circulating neutrophils. It can result from decreased (or impaired) cell production within the bone marrow or from

BOX 85.1

Causes of Neutropenia in Cats and Dogs

Decreased or Ineffective Production of Cells in the Proliferating Pool

Myelophthisis (neoplastic infiltration of the bone marrow)

Myeloproliferative disorders (D, C)
Lymphoproliferative disorders (D, C)
Systemic mast cell disease (D, C)
Malignant histiocytosis (D, C?)
Myelofibrosis (D, C)

Drug-induced neutropenia

Anticancer and immunosuppressive agents (C, D)
Chloramphenicol (C)
Griseofulvin (C)
Sulfa-trimethoprim (D, C)
Estrogen (D)
Phenylbutazone (D)
Phenobarbital (D)
Other

Toxins

Industrial chemical compounds (inorganic solvents, benzene) (D, C)
Fusarium sporotrichiella toxin (C)

Infectious diseases

Parvovirus infection (D, C)
Retrovirus infection (feline leukemia virus, feline immunodeficiency virus) (C)
Myelodysplastic or preleukemic syndromes (C)
Cyclic neutropenia (C)
Histoplasmosis (D, C)
Ehrlichiosis (D, C)
Anaplasmosis (D, C)
Toxoplasmosis (D, C)
Early canine distemper virus infection (D)
Early canine hepatitis virus infection (D)

Other

Idiopathic bone marrow hypoplasia-aplasia (D, C)
Cyclic neutropenia of gray Collies (D)
Trapped neutrophil syndrome of Border Collies (D)
Acquired cyclic neutropenia (D, C)
Steroid-responsive neutropenia (D, C)

Sequestration of Neutrophils in the Marginating Pool

Endotoxic shock (D, C)
Anaphylactic shock (D, C)
Anesthesia (D?, C?)

Sudden, Excessive Tissue Demand, Destruction, or Consumption

Infectious diseases

Peracute, overwhelming bacterial infection (e.g., peritonitis, aspiration pneumonia, salmonellosis, metritis, pyothorax) (D, C)
Viral infection (e.g., canine distemper or hepatitis, preclinical stage) (D)

- **Drug-induced disorders (D, C) (see above)**
- **Immune-mediated disorders (D, C)**
- **Paraneoplastic (D)**
- **"Hypersplenism" (D?)**

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

the increased margination or destruction of circulating neutrophils (Box 85.1). Neutropenia is relatively common in cats and dogs. The clinician should keep in mind, however, that normal cats may have neutrophil counts of 1800 to 2300/μL; this reference range is also true for Greyhounds and some of the other sighthounds.

In dogs and cats evaluated in a teaching hospital (Brown and Rogers, 2001), infectious diseases (feline leukemia virus, feline immunodeficiency virus, parvovirus) were the most common comorbid conditions, accounting for almost 52% of the cases of neutropenia. Sepsis or endotoxemia accounted for 11% of the cases, as did drug-associated neutropenia (e.g., chemotherapy, phenobarbital, antibacterials); primary bone marrow disease was found in 4% of the patients. The cause of the neutropenia was unclear in 21% of the patients. Border Collies commonly have neutropenia; this syndrome has been described as the trapped neutrophil syndrome, an autosomal recessive trait caused by a mutation in the *VPS13B* gene (Mizukami et al., 2012). Steroid-responsive (immune-mediated) neutropenia is relatively common in dogs and cats. Recently, Devine et al. reviewed the records of 35 dogs with this condition (Devine et al., 2017). The most common clinical signs were lethargy/anorexia (63%), pyrexia (46%), vomiting/diarrhea (43%), pain/lameness (34%), and lymphadenopathy (17%); 11% of the dogs were asymptomatic (Devine et al., 2017). Bone marrow cytologic evaluation revealed myeloid hyperplasia in 66% and myeloid hypoplasia in 29% of the dogs; 20% of the samples had a maturation arrest. Most dogs (97%) had a rapid and sustained response to corticosteroid therapy at immunosuppressive doses; some dogs also received additional immunosuppressive drugs. The neutropenia relapsed in 34% of the dogs on discontinuation of the immunosuppressive treatment.

Clinical signs in neutropenic cats and dogs are usually vague and nonspecific; they include anorexia, lethargy, pyrexia, and mild gastrointestinal tract signs, as described

earlier. Oral ulceration, a common feature of neutropenia in humans, does not seem to occur in small animals. Neutropenia is frequently an incidental finding in an otherwise healthy dog or cat (i.e., the patient is asymptomatic). If the neutropenia is caused by peripheral neutrophil consumption (a septic process), most animals exhibit clinical signs. Dogs and cats with parvoviral enteritis have neutropenia in association with severe vomiting, diarrhea, or both. Cats and dogs with neutropenia can occasionally present in septic shock (pale, hypoperfused, hypothermic) and should be treated aggressively.

The evaluation of neutropenic cats and dogs should include the following:

- Detailed drug history (e.g., estrogen or phenylbutazone in dogs, griseofulvin in cats; see Box 85.1)
- Vaccination history (e.g., was the cat vaccinated against panleukopenia or the dog against parvoviral enteritis?)
- Complete physical examination and imaging in search of a septic focus
- Serologic, virologic, or molecular tests for infectious diseases (e.g., feline leukemia virus, feline immunodeficiency virus, canine ehrlichiosis and anaplasmosis, parvoviral enteritis, etc.)
- If necessary, bone marrow cytologic or histopathologic studies

Evaluation of changes in a blood smear or analyzer graphics is important for establishing the pathogenesis of the neutropenia. As a general rule, benchtop hematology analyzers provide total neutrophil counts and do not distinguish mature neutrophils from bands, reemphasizing the value of evaluating the blood smear. As discussed earlier, the ProCyte Dx provides a left shift flag; in addition, toxic neutrophils or bands can easily be recognized by evaluating the graphics (Fig. 85.3). If a dog or cat has anemia and/or thrombocytopenia in association with neutropenia, and if the anemia is nonregenerative, a primary bone marrow disorder should be strongly suspected. If a dog or cat has regenerative anemia and spherocytosis in association with neutropenia, an immune-mediated disease or hemophagocytic malignant histiocytosis should be considered in the differential diagnoses.

The presence of toxic changes in the neutrophils or a left shift (see later) tend to suggest infection; that is, toxic changes and left shifts are typically absent in dogs and cats with steroid-responsive neutropenia or primary bone marrow disorders. In a study of 248 dogs with toxic neutrophil changes conducted in Israel (Aroch et al., 2005), dogs with pyometra, parvoviral infection, peritonitis, pancreatitis, and septicemia were significantly, and not surprisingly, more likely to have toxic changes than those in the control group. The mortality rate was significantly higher in the dogs

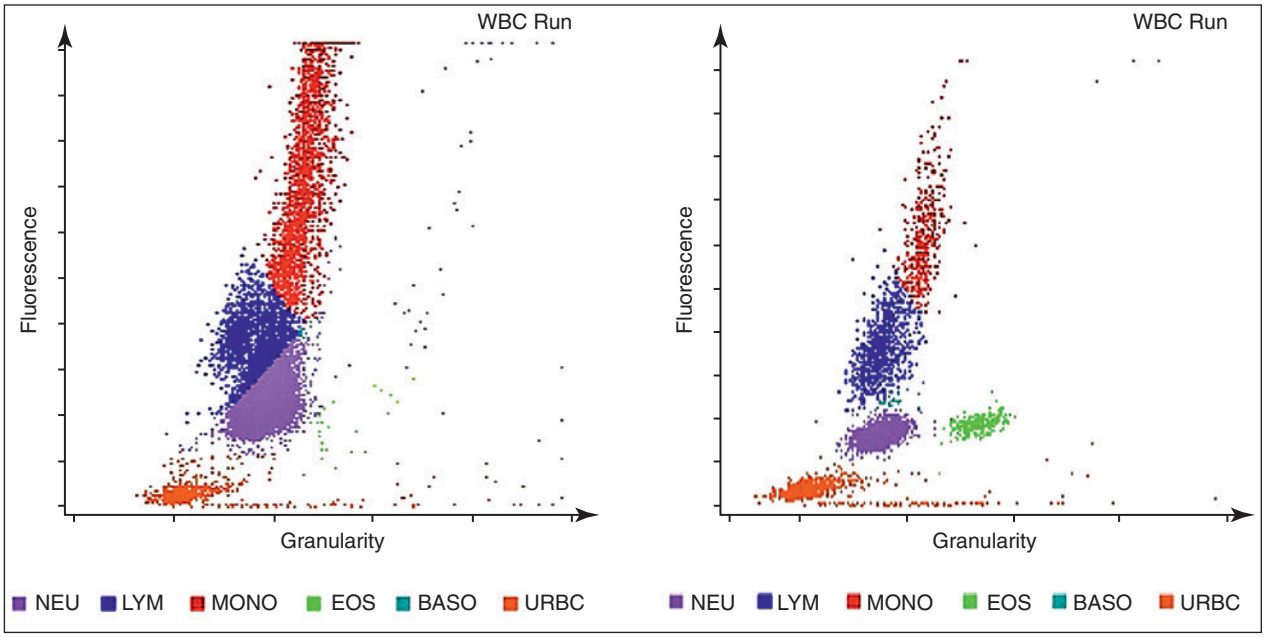


FIG 85.3
Leukocyte graphics (dot plots) from a ProCyteDx depicting left shift/neutrophil toxicity in a dog with sepsis *(left)* and in a normal dog *(right)*. Notice the absence of individual clouds and the straight line between the neutrophil *(purple)* and lymphocyte *(blue)* populations and between the lymphocyte *(blue)* and monocyte *(red)* populations. You can see the remaining normal lymphocyte population bulging on the left of the lymphocyte cloud. The wide monocyte cloud also reflects left shift/toxicity and/or activated or reactive monocytes.

with toxic neutrophils (24.2 versus 11.7%, $P < 0.001$); the cost of hospitalization was also significantly higher. Interestingly, toxic neutrophil changes were also significantly associated with acute renal failure, immune-mediated hemolytic anemia, and disseminated intravascular coagulation. Similar results were found in a study of 150 cats (Segev et al., 2006); cats with toxic neutrophils had a similar mortality rate than control cats (20% versus 15%), but the duration of hospitalization was significantly longer (3.0 versus 1.1 days).

In a recent study of 31 cats (Klainbart et al., 2017), sepsis was associated with pyothorax (32%), septic peritonitis (23%), feline panleukopenia virus infection (16%), bite wounds (16%), cellulitis/abscesses (10%), and pyometra (3%). Most cats had tachycardia and were febrile. Most cats (88%) had toxic neutrophils and/or a left shift (73%). The 30-day survival rate was 63%.

Evaluation of sequential leukograms in neutropenic dogs and cats is helpful in excluding transient or cyclic neutropenia (or cyclic hematopoiesis).

If the pathogenesis of neutropenia cannot be ascertained, sophisticated diagnostic techniques such as testing for antineutrophil antibodies, leukocyte nuclear scanning, or leukocyte kinetic studies can be performed. As noted, normal cats and Greyhounds can have low neutrophil counts. Therefore, if a cat or a Greyhound with a neutrophil count of 1800 to 2300/µL is brought in for evaluation (or, more likely, if the "neutropenia" is detected during a routine hematologic evaluation), a conservative approach (e.g., repeat the CBC in 2-3 weeks) is indicated as long as no other clinical or hematologic abnormalities are found (e.g., left shift, toxic changes).

Because corticosteroid-responsive (or immune-mediated) neutropenia has been well characterized in cats and dogs, if most infectious and neoplastic causes of neutropenia have been ruled out in an asymptomatic neutropenic animal, an in-hospital therapeutic trial of immunosuppressive doses of corticosteroids (prednisone, 2-4 mg/kg/day orally [PO] for dogs, or dexamethasone, 4 mg/cat PO once a week) can be instituted. Responses are usually observed within 24 to 96 hours of the start of treatment in these patients. Treatment is continued as for dogs with immune hemolytic anemia and other immune-mediated disorders (see Chapters 72 and 73; Fig. 85.4).

Asymptomatic, afebrile neutropenic dogs and cats should be treated with broad-spectrum bactericidal antibiotics because they are at high risk for sepsis. My drug of choice for dogs is trimethoprim-sulfamethoxazole, 15 mg/kg PO q12h; another drug that can be used in dogs and is preferred in cats is enrofloxacin (or another fluoroquinolone), 5 to 10 mg/kg PO q24h. Antibiotics with an anaerobic spectrum should not be used because they deplete intestinal anaerobes, a protective bacterial population; recent research has clearly illustrated the role of the microbiome in modulating the immune response in mammals.

Neutropenic febrile (or symptomatic) cats and dogs constitute a medical emergency and should be treated with aggressive intravenous (IV) antibiotic therapy. My treatment of choice consists of a combination of ampicillin (20 mg/kg IV q8h) and enrofloxacin (5-10 mg/kg IV q24h).

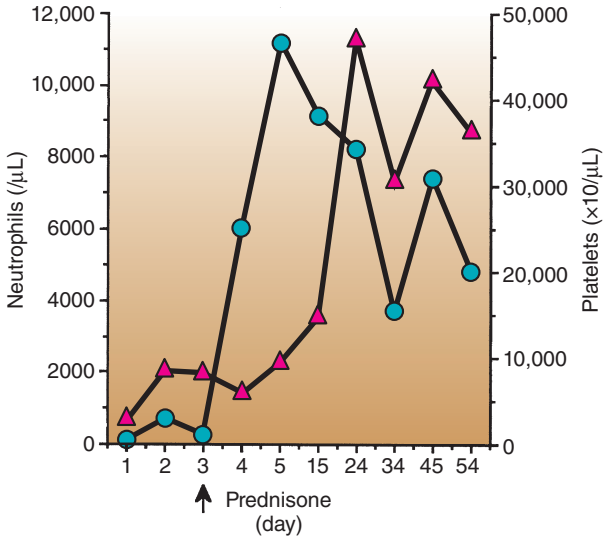


FIG 85.4
Response to therapy in a 6-year-old, female, spayed Airedale Terrier with steroid-responsive neutropenia and thrombocytopenia. Note the rapid response to immunosuppressive doses of prednisone. –•–, Polymorphonuclear neutrophils (in microliters); –Δ–, platelets ($\times 10^3/\mu L$).

Neutrophil production can be stimulated by the administration of human recombinant granulocyte colony-stimulating factor (G-CSF; 5 µg/kg subcutaneously q24h). Although results are spectacular, the responses are usually short-lived because of the counteractive effects of anti-CSF antibodies produced by the affected dog or cat. Lithium carbonate (10 mg/kg PO q12h) can increase the neutrophil counts in dogs; the therapeutic trough serum concentration of lithium is 0.8 to 1.5 mmol/L. This drug should be used with caution in dogs with a decreased glomerular filtration rate because it is primarily excreted by the kidneys. Lithium carbonate does not appear to be effective in cats and may be toxic.

NEUTROPHILIA

Neutrophilia is defined as an absolute increase in the number of neutrophils; it is the most common cause of leukocytosis in dogs and cats. Several terms used to characterize neutrophilia are defined in the following text.

The term *mature neutrophilia* refers to an increase in the number of segmented (mature) neutrophils, without an increase in the number of immature forms (e.g., bands). The term *neutrophilia with a left shift* refers to an increase in the number of mature and immature neutrophils (>300/µL, or 0.3×10^9/L bands). A regenerative left shift is associated with increased numbers of immature neutrophils in

which the number of immature forms does not exceed the number of mature neutrophils; most dogs and cats with a regenerative left shift have leukocytosis. A degenerative left shift occurs when the number of immature forms exceeds that of mature neutrophils; the number of the latter may be normal, low, or high. Degenerative left shifts are usually suggestive of an aggressive disease; toxic neutrophil changes (see earlier) are common in dogs and cats with degenerative left shifts. Disorders commonly associated with degenerative left shifts include pyothorax, septic peritonitis, bacterial pneumonia, pyometra, prostatitis, and acute pyelonephritis. The term *extreme neutrophilia* refers to situations in which the neutrophil count is above 50,000/μL (50×10^9/L); it can be associated with a left shift or mature neutrophilia. Diseases typically associated with extreme leukocytosis include septic foci (e.g., pyometra), immune-mediated diseases, hepatozoonosis, mycobacteriosis, and chronic myelogenous leukemia. A leukemoid reaction refers to a marked neutrophilia with a severe left shift, which includes metamyelocytes and myelocytes. It indicates severe inflammatory disease and may be difficult to distinguish from chronic granulocytic (myelogenous) leukemia (see Chapter 80).

Although a high percentage of cats and dogs with neutrophilia have underlying infectious disorders, neutrophilia is not synonymous with infection. Rather, neutrophilia in cats and dogs is commonly the result of inflammatory or neoplastic processes. Several disorders resulting in neutrophilia are listed in Box 85.2.

Of note, neutrophilia commonly results from endogenous epinephrine release (physiologic neutrophilia). This neutrophilia, which is associated with the release of neutrophils from the MNP, is transient (lasting 20-30 minutes after endogenous release of catecholamines) and is commonly associated with erythrocytosis and lymphocytosis, the latter primarily in cats.

The endogenous release or exogenous administration of corticosteroids results in stress- or corticosteroid-induced neutrophilia, which are associated with decreased neutrophil egress from the vasculature and increased bone marrow release of neutrophils from the storage pool. Other hematologic changes typical of a stress leukogram include lymphopenia, eosinopenia, and monocytosis; the latter is uncommon in cats. These abnormalities are commonly seen in sick dogs and cats. Dogs with hypoadrenocorticism and inflammatory/infectious diseases typically lack the neutrophilic response of normal dogs; that is, they are sick but do not have a stress leukogram.

Clinical signs in cats and dogs with neutrophilia are usually secondary to the underlying disorder. Pyrexia may or may not be present. If the patient has persistent neutrophilia, the neutrophils display toxic changes (see p. 1371), or a degenerative left shift is present, every effort should be made to identify a septic focus or an infectious agent promptly. The workup in these animals should include a thorough physical examination (e.g., abscess), thoracic and abdominal radiography (e.g., pneumonia, pleural or abdominal effusion), abdominal ultrasonography (e.g., peritonitis, pancreatic or hepatic abscess), and the collection of blood, urine, fluid, or tissue samples for cytology and bacterial and fungal cultures. As noted, autologous or allogeneic neutrophils labeled with radionuclides (e.g., technetium-99m or indium-111) can be injected intravenously and the septic focus or foci identified by gamma camera imaging, but this is rarely done; an inflammatory focus can also be detected by radiolabeled ciprofloxacin.

The treatment of dogs and cats with neutrophilia is aimed at the primary cause. Empiric antibiotic therapy with a broad-spectrum bactericidal antibiotic (e.g., trimethoprim-sulfamethoxazole, enrofloxacin, cephalosporin, amoxicillin) is an acceptable approach if a cause for the neutrophilia cannot be identified after exhaustive clinical and clinicopathologic evaluation or as the first line of treatment in a fairly asymptomatic dog or cat.

BOX 85.2

Causes of Neutrophilia in Cats and Dogs

Physiologic or Epinephrine-Induced Neutrophilia

- Fear (C)
- Excitement (?)
- Exercise (?)
- *Seizures (D, C)*
- Parturition (?)

Stress- or Corticosteroid-Induced Neutrophilia

- Pain (?)
- Anesthesia (?)
- **Trauma (D, C)**
- *Neoplasia (D, C)*
- **Hyperadrenocorticism (D)**
- Metabolic disorders (?)
- Chronic disorders (D, C)

Inflammation or Increased Tissue Demand

- Infection (bacterial, viral, fungal, parasitic) (D, C)
- Tissue trauma and/or necrosis (D, C)
- Immune-mediated disorders (D)
- *Neoplasia (D, C)*
- *Metabolic (uremia, diabetic ketoacidosis) (D, C)*
- Burns (D, C)
- Neutrophil function abnormalities (D)
- Other (acute hemorrhage, hemolysis) (D, C)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

EOSINOPENIA

Eosinopenia is defined as an absolute decrease in the number of circulating eosinophils. It is commonly seen as part of the stress leukogram or with exogenous corticosteroid administration and is usually of little clinical relevance.

EOSINOPHILIA

Eosinophilia is defined as an absolute increase in the circulating eosinophil numbers. It is relatively common in small animals and can have a variety of causes (Box 85.3). Because eosinophilia is common in dogs and cats with endoparasites or ectoparasites, no animal should undergo a thorough evaluation for eosinophilia before parasitic causes have been ruled out. In cats, flea infestation usually results in marked increases in the eosinophil count (>15,000/μL, or 15×10^9/L). In dogs, eosinophilia is frequently seen in roundworm and hookworm infestations or with dirofilariasis or dipetalonemiasis. Three other relatively common causes of eosinophilia in cats include eosinophilic granuloma complex, bronchial asthma, and eosinophilic gastroenteritis. A clinical entity resembling feline hypereosinophilic syndrome has been reported in Rottweilers (Sykes et al., 2001); in addition, lesions compatible with oral eosinophilic granulomas have been reported in Siberian Huskies. Eosinophilia can also occur in dogs and cats with mast cell tumors, but it is rare. In cats, eosinophilia may occur in association with lymphoma (i.e., tumor-associated eosinophilia).

Clinical signs in dogs and cats with eosinophilia are related to the primary disorder rather than to the hematologic abnormality. Because eosinophilia is so commonly found in animals with parasitic diseases, clinical evaluation of these animals should mainly be aimed at excluding these disorders. Once this has been done, other causes of eosinophilia should be pursued (see Box 85.3) by using the appropriate diagnostic procedure (e.g., tracheal wash or pulmonary fine-needle aspiration for pulmonary infiltrates with eosinophils, endoscopic biopsy for eosinophilic gastroenteritis). Treatment is usually aimed at the primary disorder.

A syndrome with high eosinophil counts in peripheral blood and tissue infiltration with eosinophils has been well documented in cats, Rottweilers, and occasionally other dog breeds. This syndrome is termed *hypereosinophilic syndrome* and is usually indistinguishable from eosinophilic leukemia. These patients have primarily gastrointestinal tract signs, although multisystemic signs are also common. In cats, treatment with immunosuppressive doses of corticosteroids, 6-thioguanine, cytosine arabinoside, cyclophosphamide, and other anticancer agents (see Chapter 76) has been unrewarding, and most affected patients die within weeks of diagnosis. Clinical response to some of these drugs has been documented in Rottweilers.

BOX 85.3

Causes of Eosinophilia in Cats and Dogs

Parasitic Disorders

- *Ancylostomiasis (D)*
- **Dirofilariasis (D, C)**
- **Dipetalonemiasis (D)**
- **Ctenocephalides (D, C)**
- Filaroidiasis (C)
- Aelurostrongylosis (C)
- *Ascariasis (D, C)*
- Paragonimiasis (D, C)

Hypersensitivity Disorders

- **Atopy (D, C)**
- **Flea allergy dermatitis (D, C)**
- **Food allergy (D, C)**

Eosinophilic Infiltrative Disorders

- **Eosinophilic granuloma complex (C)**
- **Feline bronchial asthma (C)**
- Pulmonary infiltrates with eosinophils (D)
- **Eosinophilic gastroenteritis/colitis (D, C)**
- *Hypereosinophilic syndrome (D, C)*

Infectious Diseases

- Upper respiratory tract viral disorders (C?)
- Feline panleukopenia (C?)
- Feline infectious peritonitis (C?)
- Toxoplasmosis (C)
- Suppurative processes (D, C)

Neoplasia

- *Mast cell tumors (D, C)*
- Lymphomas (D, **C**)
- Myeloproliferative disorders (C)
- Solid tumors (D, C)

Miscellaneous

- Soft tissue trauma (D?, C?)
- Feline urologic syndrome (C?)
- Cardiomyopathy (D?, C?)
- Renal failure (D?, C?)
- Hyperthyroidism (C?)
- Estrus (D?)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

BASOPHILIA

Basophilia is defined as an absolute increase in the basophil numbers and is commonly associated with eosinophilia. Because basophils are similar to tissue mast cells, their numbers increase in disorders characterized by excessive immunoglobulin E production and binding and in a variety of nonspecific inflammatory disorders. Causes of basophilia are listed in Box 85.4.

MONOCYTOSIS

Monocytosis refers to an absolute increase in monocyte numbers. It can occur in response to inflammatory, neoplastic, or degenerative stimuli. In some patients with acute leukemia, the WBC dot plots reveal a large monocyte cloud of abnormal configuration, even though the total monocyte numbers may be normal (see Fig. 80.4). Although monocytosis has traditionally been observed primarily in chronic inflammatory processes, it is also common in acute disorders. Causes of monocytosis in cats and dogs are listed in

BOX 85.4

Causes of Basophilia in Cats and Dogs

Disorders Associated With Immunoglobulin E Production and Binding

- Heartworm disease (**D,** C)
- *Inhalant dermatitis (D, C)*

Inflammatory Diseases

- **Gastrointestinal tract disease (D, C)**
- **Respiratory tract disease (D, C)**

Neoplasms

- *Mast cell tumors (D, C)*
- Lymphomatoid granulomatosis (D, C)
- Basophilic leukemia (D)

Associated With Hyperlipoproteinemia

- Hypothyroidism (D?)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

BOX 85.5

Causes of Monocytosis in Cats and Dogs

Inflammation

- ***Infectious disorders***
- ***Bacteria***
  - **Pyometra (D, C)**
  - **Abscesses (D, C)**
  - **Peritonitis (D, C)**
  - **Pyothorax (D, C)**
  - **Osteomyelitis (D, C)**
  - **Prostatitis (D)**
- ***Higher bacteria***
  - *Nocardia (D, C)*
  - *Actinomyces (D, C)*
  - Mycobacteria (D, C)
- ***Intracellular parasites***
  - Mycoplasma (D, C)
- ***Fungi***
  - **Blastomyces (D, C)**
  - **Histoplasma (D, C)**
  - Cryptococcus (D, C)
  - Coccidioides (D)
- ***Parasites***
  - Heartworms (D, C?)
- ***Immune-mediated disorders***
  - **Hemolytic anemia (D, C)**
  - Dermatitis (D, C)
  - *Polyarthritis (D, C)*

Trauma With Severe Crushing Injuries (D, C)
Hemorrhage Into Tissues or Body Cavities (D, C)

Stress- or Corticosteroid-Induced Disorders (D)

- **Neoplasia**
  - Associated with tumor necrosis (D, C)
  - Lymphoma (D, C)
  - Myelodysplastic disorders (D, C)
- ***Leukemias***
  - Myelomonocytic leukemia (D, C)
  - Monocytic leukemia (D, C)
  - Myelogenous leukemia (D, C)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

Box 85.5. The monocytosis in dogs is typically more pronounced than that in cats; monocytosis is extremely rare in Greyhounds.

Monocytosis is part of a stress leukogram in dogs. It can result from a variety of bacterial, fungal, and protozoal diseases. In the Midwest, systemic fungal disorders (e.g., histoplasmosis and blastomycosis) are relatively common causes. Because monocytes are precursors of tissue macrophages, granulomatous and pyogranulomatous reactions commonly result in monocytosis (see Box 85.5). In addition, immune-mediated injury resulting in cell destruction (e.g., immune hemolysis, polyarthritis) and certain neoplasms (e.g., lymphomas) may cause monocytosis. Some neoplasms secrete CSFs for monocytes and can result in marked monocytosis (>5000/μL or 5×10^9/L). Although rare, monocytic leukemia can occur.

The nature of the clinical evaluation in patients with monocytosis is similar to that used with neutrophilia: it should concentrate on identifying infectious foci. If an immune-mediated disorder is suspected, arthrocentesis to obtain fluid for analysis or other immune tests (see Chapters 69 and 71) should be performed. Treatment should be aimed at the primary disorder.

LYMPHOPENIA

Lymphopenia is defined as an absolute decrease in the lymphocyte count. It constitutes one of the most common hematologic abnormalities in hospitalized or sick dogs and cats, in which it is attributed to the effects of endogenous corticosteroids (stress leukogram). The typical lymphocyte count in a sick dog or cat is 1000 to 1500/μL. Lymphopenia is also commonly identified in dogs and cats with chronic loss of lymph, such as those with chylothorax or intestinal lymphangiectasia (Box 85.6).

In general, cats and dogs with lymphopenia have obvious clinical abnormalities. As a general rule, it should be ignored (i.e., a diagnosis should not be pursued) in sick cats and dogs and in those receiving corticosteroids or chemotherapy. The lymphocyte count should be reevaluated after the clinical abnormalities have resolved or steroid therapy has been

BOX 85.6

Causes of Lymphopenia in Cats and Dogs

Corticosteroid or Stress-Induced Disorders (D, C)
(see Box 85.2)

Loss of Lymph

- **Lymphangiectasia (D, C)**
- **Chylothorax (D, C)**

Impaired Lymphopoiesis

- **Chemotherapy (D, C)**
- **Long-term corticosteroid use (D, C)**

Viral Diseases

- *Parvoviruses (D, C)*
- Feline infectious peritonitis (C)
- *Feline leukemia virus (C)*
- *Feline immunodeficiency virus (C)*
- Canine distemper (D)
- Canine infectious hepatitis (D)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

BOX 85.7

Causes of Lymphocytosis in Cats and Dogs

Physiologic or Epinephrine-Induced Disorders (C)
(see Box 85.2)

Prolonged Antigenic Stimulation

- ***Chronic infection***
  - **Ehrlichiosis (D, C?)**
  - **Anaplasmosis (D, C)**
  - Chagas' disease (D)
  - Babesiosis (D)
  - Leishmaniasis (D)
- ***Hypersensitivity reactions (?)***
- ***Immune-mediated disease (?)***
- ***Postvaccinal reaction (D, C)***

Leukemia

- **Lymphocytic (D, C)**
- **Lymphoblastic (C, D)**

Hypoadrenocorticism (D)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
C, Cat; *D,* dog; *?,* poorly documented.

discontinued. Contrary to popular belief, lymphopenia does not appear to predispose to infection.

In addition, I pay particular attention to the absence of lymphopenia in a sick dog (or cat), because it suggests that there is a lymphocyte response (i.e., vector borne diseases, immune mediated diseases), that the stress leukogram is absent due to lack of corticosteroids (Addison), or that the analyzer is counting other cells as lymphocytes.

LYMPHOCYTOSIS

Lymphocytosis is defined as an absolute increase in lymphocyte numbers. It is common in several clinical situations, including fear (cats; see earlier, "Neutrophilia"), vaccination (dogs and possibly cats), chronic ehrlichiosis (dogs), anaplasmosis (dogs and cats), Addison disease (hypoadrenocorticism, dogs), and chronic lymphocytic leukemia (CLL). The lymphocytes are morphologically normal in all these disorders, with the exception of vaccination reactions, in which reactive lymphocytes (larger cells with a dark blue cytoplasm) are commonly seen. High numbers of morphologically abnormal (blast) lymphoid cells are found in dogs and cats with acute lymphoblastic leukemia (see Chapter 80).

In cats with marked lymphocytosis and neutrophilia, endogenous release of catecholamines should be ruled out as the cause of these hematologic abnormalities. If the cat is fractious and blood cannot be collected without a considerable struggle, a blood sample should be collected under chemical restraint.

Recent vaccination should be ruled out in dogs with lymphocytosis and reactive lymphocytes in the blood smear. Most dogs with lymphocyte counts of more than 10,000 cells/μL (10×10^9/L) have chronic ehrlichiosis, CLL, or leishmaniasis; dogs with monocytic ehrlichiosis or anaplasmosis frequently have increased numbers of large granular lymphocytes (LGLs), larger lymphocytes with abundant cytoplasm, and large azurophilic cytoplasmic granules. LGL lymphocytosis can also occur in dogs with CLL. Lymphocyte counts of more than 20,000 cells/μL (20×10^9/L) are extremely rare in dogs with ehrlichiosis; that is, dogs with more than 20,000 lymphocytes/μL more likely have CLL. A high proportion of these dogs also has hyperproteinemia caused by a monoclonal or polyclonal gammopathy (see Chapter 89). The clinical and hematologic features of monocytic ehrlichiosis and CLL are similar (e.g., cytopenia, hyperproteinemia, hepatosplenomegaly, lymphadenopathy). Serologic tests or polymerase chain reaction (PCR) testing for *Ehrlichia canis,* immunophenotyping of peripheral blood lymphocytes, PCR assay for clonality, and bone marrow aspiration findings may be helpful in differentiating these two disorders. Bone marrow cytologic findings in dogs with chronic ehrlichiosis usually consist of generalized hematopoietic hypoplasia and plasmacytosis, whereas hypoplasia with increased numbers of lymphocytes is more common in dogs with CLL; some dogs with CLL have normal bone marrow cytologic findings. Causes of lymphocytosis in cats and dogs are listed in Box 85.7.

Suggested Readings

Aroch I, et al. Clinical, biochemical, and hematological characteristics, disease prevalence, and prognosis of dogs presenting with neutrophil cytoplasmic toxicity. *J Vet Intern Med*. 2005;19:64.

Avery AC, Avery PR. Determining the significance of persistent lymphocytosis. *Vet Clin North Am Small Anim Pract*. 2007;37:267.

Brown CD, et al. Evaluation of clinicopathologic features, response to treatment, and risk factors associated with idiopathic neutropenia in dogs: 11 cases (1990-2002). *J Am Vet Med Assoc*. 2006;229:87.

Brown MR, Rogers KS. Neutropenia in dogs and cats: a retrospective study of 261 cases. *J Am Anim Hosp Assoc*. 2001;37:131.

Carothers M, et al. Disorders of leukocytes. In: Fenner WR, eds. *Quick reference to veterinary medicine*. ed 3. New York: JB Lippincott; 2000:149.

Center SA, et al. Eosinophilia in the cat: a retrospective study of 312 cases (1975 to 1986). *J Am Anim Hosp Assoc*. 1990;26:349.

Couto CG. Immune-mediated neutropenia. In: Feldman BF, et al, eds. *Schalm's veterinary hematology*. ed 5. Philadelphia: Lippincott Williams & Wilkins; 2000:815.

Couto GC, et al. Disorders of leukocytes and leukopoiesis. In: Sherding RG, eds. *The cat: diseases and clinical management*. ed 2. New York: Churchill Livingstone; 1994.

Devine L, et al. Presumed primary immune-mediated neutropenia in 35 dogs: a retrospective study. *J Small Anim Pract*. 2017;58:307.

Huibregtse BA, et al. Hypereosinophilic syndrome and eosinophilic leukemia: a comparison of 22 hypereosinophilic cats. *J Am Anim Hosp Assoc*. 1994;30:591.

Klainbart S, et al. Clinical, laboratory, and hemostatic findings in cats with naturally occurring sepsis. *J Am Vet Med Assoc*. 2017;251:1025.

Lucroy MD, Madewell BR. Clinical outcome and associated diseases in dogs with leukocytosis and neutrophilia: 118 cases (1996-1998). *J Am Vet Med Assoc*. 1999;214:805.

Lucroy MD, Madewell BR. Clinical outcome and diseases associated with extreme neutrophilic leukocytosis in cats: 104 cases (1991-1999). *J Am Vet Med Assoc*. 2001;218:736.

Mizukami K, et al. Trapped neutrophil syndrome in a border collie dog: clinical, clinicopathologic, and molecular findings. *J Vet Med Sci*. 2012;74:797.

Schnelle AN, Barger AM. Neutropenia in dogs and cats: causes and consequences. *Vet Clin North Am Small Anim Pract*. 2012;42:111.

Segev G, Klement E, Aroch I. Toxic neutrophils in cats: clinical and clinicopathologic features, and disease prevalence and outcome–a retrospective case control study. *J Vet Intern Med*. 2006;20:20.

Sykes JE, et al. Idiopathic hypereosinophilic syndrome in 3 Rottweilers. *J Vet Intern Med*. 2001;15:162.

Teske E. Leukocytes. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. ed 6. Ames, Iowa: Wiley-Blackwell; 2010:261.

Weltan SM, et al. A case-controlled retrospective study of the causes and implications of moderate to severe leukocytosis in dogs in South Africa. *Vet Clin Pathol*. 2008;37:164.

Williams MJ, et al. Canine lymphoproliferative disease characterized by lymphocytosis: immunophenotypic markers of prognosis. *J Vet Intern Med*. 2008;22:506.

CHAPTER 86

Combined Cytopenias and Leukoerythroblastosis



DEFINITIONS AND CLASSIFICATION

Combined cytopenias commonly result from decreased bone marrow (BM) production or, less frequently, from increased destruction or sequestration of circulating cells. The following terms are used throughout this chapter. *Bicytopenia* is a decrease in the numbers of two circulating blood cell lines (anemia and neutropenia, anemia and thrombocytopenia, or neutropenia and thrombocytopenia). If all three cell lines are affected (anemia, neutropenia, thrombocytopenia), this is termed *pancytopenia* (from the Greek word *pan,* meaning "all"). When evaluating a complete blood count (CBC) for leukopenia, it is best to evaluate only the neutrophils (i.e., neutropenia) because in some patients with neoplastic or reactive lymphocytosis, the total white blood cell (WBC) count may be normal or even high, but the neutrophil count is low. In most cases, if anemia is present, it is nonregenerative. If regenerative anemia occurs in association with other cytopenias, the cause usually is peripheral destruction of cells. A *leukoerythroblastic reaction* (LER, or leukoerythroblastosis) refers to the presence of immature WBCs (left shift) and nucleated red blood cells (nRBCs) in the circulation. In these cases, the WBC count is usually high, but it can be normal or low.

As noted, cytopenias can develop as a result of decreased production or increased peripheral destruction of the affected cell line(s). In general, bicytopenias and pancytopenias result from primary BM disorders (i.e., there is a problem in the "cell factory"; Box 86.1), although they may also result from peripheral blood cell destruction, such as what occurs in sepsis, disseminated intravascular coagulation (DIC), and some infectious and immune-mediated diseases.

LERs result from a variety of mechanisms (Box 86.2), but in general the presence of immature blood cells in the circulation is secondary to their premature release from the BM or from other hematopoietic organs (spleen, liver). This premature release can result from the following: (1) an increased demand for blood cells (e.g., hemolytic anemia, blood loss, peritonitis), resulting in a shorter transit time through the BM compartments or extramedullary hematopoietic sites; or (2) the crowding out of normal BM precursors (e.g., leukemia, BM lymphoma). They may also be prematurely released from a site of extramedullary hematopoiesis (EMH) (i.e., spleen, liver) as a result of the absence of normal feedback mechanisms. Because the nuclei of the nRBCs are pitted primarily in the spleen, splenectomized patients may have LERs. Recently, the presence of circulating nRBCs (normoblastemia) in dogs undergoing anticancer chemotherapy was well characterized (Moretti et al., 2015). In addition, normoblastemia is commonly seen in healthy Miniature Schnauzers and in Dachshunds.

CLINICOPATHOLOGIC FEATURES

The clinical signs and physical examination findings in dogs and cats with combined cytopenias or LERs are usually related to the underlying disorder rather than the hematologic abnormalities per se, with the exception of pallor and spontaneous bleeding (petechiae, ecchymoses) secondary to anemia and thrombocytopenia, respectively. Pyrexia may be present if the patient is markedly neutropenic and is septic or bacteremic.

An important aspect of the clinical evaluation of these patients is the history. A detailed history should be obtained, inquiring specifically about the therapeutic use of drugs (e.g., estrogen or phenylbutazone in dogs, griseofulvin or chloramphenicol in cats), exposure to benzene derivatives (rare), travel history, vaccination status, and exposure to other animals, among others. Most drugs that cause anemia or neutropenia can also cause combined cytopenias (see Boxes 82.2 and 85.1).

The physical examination of dogs and cats with combined cytopenias may reveal the presence of spontaneous hemorrhages compatible with a primary hemostatic disorder (e.g., thrombocytopenia) or pallor secondary to the anemia. Several physical examination findings may help the clinician establish a more presumptive or definitive diagnosis in patients with cytopenias or LER. Of particular interest is the finding of male-feminizing signs in a male dog (usually

BOX 86.1

Causes of Bicytopenia and Pancytopenia in Dogs and Cats

Decreased cell production

Bone Marrow Hypoplasia-Aplasia

Idiopathic
Chemicals (e.g., benzene derivatives)
Estrogen (endogenous or exogenous)
Drugs (chemotherapeutic agents, antibiotics, anticonvulsants, colchicine, nonsteroidal antiinflammatories)
Radiation therapy
Immune-mediated disorders
Infectious (parvovirus, FeLV, feline immunodeficiency virus, ehrlichiosis, leishmaniasis, and anaplasmosis)

Bone Marrow Necrosis

Infectious disorders (sepsis, parvovirus)
Toxins (mycotoxins)
Neoplasms (acute and chronic leukemias, metastatic neoplasia)
Other (hypoxia, DIC)

Bone Marrow Fibrosis-Sclerosis

Myelofibrosis
Osteosclerosis
Osteopetrosis

Myelophthisis

Neoplasms
Acute leukemias
Chronic leukemias
Lymphoma
Multiple myeloma
Systemic mast cell disease
Malignant histiocytosis
Metastatic neoplasms
Granulomatous disorders
Histoplasma capsulatum
Mycobacterium spp.
Storage diseases
Myelodysplasia
Increased Cell Destruction and Sequestration
Immune-Mediated Disorders
Evans syndrome
Sepsis
Microangiopathy
DIC
Hemangiosarcoma

Splenomegaly

Congestive splenomegaly
Hypersplenism
Hemolymphatic neoplasia
Other neoplasms
Hemophagocytic malignant histiocytosis or histiocytic sarcomas

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
DIC, Disseminated intravascular coagulation; *FELV,* feline leukemia virus.

a cryptorchid) with pancytopenia, which may indicate the presence of a Sertoli cell tumor or, less frequently, an interstitial cell tumor or a seminoma with secondary hyperestrogenism. The finding of generalized lymphadenopathy, hepatomegaly or splenomegaly, or intraabdominal or intrathoracic masses may direct the clinician toward a specific group of presumptive diagnoses. For example, the finding of a cranial or midabdominal mass in a dog with regenerative anemia, thrombocytopenia, and LER is highly suggestive of splenic hemangiosarcoma.

The presence of diffuse splenomegaly suggests that the spleen may be sequestering or destroying circulating blood cells or that EMH is occurring in response to a primary BM disorder. Cytologic evaluation of spleen specimens obtained by percutaneous fine-needle aspiration is always indicated in dogs and cats with cytopenias and diffuse splenomegaly to determine whether the enlarged spleen is the cause or consequence of the cytopenia (see Chapter 88).

Serologic studies and/or polymerase chain reaction (PCR) assays for infectious diseases is usually indicated in dogs and cats with bicytopenias or pancytopenias. Infectious diseases associated with bicytopenias and pancytopenias commonly diagnosed on serologic or PCR results include monocytic ehrlichiosis in dogs, anaplasmosis in dogs and cats, *Babesia gibsoni* infection in dogs (usually in Pitbulls, where there is combined regenerative anemia and thrombocytopenia), leishmaniasis in dogs (and occasionally in cats), systemic mycoses (i.e., histoplasmosis) in cats (and rarely in dogs), and feline leukemia virus (FeLV) and feline immunodeficiency virus infections in cats. If the clinical and hematologic features of the case point toward an immune-mediated disease (e.g., presence of polyarthritis or proteinuria, spherocytosis), a direct Coombs test and antinuclear antibody test should be done (see Chapter 71). It is also helpful to submit fluid obtained from one or more joints for cytologic evaluation because the presence of suppurative nonseptic arthritis suggests an immune pathogenesis or a vector-borne disease.

Because establishing whether the cytopenia is the result of peripheral cell destruction or a BM disorder is important,

BOX 86.2

Causes of Leukoerythroblastosis in Dogs and Cats

EMH*
Immune hemolytic anemia
Blood loss anemia
Sepsis
DIC
Chronic hypoxia (i.e., congestive heart failure)
Neoplasia
- **Hemangiosarcoma**
- Lymphoma
- *Leukemias*
- Multiple myeloma
- Malignant histiocytosis

Other
- Diabetes mellitus
- Hyperthyroidism
- Hyperadrenocorticism
- Splenectomy

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.
DIC, Disseminated intravascular coagulation; *EMH,* extramedullary hematopoiesis; *LER,* leukoerythroblastic reaction.
*Hematopoiesis may play a role in the pathogenesis of the LER in several of the disorders mentioned in the text.

evaluation of the cell factory is logical if no evidence of RBC regeneration in the blood smear or CBC exists (see Chapter 82). Therefore BM aspiration and, ideally, BM core biopsy to obtain specimens for histopathologic studies should be performed in all dogs and cats with combined cytopenias, except for dogs with highly likely or confirmed Evans syndrome and dogs and cats with DIC; that is, the anemia is regenerative, so it is assumed that the factory is working properly. Algorithms for the evaluation of BM findings in dogs and cats with bicytopenia and pancytopenia are shown in Figs. 86.1 and 86.2. In private practice, obtaining a BM aspirate is usually easier; BM core biopsies are usually performed at specialty practices.

A BM evaluation should also be part of the clinical workup in animals with LERs to determine whether the immature WBCs and RBCs in the circulation are secondary to a primary BM disorder or a disorder such as EMH. Because abdominal neoplasms, particularly hemangiosarcoma, are commonly associated with LERs in dogs, abdominal ultrasonography should be done. If diffuse splenomegaly is detected, percutaneous fine-needle aspiration of the spleen should be performed. If splenic or hepatic masses or both are present, the patient should be evaluated as described in Chapter 78.

Abrams-Ogg et al. (2012) evaluated the use of a 15-gauge needle and power driver in comparison to a standard

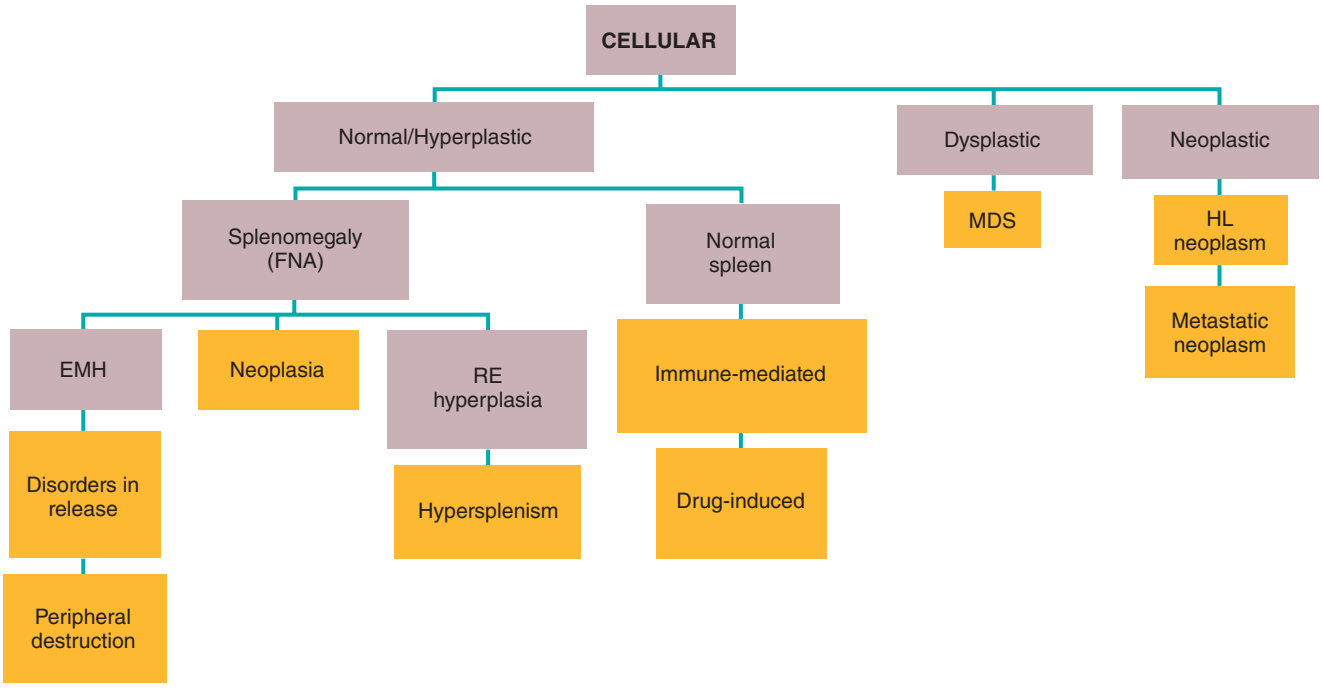


FIG 86.1
Algorithm for the diagnosis of a pancytopenic animal with hypercellular bone marrow. *EMH,* Extramedullary hematopoiesis; *FNA,* fine-needle aspiration; *HL,* hemolymphatic; *MDS,* myelodysplastic syndrome; *RE,* reticuloendothelium. *Orange boxes* indicate final diagnoses.

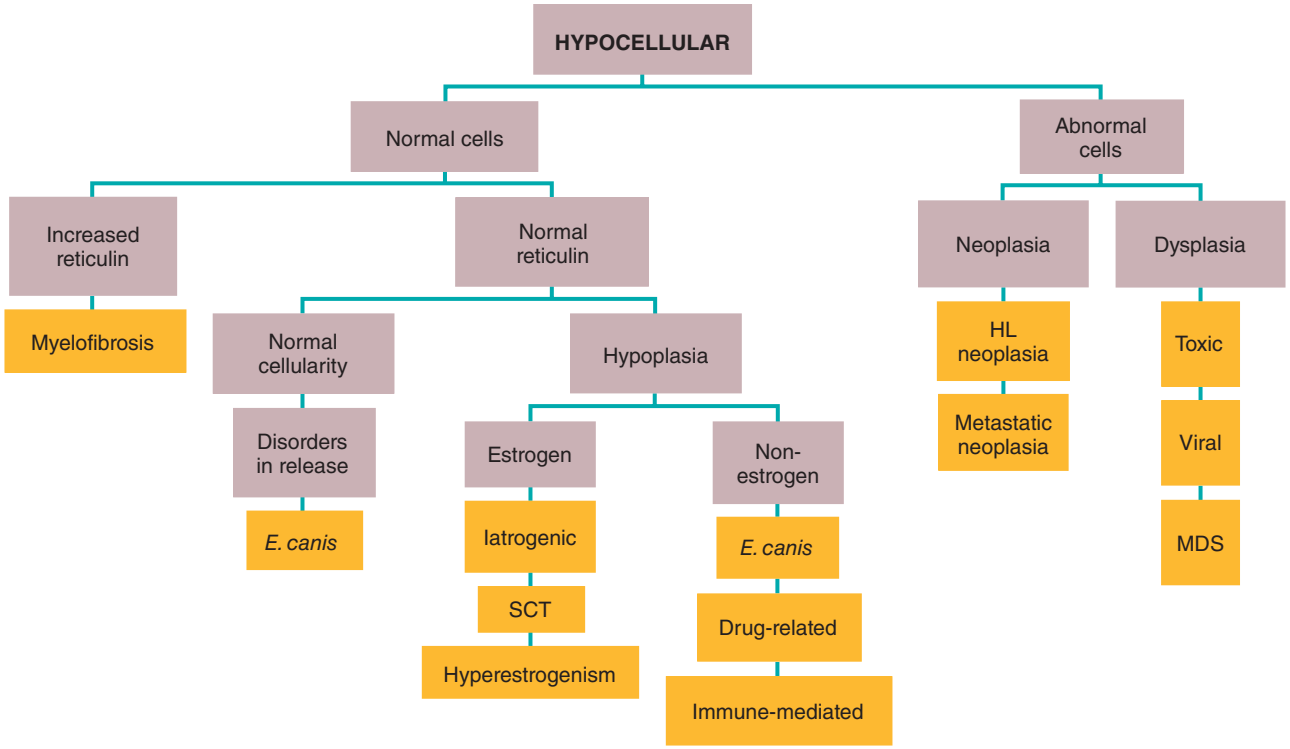


FIG 86.2
Algorithm for the diagnosis of a pancytopenic animal with hypocellular bone marrow. *HL,* Hemolymphatic; *MDS,* myelodysplastic syndrome; *SCT,* Sertoli cell tumor. *Orange boxes* indicate final diagnoses.

13-gauge Jamshidi needle to obtain BM biopsies in experimental Beagles. Use of a 15-gauge needle to obtain a humeral BM biopsy was significantly easier than obtaining a humeral BM biopsy using a 13-gauge needle or an iliac BM biopsy using a 15-gauge needle. The quality of the biopsies obtained with a 13-gauge needle was better than for biopsies of the humerus or ilium using a 15-gauge needle. Only sites sampled with a 13-gauge needle were identifiable grossly after the procedure. In most biopsies, cell density and cellularity were lower when a 15-gauge needle was used.

Weiss (2006) reviewed BM aspirates, core biopsies, and medical records of 717 dogs evaluated for presumptive BM disorders. Approximately 2% of the specimens evaluated were nondiagnostic, 22% were normal, 26% had changes secondary to another primary disease, 24% had nondysplastic and nonneoplastic conditions, 9% had dysplasia, and 18% had neoplasia. Less than 5% of the specimens evaluated had BM hypoplasia and approximately 20% were hyperplastic; acute leukemias were more common than chronic leukemias.

Turinelli et al. recently reviewed the cytomorphologic findings in BM aspirates in both dogs (Turinelli et al., 2015) and cats (Turinelli and Gavazza, 2018). Seventy percent of 295 canine BM samples were diagnostic; 25% were classified as BM (myeloid and or erythroid) hyperplasia, 19.3% were normal, 12.9% had hematopoietic malignancy, 7.8% had aplasia/hypoplasia, and 1.3% had dysplasia. In cats, 46.7% of 152 BM samples were classified as hyperplastic, 15.1% were dysplastic, 13.8% were normal, 11.2% were hematopoietic malignancies, and 9.9% were aplastic/hypoplastic (Turinelli and Gavazza, 2018).

BONE MARROW APLASIA-HYPOPLASIA

BM aplasia-hypoplasia is a disorder characterized by peripheral blood cytopenias and a paucity or absence of hematopoietic precursors in the BM. As noted, BM aplasia-hypoplasia is commonly associated with the administration of certain drugs, such as griseofulvin or chloramphenicol in cats and phenylbutazone or estrogen in dogs. It is also commonly associated with infectious diseases, such as canine monocytic ehrlichiosis, leishmaniasis, and FeLV infection. A corticosteroid-responsive syndrome of combined cytopenias or pancytopenia has been recognized in dogs and cats in our clinic. Some of these patients with pancytopenia have hypercellular BM (see later), suggesting that the cells are destroyed peripherally or at the late stages of BM production.

BM aspirates from dogs and cats with BM aplasia or hypoplasia typically show hypocellularity or acellularity, and a BM biopsy is frequently necessary to obtain specimens for histopathologic analysis so that a definitive diagnosis can be made. Once infectious diseases (e.g., *Ehrlichia canis* titer or rapid assay, FeLV p27 determination) and drug exposure

have been ruled out, a therapeutic trial of immunosuppressive doses of corticosteroids (with or without other immunosuppressive drugs; see Chapter 72) may be warranted. Anabolic steroids and erythropoietin do not appear to be beneficial in these patients.

Myelophthisis

Infiltration of the BM with neoplastic or inflammatory cells can lead to the crowding out of normal hematopoietic precursors and therefore the development of peripheral blood cytopenias. Disorders resulting in myelophthisis are listed in Box 86.1. Often these animals are evaluated because of anemia, although fever and bleeding caused by neutropenia and thrombocytopenia, respectively, can also be presenting complaints. The presence of hepatomegaly, splenomegaly, or lymphadenopathy in a dog or cat with anemia or combined cytopenias is highly suggestive of some of the neoplastic or infectious disorders listed in Box 86.1.

A definitive diagnosis in dogs and cats with myelophthisis is obtained by evaluating the cytologic or histopathologic characteristics of a BM specimen. Given the fact that certain neoplastic or granulomatous disorders can show a patchy or multifocal distribution, the findings yielded by a BM core biopsy specimen are usually more reliable than those yielded by an aspirate. Once a cytologic or histopathologic diagnosis is obtained, treatment is aimed at the primary neoplasm (i.e., with chemotherapy) or infectious agent (see specific sections for detailed discussion).

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDSs) include a host of hematologic and cytomorphologic changes that may precede the development of acute leukemias by months or years; in humans, they are associated with specific molecular genetic changes. In addition to the morphologic abnormalities in blood and BM, functional abnormalities of granulocytes and platelets have been documented in humans with MDS. Therefore recurrent infections, spontaneous bleeding tendencies, or both are common in these patients, even when the neutrophil and platelet counts are within normal limits. These abnormalities have also been observed in cats with MDS.

MDS has been recognized in dogs and cats but appears to be more common in retrovirus-infected cats. In dogs, clinical signs are nonspecific and include lethargy, depression, and anorexia. Physical examination findings include hepatosplenomegaly, pallor, and pyrexia; hematologic changes include pancytopenia or bicytopenia, macrocytosis, normoblastemia, and reticulocytopenia. Acute myelogenous leukemia (AML) subsequently developed 3 months after the initial diagnosis of MDS in one patient (Couto et al., 1984). The cytologic BM abnormalities were similar to those described in cats (see later). Some authors have proposed classifying dogs with primary MDSs into those with refractory anemia and those with true myelodysplasia, following similar classification schemes used in humans. However, because almost no clinical information was provided for the dogs that were evaluated, that classification scheme is of questionable clinical relevance.

Several reports of MDS in cats have appeared in the literature. More than 80% of cats in whom the FeLV status was investigated were found to be viremic. Most cats were evaluated because of nonspecific clinical signs such as lethargy, weight loss, and anorexia. Other signs, such as dyspnea, recurrent infections, and spontaneous bleeding, were observed in a few cats. Physical examination revealed hepatosplenomegaly in more than half of the cats; generalized lymphadenopathy and pyrexia were detected in approximately one third. In my experience, secondary myelodysplasia associated with infectious, inflammatory, or immune-mediated diseases is quite common in cats, so a cytologic diagnosis of MDS should be interpreted with caution (i.e., it is not always a "death sentence"), and a search for comorbidities should be conducted.

Hematologic abnormalities in cats with MDS are similar to those seen in dogs; they include isolated or combined cytopenias, macrocytosis, reticulocytopenia, metarubricytosis, and macrothrombocytosis. Morphologic changes in the BM include a normal to increased cellularity, less than 30% blasts, an increased myeloid-to-erythroid ratio, dyserythropoiesis, dysmyelopoiesis, and dysthrombopoiesis. Megaloblastic RBC precursors are common, with occasional binucleated, trinucleated, or tetranucleated rubricytes or metarubricytes. The morphologic abnormalities in the myeloid cell line include giant metamyelocytes and asynchronous nuclear-cytoplasmic maturation.

Acute leukemia subsequently developed within weeks to months of the diagnosis in approximately one third of cats with MDS described in the literature. MDS commonly progresses to AML in humans, with only isolated reports of progression to acute lymphocytic leukemia (ALL). However, according to Maggio et al. (1978), in one series of 12 cats with MDS, ALL subsequently developed in 9. This may reflect the fact that cytochemical staining was not done to classify the leukemic cells, and cells were thus morphologically classified as lymphoid when they were myeloid. However, because all the cats that showed progression to ALL were also viremic with FeLV, the hematologic changes preceding the development of leukemia did not reflect a "spontaneous" hematologic disorder (as seen in human beings and dogs) but were rather a manifestation of the morphologic and functional changes induced by FeLV.

The management of dogs and cats with MDS is still controversial. A variety of treatments have been used in humans with MDS, but none has proved effective. Chemotherapy, supportive therapy, anabolic steroids, inductors of differentiation, hematopoietic growth factors, and androgenic steroids, among others, have been reported to be of benefit in some humans with MDS. Currently, the preferred approach in humans is treatment with supportive therapy and inductors of differentiation or hematopoietic growth factors. Because most patients are older, chemotherapy does not constitute the first treatment option, given its toxicity. I recommend supportive therapy (e.g., fluids, blood components, antibiotics) and low-dose cytosine arabinoside as an

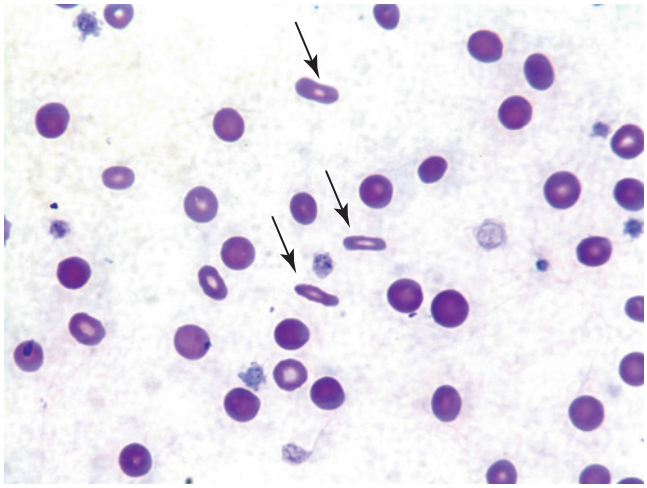


FIG 86.3
Elliptocytosis in an Airedale Terrier with myelofibrosis. Elliptocytes *(arrows)* are intermixed with normal RBCs and spherocytes. The patient had complete resolution of the hematologic and morphologic RBC changes after treatment with corticosteroids and azathioprine (Wright-Giemsa stain; ×1000).

inductor of differentiation (see Box 80.3). Novel therapeutic approaches in humans with MDS include primarily targeting the MDS clone or using nonspecific azanucleosides such as azacytidine, targeted molecular therapy, immunotherapy, and hypomethylating agents.

MYELOFIBROSIS AND OSTEOSCLEROSIS

Fibroblasts or osteoblasts within the BM can proliferate in response to retroviral infections, chronic noxious stimuli, or unknown causes, leading to fibrous or osseous replacement of the BM cavity, thereby displacing the hematopoietic precursors. These syndromes are termed *myelofibrosis* and *osteosclerosis,* respectively. Although both syndromes are rare, they have been observed in FeLV-infected cats and in dogs with chronic hemolytic disorders, such as the pyruvate kinase deficiency anemia. Peripheral blood elliptocytosis and dacryocytosis appear to be a common feature in dogs with myelofibrosis (Fig. 86.3). A limited number of dogs and cats with idiopathic myelofibrosis have been reported; in some of these cases, previous exposure to drugs (e.g., phenobarbital, phenytoin, phenylbutazone, colchicine) was documented. In my experience, the clinical and hematologic features associated with myelofibrosis in dogs frequently resolve after immunosuppressive treatment with a combination of corticosteroids and azathioprine (see Chapter 72).

A presumptive diagnosis of osteosclerosis or osteopetrosis is made on the basis of the presence of combined cytopenias together with increased osseous radiographic density and can be confirmed by a core biopsy of the BM. Unfortunately, no effective treatment is currently available.

Suggested Readings

Abrams-Ogg ACG, et al. Comparison of canine core bone marrow biopsies from multiple sites using different techniques and needles. *Vet Clin Pathol*. 2012;41:235.

Couto CG, et al. Preleukemic syndrome in a dog. *J Am Vet Med Assoc*. 1984;184:1389.

Harvey JW. Canine bone marrow: normal hematopoiesis, biopsy techniques, and cell identification and evaluation. *Compend Cont Educ*. 1984;6:909.

Kunkle GA, et al. Toxicity of high doses of griseofulvin in cats. *J Am Vet Med Assoc*. 1987;191:322.

Maggio L, et al. Feline preleukemia: an animal model of human disease. *Yale J Biol Med*. 1978;51:469.

Moretti P, et al. Nucleated erythrocytes in blood smears of dogs undergoing chemotherapy. *Vet Comp Oncol*. 2015;15:215.

Reeder JP, et al. Effect of a combined aspiration and core biopsy technique on quality of core bone marrow specimens. *J Am Anim Hosp Assoc*. 2013;49:16.

Scott-Moncrieff JCR, et al. Treatment of nonregenerative anemia with human gamma-globulin in dogs. *J Am Vet Med Assoc*. 1995;206:1895.

Turinelli V, Gavazza A. Retrospective study of 152 feline cytological bone marrow examinations: preliminary classification and ranges. *J Fel Med Surg*. 2018;[epub ahead of print].

Turinelli V, et al. Canine bone marrow cytological examination, classification and reference values: a retrospective study of 295 cases. *Res Vet Sci*. 2015;103:224.

Weiss DJ. A retrospective study of the incidence and the classification of bone marrow disorders in the dog at a veterinary teaching hospital (1996-2004). *J Vet Intern Med*. 2006;20:955.

Weiss DJ. Bone marrow necrosis in dogs: 34 cases (1996-2004). *J Am Vet Med Assoc*. 2005;227:263.

Weiss DJ. Hemophagocytic syndrome in dogs: 24 cases (1996-2005). *J Am Vet Med Assoc*. 2007;230:697.

Weiss DJ, et al. A retrospective study of canine pancytopenia. *Vet Clin Pathol*. 1999;28:83.

Weiss DJ, Smith SA. A retrospective study of 19 cases of canine myelofibrosis. *J Vet Intern Med*. 2002;16:174.

Weiss DJ, Smith SA. Primary myelodysplastic syndromes of dogs: a report of 12 cases. *J Vet Intern Med*. 2000;14:491.

CHAPTER 87

Disorders of Hemostasis



GENERAL CONSIDERATIONS

Spontaneous or excessive bleeding is relatively common in dogs and rare in cats. As a general rule, a systemic hemostatic abnormality is the underlying cause of excessive bleeding in dogs and cats that have sustained trauma or are undergoing a surgical procedure, and in dogs evaluated because of spontaneous bleeding tendencies. Spontaneous bleeding disorders are extremely common in dogs evaluated at our clinic but are rare in cats. Approaching these patients' bleeding in a logical and systematic fashion allows the clinician to confirm the presumptive diagnosis in most cases.

In addition to bleeding, abnormal hemostatic mechanisms can also cause thrombosis and thromboembolism (TE), potentially leading to organ failure. Thromboembolic disorders are rare in dogs and cats without underlying cardiovascular disorders (e.g., cats with hypertrophic cardiomyopathy and aortic TE; see Chapter 12), but they are now increasingly being recognized and documented in dogs with liver disease, protein losing nephropathy, endocrinopathies, and other diseases.

The most common disorder leading to spontaneous bleeding in dogs seen at our clinic is thrombocytopenia, mainly due to immune-mediated mechansims. Other common hemostatic disorders leading to spontaneous bleeding in dogs evaluated at our hospital include disseminated intravascular coagulation (DIC) and rodenticide poisoning. Congenital clotting factor deficiencies resulting in spontaneous bleeding are rare. Although von Willebrand disease (vWD) is common in certain breeds (see p. 1398), it is not a common cause of spontaneous bleeding in our patients. Abnormalities in hemostasis screens are frequently noted in cats with liver disease, feline infectious peritonitis (FIP), or neoplasia; however, spontaneous or intra- or postoperative bleeding tendencies are extremely rare in these patients. Decreased production of platelets (thrombocytopenia) or virus-induced thrombocytopathia resulting in spontaneous bleeding is occasionally seen in cats with retrovirus-induced bone marrow disorders.

PHYSIOLOGY OF HEMOSTASIS

Under normal conditions, injury to a blood vessel leads to immediate vascular changes (e.g., vasoconstriction) and rapid activation of the hemostatic system. Changes in axial blood flow lead to exposure of circulating blood to subendothelial collagen, resulting in the rapid adhesion of platelets to the affected area. The adhesion of platelets to the subendothelium is mediated by adhesive proteins, such as von Willebrand factor (vWF) and fibrinogen, among others. After adhering to the area of endothelial damage, platelets aggregate and form the primary hemostatic plug, which is short-lived (seconds) and unstable. The primary hemostatic plug serves as a framework in which secondary hemostasis occurs because most of the clotting factors assemble the thrombus or clot on the platelet plug.

Although the intrinsic, extrinsic, and common coagulation pathways have been well characterized and are still used to teach physiology of hemostasis, coagulation in vivo does not necessarily follow these distinct pathways. Also, the cellular and biochemical phases of coagulation occur almost simultaneously. For example, factors XII and XI do not appear to be necessary for the initiation of coagulation; for example, dogs and cats with factor XII deficiency do not have spontaneous bleeding tendencies. It is now generally accepted that the physiologic mechanism responsible for clotting in vivo is primarily tissue factor (TF) activation of factor VII. In the past 2 decades, the traditional coagulation cascade has been thought of as a common pathway from early in the process; the traditional intrinsic, extrinsic, and common pathways are now known to be interrelated (Furie and Furie, 2008).

In the traditional scheme, activation of the contact phase of the coagulation cascade occurs almost simultaneously with platelet adhesion and aggregation (Fig. 87.2) and leads to the formation of fibrin through the intrinsic coagulation cascade. A good mnemonic is to refer to the intrinsic system as the "dime store" coagulation cascade: "It is not $12, but $11.98" (for factors XII, XI, IX, and VIII). Factor XII is activated by contact with the subendothelial collagen and

by the platelet plug; once it has been activated, fibrin, or the secondary hemostatic plug, forms. Prekallikrein (Fletcher factor) and high-molecular-weight kininogen (HMWK) are important co-factors for factor XII activation. The role of the contact phase of coagulation in vivo is questionable. The secondary hemostatic plug is stable and long-lasting. In addition, whenever tissue trauma occurs, the release of tissue procoagulants (collectively referred to as TF) results in activation of the extrinsic coagulation cascade, also leading to the formation of fibrin (see Fig. 87.2). As discussed earlier, all these steps occur almost simultaneously, and fibrin formation starts within seconds of the endothelial damage. TF is ubiquitous and present on the membrane of most cells, with the exception of normal endothelium. As noted, this pathway is now thought to be responsible for initiating clotting in mammals.

The stimuli that activate coagulation also activate the fibrinolytic and kinin pathways. Fibrinolysis is extremely important as a safeguard mechanism because it prevents excessive clot or thrombus formation. When plasmin lyses fibrinogen and fibrin, it generates fibrin degradation products (FDPs), which impair additional platelet adhesion and aggregation in the site of injury. Once fibrin has been stabilized by complexing factor XIII, plasmin biodegradation generates D-dimers instead. The activation of plasminogen into plasmin results in the destruction (lysis) of an existing clot (or thrombus) and interferes with the normal clotting mechanisms—inhibition of platelet aggregation and clotting factor activation in the affected area. Therefore excessive fibrinolysis usually leads to spontaneous bleeding. Two molecules stimulate plasminogen activation into plasmin, tissue plasminogen activator (tPA) and urokinase-type plasminogen activator. Three plasminogen activator inhibitors (PAIs), PAI-1, PAI-2, and PAI-3, inhibit fibrinolysis, thus leading to thrombosis.

Other systems that oppose blood coagulation also become operational once intravascular clotting has occurred. The best characterized include antithrombin (AT), a protein synthesized by hepatocytes that acts as a co-factor for heparin and inhibits the activation of factors IX, X, and thrombin. AT also inhibits tPA. Proteins C and S are two vitamin K–dependent anticoagulants also produced by hepatocytes. These three factors are some of the natural anticoagulants that prevent excessive clot formation.

CLINICAL MANIFESTATIONS OF SPONTANEOUS BLEEDING DISORDERS

In the evaluation of a cat or dog with spontaneous or excessive bleeding, the clinician should ask the owners the following questions, which may provide additional clues to the pathogenesis of the coagulopathy:

- Is this the first bleeding episode? If it is occurring in a mature animal, an acquired coagulopathy is suspected. (*Note:* We have seen dogs with hemophilia A present with their first bleeding episode at 8 years of age.)
- Has the patient had any surgeries before this and, if so, did it bleed excessively? If the pet has had previous bleeding episodes during elective surgeries as a young animal, a congenital coagulopathy is suspected.
- Do any littermates have similar clinical signs? Did the litter have an increased perinatal mortality rate? These findings also support a congenital coagulopathy.
- Has the animal recently been vaccinated with modified-live vaccines? Modified-live vaccines can cause thrombocytopenia, platelet dysfunction, or both.
- Is the patient currently receiving any medication that may cause thrombocytopenia or platelet dysfunction (e.g., nonsteroidal antiinflammatory drugs [NSAIDs], sulfas, antibiotics, phenobarbital)?
- Does the patient have access to rodenticides or does it roam freely? This may indicate rodenticide toxicity.

The clinical manifestations of primary hemostatic abnormalities are different from those of secondary hemostatic abnormalities (Box 87.1). The clinician should be able to classify the type of coagulopathy on the basis of the physical examination findings before submitting any samples for clinicopathologic evaluation. This is easy to conceptualize by thinking about the normal coagulation mechanisms. For example, a functional primary hemostatic plug cannot form in a cat or dog with severe thrombocytopenia or platelet dysfunction. Because this plug is short-lived and eventually covered with fibrin (generated through the secondary hemostatic mechanisms), the patient experiences multiple, short-lived bleeds that are arrested as soon as fibrin is formed, resulting in multiple small and superficial hemorrhages around blood vessels. This is analogous to turning on and off a faucet connected to a garden hose with multiple perforations (an irrigator); multiple spurts of water (blood) form adjacent to the hose (the vessel; Fig. 87.3, *A*). On the other hand, a short-lived primary hemostatic plug can form in a cat or dog with severe clotting factor deficiencies (e.g., hemophilia, rodenticide poisoning); enough functional platelets are present, but fibrin cannot be generated. The result of this



BOX 87.1

Clinical Manifestations of Primary and Secondary Hemostatic Defects

Primary Hemostatic Defect

Petechiae common
Hematomas rare
Bleeding in skin and mucous membranes
Bleeding immediately after venipuncture

Secondary Hemostatic Defect

Petechiae rare
Hematomas common
Bleeding into muscles, joints, and body cavities
Delayed bleeding after venipuncture

is a delayed, continuous, long-lasting bleed, leading to hematoma formation or bleeding into a body cavity. This is analogous to turning on a faucet connected to a regular garden hose with a single large opening; in this situation, water (blood) continues to flow and collect in large amounts next to the opening in the hose (vessel; see Fig. 87.3, *B*).

Spontaneous bleeding infrequently occurs in cats and dogs with excessive fibrinolysis. I have evaluated a limited number of dogs with protein-losing nephropathy and nephrotic syndrome in which spontaneous bleeding (i.e., petechiae and ecchymoses) appeared to result from enhanced fibrinolysis. However, fibrinolysis is relatively difficult to evaluate using laboratory methods other than thromboelastography (TEG), so additional data are being currently generated on this area.

Dogs (and cats) with primary hemostatic defects (i.e., platelet disorders) therefore have typical manifestations of superficial bleeding, consisting of petechiae, ecchymoses, bleeding from mucosal surfaces (e.g., melena, hematochezia, epistaxis, hematuria), and prolonged bleeding immediately after venipuncture. In clinical practice, most primary hemostatic disorders are caused by decreased numbers of circulating platelets (thrombocytopenia). Recently, a bleeding score for thrombocytopenic dogs was proposed for dogs (Makielski et al., 2018). Primary hemostatic defects occasionally result from primary or secondary platelet dysfunction (e.g., uremia, vWD, monoclonal gammopathies, vector-borne diseases). Primary hemostatic defects caused by vascular disorders are extremely rare in cats and dogs and will not be discussed.

Clinical signs in dogs and cats with secondary hemostatic defects (i.e., clotting factor deficiencies) consist of deep bleeding, including bleeding into body cavities and joints, and deep hematomas, most of which are discovered as a lump or mass. Certain congenital coagulopathies, including factor XII, prekallikrein, and HMWK deficiencies, result in a marked prolongation of the activated coagulation time (ACT) or activated partial thromboplastin time (aPTT) without spontaneous or prolonged bleeding (see later).

Most secondary bleeding disorders seen in clinical practice are caused by rodenticide poisoning or liver disease; selective congenital clotting factor deficiencies occasionally can lead to spontaneous secondary bleeding disorders. A combination of primary and secondary bleeding disorders (mixed disorders) is seen almost exclusively in dogs and cats with DIC.

We recently described a syndrome of delayed postoperative bleeding in former racing Greyhounds that occurs in approximately 25% to 30% of dogs who undergo surgery. It consists of superficial bleeding around the surgical site starting 36 to 48 hours after the surgery, which becomes systemic and is often life-threatening (Lara García et al., 2008; Marin et al., 2012a and b). We have also observed a similar syndrome in other sighthound breeds, including Deerhounds and Italian Greyhounds. For additional discussion, see Chapter 83.

CLINICOPATHOLOGIC EVALUATION OF THE BLEEDING PATIENT

Clinicopathologic evaluation of the hemostatic system is indicated primarily in two subsets of patients: in those with spontaneous or prolonged bleeding, and before surgery in patients with disorders commonly associated with bleeding tendencies (e.g., splenic hemangiosarcoma [HSA] and DIC in dogs; liver disease and clotting factor deficiency in dogs and cats) or a suspected congenital coagulopathy (e.g., before ovariohysterectomy in a Doberman Pinscher suspected of having subclinical vWD).

When evaluating a cat or dog with a spontaneous bleeding disorder, the clinician should keep in mind that the preliminary clinical diagnosis can usually be confirmed by performing some simple point-of-care (real-time) tests. If these tests do not yield a definitive answer, or if a more specific diagnosis is needed (e.g., the identification of specific clotting factor deficiencies), a plasma sample can be submitted to a referral veterinary diagnostic laboratory or specialized coagulation laboratory (e.g., New York State Diagnostic Laboratory, Cornell University, Ithaca, NY). As discussed later, TEG is now widely used to evaluate patients with coagulopathies.

Some simple point-of-care tests include the evaluation of a blood smear or the graphics from the hematology analyzer; determination of the ACT, one-stage prothrombin time (OSPT), and APTT; quantification of FDP or D-dimer concentrations; and buccal mucosa bleeding time (BMBT; Table 87.1). Examination of a good-quality, well-stained blood smear (e.g., Diff-Quik) provides important clues regarding platelet numbers and morphology, as does evaluation of graphics generated by flow cytometry hematology analyzers.

The first part of this examination should involve scanning the smear at low power to identify platelet clumps;

TABLE 87.1

Simple Point-of-Care Tests for Rapid Classification of Hemostatic Disorders

TEST	RESULTS	MOST LIKELY DISORDER(S)*
Platelet estimation in blood smear	Low	Thrombocytopenia
ACT	Prolonged	Intrinsic, common system defect
FDP–D-dimer	Positive	Enhanced fibrinolysis, thrombosis, thromboembolism, DIC
BMBT	Prolonged	Thrombocytopenia, thrombocytopathia

ACT, Activated clotting time; *BMBT,* buccal mucosa bleeding time; *DIC,* disseminated intravascular coagulation; *FDP,* fibrin degradation product.
*If prolonged (or positive).

platelet clumping commonly results in pseudothrombocytopenia. Next the oil immersion lens should be used to examine several representative monolayer fields (i.e., where approximately 50% of the red blood cells [RBCs] touch each other), and the number of platelets in five fields should be averaged. In dogs, 12 to 15 platelets should be present in each oil immersion field; in normal cats, 10 to 12 platelets per field should be seen. As a general rule, each platelet in an oil immersion field represents 12,000 to 15,000 platelets/μL (the number of platelets/oil immersion field × 15,000 = platelets/μL). Cats and dogs with platelet counts of >30,000/μL and normal platelet function do not bleed spontaneously. Therefore the cause of bleeding is usually not thrombocytopenia if more than two or three platelets are visualized in each oil immersion field. The evaluation of platelet numbers should also include evaluation of the morphology of individual platelets because abnormal platelet morphology may reflect impaired platelet function.

As mentioned earlier, evaluation of the RBC dot plots in a LaserCyte or ProCyte Dx Hematology Analyzer (IDEXX Laboratories, Westbrook, ME) also provides valuable information on platelet numbers and clumping. For a discussion of dot plot evaluation, see Fig. 87.1.

The second set of point-of-care tests of hemostatic function are the ACT, OSPT, and aPTT. For the aPTT, 2 mL of whole fresh blood (WFB) is added to a tube containing diatomaceous earth; this activates the contact phase of coagulation, thus assessing the integrity of the intrinsic and common pathways (factors I, II, V, VIII, and IX to XII; see Fig. 87.2). If the activity of individual clotting factors involved in these pathways has decreased by more than 70% to 75%, the ACT is prolonged (normal, 60-90 seconds). Common coagulopathies associated with prolongation of the ACT are listed in Table 87.2. This test is rarely done today because of the availability of simple point-of-care instruments.

We routinely use a point-of-care instrument in dogs and cats (Coag Dx Analyzer, IDEXX Laboratories). This

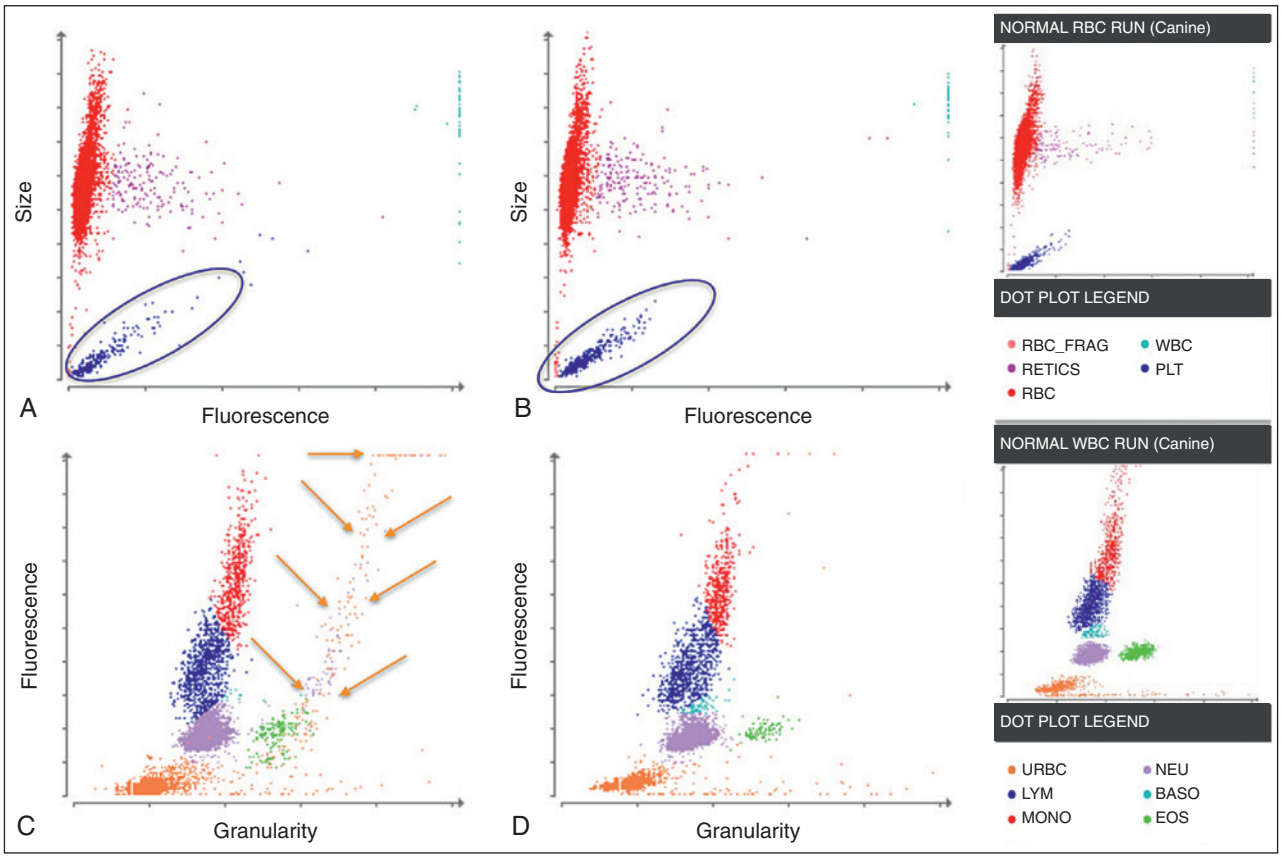


FIG 87.1
Dotplots from a dog with pseudothrombocytopenia **(A and C)**, and the same dog after obtaining a new blood sample **(B and D)** obtained with a ProCyteDx hematology analyzer. In the red blood cell graphics, note the lower density of platelet *(blue circle)* in panel A, compared with B (new blood sample). In the leukocyte graphics please note the curvilinear "cloud" *(orange arrows)* in panel C that represents platelet clumping and is no longer present in panel D (new sample). Normal RBC and WBC graphics are provided in the right. *BASO*, Basophils; *EOS*; eosinophils; *LYM*, lymphocytes; *MONO*, monocytes; *NEU*, neutrophils; *PLT*, platelets; *RBC*, red blood cells; *RBC_FRAG*, red blood cell fragments; *RETICS*, reticulocytes; *URBC*, unlysed red blood cells; *WBC*, white blood cells.

instrument performs determinations of the aPTT or OSPT with only a small volume of blood for each test; nonanticoagulated or citrated samples can be used. The reference ranges for the aPTT with this instrument are different from those for the aPTT determined in referral diagnostic laboratories.

The third real-time test that can be easily performed in practice is determination of the FDP or D-dimer concentration with the commercially available latex agglutination tests; circulating FDPs or D-dimers are generated during the cleavage of fibrin and fibrinogen (i.e., fibrinolysis) before or after binding to factor XIII, respectively. This test is commonly positive in dogs, some cats with DIC, and some patients with thrombosis or TE. The FDP test is also positive in more than half of dogs with bleeding caused by rodenticide poisoning, likely because vitamin K antagonists are believed to release fibrinolysis by inhibiting the production of PAI-1.

A fourth point-of-care test that can be performed primarily in dogs is the BMBT (Box 87.2), in which a template (SimPlate, various manufacturers) is used to make an incision in the buccal mucosa and the time until bleeding completely ceases is determined. The BMBT is abnormal in cats and dogs with thrombocytopenia or with platelet dysfunction. In an animal with clinical signs of a primary bleeding disorder (e.g., petechiae, ecchymoses, mucosal bleeding) and a normal platelet count, a prolonged bleeding time indicates an underlying platelet dysfunction (e.g., resulting from NSAID therapy or vWD) or, less likely, a vasculopathy.

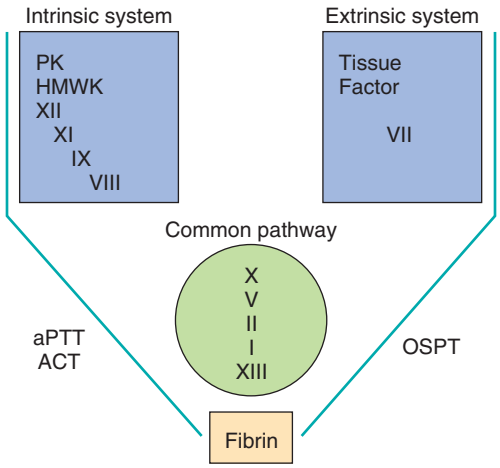


FIG 87.2
Traditional intrinsic, extrinsic, and common coagulation pathways. *ACT,* Activated coagulation time; *aPTT,* activated partial thromboplastin time; *HMWK,* high-molecular-weight kininogen; *OSPT,* one-stage prothrombin time; *PK,* prekallikrein.

BOX 87.2

Procedure for Determining Buccal Mucosa Bleeding Time in Dogs

1. Position the animal in lateral recumbency with manual restraint.
2. Place a 5-cm wide strip of gauze around the maxilla to fold up the upper lip, causing moderate engorgement of the mucosal surface.
3. Position the SimPlate against the upper lip mucosa and push the trigger.
4. Start a stopwatch when the incisions are made.
5. Blot the blood with a gauze or blotting paper placed 1 to 3 mm ventral to the incision without dislodging the clot.
6. Stop the stopwatch when the incision ceases to bleed.
7. Normal times are 2 to 3 minutes.

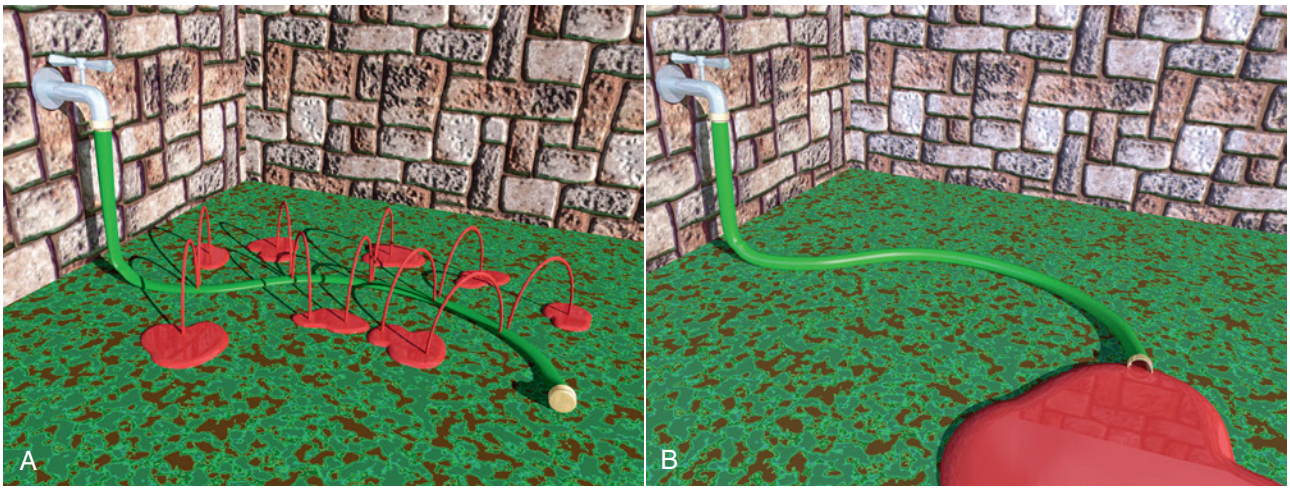


FIG 87.3
Illustrative depiction of primary **(A)** and secondary **(B)** hemostatic bleeding. **A,** Development of petechiae and ecchymoses. **B,** Formation of a hematoma or blood in a body cavity. For a detailed description, see text. (Artwork by Tim Vojt. Reproduced with the permission of The Ohio State University.)

TABLE 87.2

Interpretation of Hemostasis Screens

DISORDER	BT	ACT	OSPT*	aPTT	PLATELETS	FIBRINOGEN	FDP/D-DIMER
Thrombocytopenia	↑	N	N	N	↓	N	N
Thrombocytopathia	↑	N	N	N	N	N	N
vWD	↑	N/↑?	N	N/↑?	N	N	N
Hemophilias	N	↑	N	↑	N	N	N
Rodenticide toxicity	N/↑	↑	↑↑	↑	N/↓	N/↓	N/↑
DIC	↑	↑	↑	↑	↓	N/↓	↑
Liver disease	N/↑	↑	N/↑	↑	N/↓	N/↓	N

ACT, Activated coagulation test; *aPTT,* activated partial thromboplastin time; *BT,* bleeding time; *DIC,* disseminated intravascular coagulation; *FDP,* fibrin degradation product; *N,* normal or negative; *OSPT,* one-stage prothrombin time; *vWD,* von Willebrand disease; ↑, high or prolonged; ↓, decreased or shortened; *?,* questionable.
*OSPT and aPTT are considered prolonged if they are 25% or more than the concurrent controls.

Unfortunately, the BMBT has high interoperator and intraoperator variability (as high as 80%), and the results are not reproducible, even by the same operator. The PFA-100 (see later) has largely replaced the BMBT in most veterinary teaching hospitals.

By performing these simple tests after evaluating the clinical features of the bleeding disorder, the clinician should be able to narrow down the number of differential diagnoses. For example, the blood smear evaluation reveals whether the patient is thrombocytopenic or not. If the patient is not thrombocytopenic but petechiae and ecchymoses are present, a prolonged bleeding time or PFA-100 closure time support the existence of a platelet function defect (although this situation is uncommon). A prolonged ACT or aPTT indicates an abnormality in the intrinsic or common pathways, a prolonged OSPT documents a defect in the extrinsic pathway (i.e., factor VII), and a positive test result for FDPs or D-dimer supports the presence of primary or secondary fibrinolysis.

If further confirmation of a presumptive diagnosis is required, plasma can be submitted to a referral laboratory or a specialized coagulation laboratory (see p. 1393). Most commercial veterinary diagnostic laboratories routinely evaluate hemostatic profiles. Samples should be submitted in a purple-topped tube (sodium EDTA) for platelet count, a blue-topped tube (sodium citrate) for coagulation studies (OSPT, aPTT, fibrinogen concentration, D-dimer), and a special blue-topped tube (Thrombo-Wellcotest, Thermo Fisher Scientific, Lenexa, KS) for FDP determination (the last tube is usually supplied by the diagnostic laboratory). The blue-topped tubes are now primarily available in 3.2% sodium citrate concentrations. The results of routine hemostasis assays are not affected by the concentration of citrate used (Morales et al., 2007). It is important to submit the right samples in the appropriate anticoagulant. The guidelines for sample submission to commercial laboratories are summarized in Table 87.3.

TABLE 87.3

Specimens Required for Laboratory Evaluation of Hemostasis

SAMPLE	TUBE TOP COLOR	TEST(S)
EDTA blood	Purple	Platelet count
Citrated blood	Blue	OSPT, aPTT, fibrinogen, AT, vWF, clotting factor assays, D-dimer, TEG, PFA-100
Thrombin	Blue	FDP

aPTT, Activated partial thromboplastin time; *AT,* antithrombin; *EDTA,* ethylenediamine tetraacetic acid; *FDP,* fibrin degradation product; *OSPT,* one-stage prothrombin time; *PFA-100,* platelet function analyzer; *TEG,* thromboelastograph; *vWF,* von Willebrand factor assay.

A routine coagulation screen (or hemostatic profile) usually contains the OSPT, aPTT, platelet count, fibrinogen concentration, and FDP and D-dimer concentration. In some laboratories, AT activity may also be included. The OSPT primarily evaluates the extrinsic pathway, whereas the aPTT primarily evaluates the intrinsic pathway. Because the end product in these assays is always fibrin formation, both tests also evaluate the common pathway (see Fig. 87.2). The D-dimer assay evaluates for systemic fibrinolysis, as does the FDP test; however, as noted, the D-dimer is formed after fibrin has been stabilized by factor XIII. Thus it is more indicative of intravascular thrombus formation. The interpretation of routine hemostasis profiles is summarized in Table 87.2.

New instruments now allow evaluation of other aspects of hemostasis. For example, the platelet function analyzer PFA-100 (Siemens Healthcare Diagnostics, Deerfield, IL) is

a simple, cage-side instrument for evaluating platelet adhesion and aggregation. This instrument is available in several specialized clinical hemostasis laboratories and has been extensively evaluated in dogs. The PFA-100 is sensitive for the screening of vWD. The Thromboelastograph Hemostasis Analyzer system (TEG; Haemonetics, Braintree, MA), also available in several specialized hemostasis laboratories, uses native or anticoagulated blood activated with a variety of agonists. This instrument evaluates global hemostasis, including platelet adhesion and aggregation, fibrin formation, fibrinolysis, and clot retraction. The TEG is ideal to monitor response to blood component therapy in patients with coagulopathies. I have found that it provides a wealth of information in patients with hypercoagulability and those with spontaneous bleeding and normal results of hemostasis profiles. Platelet mapping is a new TEG-based method that allows the titration of antiplatelet agents in humans; we have found it to be very reliable in dogs. However, this analyzer requires a fresh (<2 hours) blood sample, so the patient likely needs to be referred to the center where the tests will be conducted.

As noted, if an unusual coagulopathy or specific clotting factor deficiency is suspected, blood should be submitted to a specialized veterinary coagulation laboratory. Congenital and acquired clotting factor deficiencies that occur in cats and dogs are listed in Box 87.3.

Thrombocytopenia can be caused by decreased production or increased destruction, consumption, or sequestration of platelets; therefore a bone marrow aspiration for cytologic evaluation is indicated in cats and dogs with thrombocytopenia of unknown cause. Other tests can also be performed in thrombocytopenic cats and dogs, including determinations of titers or a polymerase chain reaction (PCR) assay for vector-borne diseases, or evaluation for retrovirus infection (see Chapters 91 and 96).

Finally, clinicians occasionally encounter a patient with abnormal results of hemostasis profiles but without spontaneous bleeding. The most common abnormality in the hemostasis profile of a dog or cat without a tendency to bleed is a prolongation of the aPTT. Often the prolongation is marked (>50% above the control or upper limit of the reference range for the laboratory). If this abnormality is found during a presurgical evaluation, the surgery may be delayed needlessly if the clinician is not familiar with some of the following clinical conditions. As noted, dogs and cats with factor XII deficiency do not bleed but have a prolonged aPTT; determination of factor XII activity will provide a diagnosis. Prekallikrein and HMWK are co-factors for the contact activation of factor XII. Dogs with prekallikrein or HMWK deficiencies have prolonged aPTT but do not bleed; incubation of the plasma samples for a few hours overrides the factor deficiency and corrects the aPTT. Finally, the presence of circulating anticoagulants, also referred to as lupus anticoagulants or antiphospholipid antibodies, results in prolongation of the aPTT without bleeding. A simple test to determine whether the patient with a prolonged aPTT has a clotting factor deficiency (e.g., factor XII) or circulating anticoagulants is to perform an aPTT after diluting the patient's sample 50:50 with normal or pooled dog plasma (dilution assay). As noted, the aPTT becomes prolonged when the patient has less than 30% activity of an individual factor. If the patient has factor XII deficiency, for example, and 0% factor XII activity, mixing the sample 50:50 with normal dog plasma (with a factor XII activity of 100%) will result in a final factor XII activity of 50% and thus the aPTT will be normal. Circulating anticoagulants also inhibit the clotting factors in normal dog plasma, so when the samples are mixed 50:50, the aPTT remains prolonged. Recently, the presence of prolonged aPTT and antiphospholipid antibodies was documented in healthy Bernese Mountain dogs (Nielsen et al., 2011a and b).

BOX 87.3

Congenital and Acquired Clotting Factor Defects

Congenital Clotting Factor Defects

Factor I, or hypofibrinogenemia and dysfibrinogenemia (Bichon Frise, Borzoi, Collie; DSH)
Factor II, or hypoprothrombinemia (Boxer, Otterhound, English Cocker Spaniel)
Factor VII, or hypoproconvertinemia (Alaskan Klee Kai, Beagle, Malamute, Scottish Deerhound, Schnauzer; DSH)
Factor VIII, or hemophilia A (many breeds but mainly German Shepherd Dogs and Golden Retrievers; DSH)
Factor IX, or hemophilia B (many breeds of dogs; DSH and many cat breeds)
Factor X, or Stuart-Prower trait (Cocker Spaniel, Jack Russell Terrier; DSH)
Factor XI, or hemophilia C (English Springer Spaniels, Great Pyrenees, Kerry Blue Terriers; DSH)
Factor XII, or Hageman factor (Miniature Poodles, Shar Pei; DSH, DLH, Siamese, Himalayan cats)
Prekallikrein (Fletcher factor) deficiency (various dog breeds)

Acquired Clotting Factor Defects

Liver disease

Decreased production of factors
Qualitative disorders?
Cholestasis

Vitamin K antagonists (rodenticides)

DIC

DIC, Disseminated intravascular coagulation; *DLH,* domestic long-haired cat; *DSH,* domestic short-haired cat.
Modified from Brooks MB: Hereditary coagulopathies. In Weiss DJ, Wardrop KJ, editors: *Schalm's veterinary hematology,* ed 6, Ames, Iowa, 2010, Wiley-Blackwell, p 661.

MANAGEMENT OF THE BLEEDING PATIENT

Several basic principles apply to the management of cats and dogs with spontaneous bleeding disorders. Specific

principles are discussed in the following paragraphs. In general, a patient with a spontaneous bleeding disorder should be managed aggressively because these disorders are potentially life-threatening; at the same time, iatrogenic bleeding should be minimized. As a general rule, trauma should be minimized, and the patient must be kept quiet, preferably confined to a cage and leash-walked, if necessary. Exercise should be avoided or markedly restricted.

Venipunctures should be done with the smallest gauge needle possible, and pressure should be applied to the puncture site for a minimum of 5 minutes. A compressive bandage should also be applied to the area once pressure has been released. If repeated samples for packed cell volumes (PCVs) and plasma protein determinations are necessary, they should be obtained from a peripheral vein with a 25-gauge needle to fill one or two microhematocrit tubes by capillarity. A bandage should be applied after each venipuncture.

Invasive procedures should be minimized. For example, urine samples should never be collected by cystocentesis because of the risk of intraabdominal, intravesical, or intramural bladder bleeding. Certain invasive procedures, however, can be performed safely. These include bone marrow aspiration, fine-needle aspiration (FNA) of lymph nodes or superficial masses, FNA of the spleen (the thick fibromuscular capsule of the carnivore spleen seals the needle hole as soon as the needle is removed), and intravenous catheter placement, although seepage from the catheter is common in thrombocytopenic patients.

Certain types of surgeries can also be safely performed in some cats and dogs with coagulopathies. For example, pedicle surgery (e.g., splenectomy) can be performed with minimal bleeding (i.e., seepage from the abdominal wound) in dogs with marked thrombocytopenia (i.e., <25,000 platelets/μL).

A transfusion of blood or blood components is indicated in some dogs and cats with spontaneous bleeding disorders. WFB or a combination of packed RBCs and fresh-frozen plasma (FFP) should be used if the animal is anemic and lacking one or more clotting factors; plasma transfusions are of no benefit in thrombocytopenic animals. FFP can be used to replenish clotting factors in a cat or dog with a normal or mildly decreased PCV (i.e., the animal is not symptomatic). Although it was traditionally thought that stored blood and frozen plasma were deficient in factors V and VIII and were not hemostatically active, it was recently demonstrated that frozen, 5-year-old plasma is hemostatically active (Urban et al., 2013). In general, WFB, platelet-rich plasma, and platelet transfusions rarely provide sufficient platelets to halt spontaneous bleeding in a cat or dog with thrombocytopenia, particularly if the bleeding is the result of platelet consumption. Some guidelines for transfusion therapy are discussed in Chapter 82.

Nonspecific procoagulants such as epsilon-aminocaproic acid (EACA) or tranexamic acid have been used successfully to manage spontaneous bleeding in a variety of clinical situations (Marin et al., 2012a and b). In Greyhounds with delayed postoperative bleeding, 500 to 1000 mg (≈15-50 mg/kg) of EACA, orally (PO) q8h for 5 days, successfully prevents or resolves spontaneous bleeding. We have also used this protocol successfully in thrombocytopenic dogs, dogs with bleeding hemangiosarcomas, trauma patients, and those with hemophilia.

A recent study of tranexamic acid, used as a 10 mg/kg IV injection followed by q3h infusion (10 mg/kg) did not result in toxicity or consistent changes in TEG results (Kelmer et al., 2015); rapid IV injection of tranexamic acid typically induces vomiting.

Recent studies evaluated the efficacy of both aminocaproic acid or *Yunnan baiyao*, a traditional Chinese herbal drug, in both normal dogs and dogs with bleeding right atrial masses and pericardial effusion.

One study found *Yunnan baiyao* to be safe but it did not induce changes in the TEG tracing or parameters in 10 normal Beagles (Frederick et al., 2017); however, Tansey et al. (2018) reported that using it at a dosage of 1 capsule q12h in client-owned dogs of over 15 kg, this herb increases clot strength and is well tolerated. Reported dosages for this compound range from 1 capsule once a day to 3 capsules 3 times a day.

In a retrospective case-controlled study of 67 dogs with right atrial masses and pericardial effusion, both *Yunnan baiao* and aminocaproic acid, either singly or in combination, were found to be safe (Murphy et al., 2017) but they did not significantly affect outcome, when compared with control dogs.

PRIMARY HEMOSTATIC DEFECTS

Primary hemostatic defects are characterized by the presence of superficial and mucosal bleeding (e.g., petechiae, ecchymoses, hematuria, epistaxis) and are usually associated with thrombocytopenia. Platelet dysfunction is a rare cause of spontaneous bleeding in dogs and cats. Primary hemostatic defects caused by vascular problems are extremely rare and thus are not discussed here. These defects are the most common cause of spontaneous bleeding in dogs seen at our hospital.

THROMBOCYTOPENIA

Thrombocytopenia represents the most common cause of spontaneous bleeding in dogs seen at our clinic. Decreased numbers of circulating platelets can be the result of one or more of the following abnormalities (Box 87.4):

- Decreased platelet production
- Increased platelet destruction
- Increased platelet consumption
- Increased platelet sequestration

Increased platelet destruction represents the most common cause of thrombocytopenia in dogs in our clinic but is rare in cats. Usually, the peripheral destruction of platelets results from immune-mediated, drug-related, and

BOX 87.4

Causes of Thrombocytopenia in Dogs and Cats

Decreased Platelet Production

Immune-mediated megakaryocytic hypoplasia
Idiopathic bone marrow aplasia
Drug-induced megakaryocytic hypoplasia (estrogens, phenylbutazone, melphalan, lomustine β-lactams)
Myelophthisis
Cyclic thrombocytopenia
Retroviral infection
Canine monocytic ehrlichiosis
Feline monocytic ehrlichiosis?

Increased Platelet Destruction, Sequestration, or Utilization

Immune-mediated thrombocytopenia
Infectious (e.g., *Anaplasma* spp., *Bartonella* spp., sepsis)
Live viral vaccine–induced thrombocytopenia
Drug-induced thrombocytopenia
Microangiopathy
Disseminated intravascular coagulation
Hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura
Vasculitis
Splenomegaly
Splenic torsion
Endotoxemia
Acute hepatic necrosis
Neoplasia (immune mediated, microangiopathy)

Note: Entries in **boldface** are common causes; entries in *italics* are relatively common causes; entries in regular typeface are uncommon causes.

infectious mechanisms; increased platelet consumption occurs most commonly in dogs and cats with DIC (see later), and sequestration is usually caused by splenomegaly or, rarely, hepatomegaly (see Box 87.4).

Approach to the Patient With Thrombocytopenia

Before assessing a patient with primary hemostatic bleeding, the clinician must remember that in some breeds, platelet counts below the reference range for dogs are common. Platelet counts in Greyhounds typically range from 80,000 to 120,000/μL, whereas in Cavalier King Charles Spaniels with macrothrombocytopenia, platelet counts < 50,000/μL are common. In the latter the global platelet function is normal. Because of the tendency of feline platelets to clump in the EDTA tube, we see a few cats per year referred for evaluation of asymptomatic thrombocytopenia. Evaluation of the blood smear or hematology analyzer graphics in those cats reveals platelet clumping, and hence, pseudothrombocytopenia. Iloprost, a prostaglandin I_2 analogue added to the blood collection tube, can effectively decrease platelet aggregation in cats and eliminate or minimize thrombocytopenia (Riond et al., 2015).

Once thrombocytopenia has been confirmed by a platelet count, evaluation of a blood smear or analyzer graphics, its pathogenesis should be identified. The absolute platelet count may offer clues to its cause; for example, platelet counts of <25,000/μL are common in dogs with immune-mediated thrombocytopenia (IMT), whereas platelet counts of 50,000 to 75,000/μL are more common in dogs with ehrlichiosis, anaplasmosis, lymphoma with splenic involvement, or rodenticide toxicity.

The patient's drug history should be obtained from the owner. If the pet is receiving any medication, the thrombocytopenia should be considered drug-related until proven otherwise. The drug should be discontinued, if possible, and the platelet count reevaluated within 2 to 6 days. If the count returns to normal, a retrospective diagnosis of drug-associated thrombocytopenia is made. Drugs that have been associated with thrombocytopenia in cats and dogs can also cause anemia and neutropenia (see Boxes 82.2 and 85.1).

Because retroviral disorders commonly affect the bone marrow and may result in thrombocytopenia in cats, feline leukemia virus (FeLV) and feline immunodeficiency virus tests should be performed first. A bone marrow aspiration is indicated in a thrombocytopenic cat with no history of previous medication and a negative retrovirus status. The risk of bleeding during or after bone marrow aspiration in a thrombocytopenic animal is minimal. If determined by the laboratory, a mean platelet volume is high in most cats with FeLV infection (i.e., macrothrombocytosis); however, macrothrombocytes are also seen in cats and dogs with peripheral platelet destruction, consumption, or sequestration, in which they may be analogous to reticulocytes (young, immature, large platelets) and in normal Cavalier King Charles Spaniels.

Bone marrow evaluation may also be indicated for dogs with thrombocytopenia. Given the high prevalence of IMT, at our clinic we usually elect to treat a dog with a presumed diagnosis of IMT. If the patient does not respond to immunosuppressive drugs within 2 to 3 days, a bone marrow aspiration may be performed.

Hyperplasia of megakaryocytes occurs in response to peripheral destruction, consumption, or sequestration of platelets. Occasionally dogs and cats with IMT have decreased numbers of megakaryocytes and abundant free megakaryocyte nuclei in the bone marrow. This is thought to be mediated by antibodies directed against platelets that also destroy the megakaryocytes. Infiltrative or dysplastic bone marrow disorders causing thrombocytopenia are easy to identify on a bone marrow smear.

Because IMT is a diagnosis of exclusion, vector-borne diseases (e.g., canine ehrlichiosis or anaplasmosis, Rocky Mountain spotted fever, leishmaniasis, babesiosis, bartonellosis) should theoretically be ruled out by evaluating the appropriate serology or PCR and a blood smear. In thrombocytopenic dogs, we perform a SNAP-4DX Plus test (IDEXX Laboratories) as the first line of diagnostics to rule out *Ehrlichia*, *Anaplasma*, and *Borrelia* as causative agents; however, acutely infected dogs may be thrombocytopenic

and have a negative test result because they have not yet mounted an appropriate immune response.

As discussed in Chapter 95, some of these diseases have breed distribution (i.e., leishmaniasis in Foxhounds in the United States) or geographic distribution (e.g., leishmaniasis in Mediterranean countries). As a general rule, if the patient is asymptomatic other than the bleeding, the thrombocytopenia is not likely caused by sepsis or vector-borne diseases, although occasionally asymptomatic thrombocytopenic dogs have subclinical vector-borne diseases, such as anaplasmosis or rickettsiosis. If sepsis is suspected on the basis of clinical signs and clinicopathologic findings (e.g., fever, tachycardia, poor perfusion, toxic leukocyte changes, degenerative left shift in the leukogram, hypoglycemia, hyperbilirubinemia), urine and blood should be obtained for bacterial cultures; as discussed earlier, cystocentesis should be avoided in bleeding patients.

The presence of spherocytic hemolytic anemia or autoagglutination in a dog with thrombocytopenia is highly suggestive of Evans syndrome (combination of IMT and immune hemolytic anemia [IHA]). A direct Coombs test is usually positive in these cases. On rare occasions, a direct Coombs test is positive in a dog with IMT and borderline anemia, further supporting a diagnosis of Evans syndrome (see Chapters 73 and 82).

A hemostasis screen should always be performed to rule out DIC in a thrombocytopenic animal found to have RBC fragments in a blood smear or evidence of secondary bleeding (e.g., hematomas, bleeding into body cavities). The rest of the hemostasis screen is usually normal in dogs and cats with selective thrombocytopenia.

Several tests are available to evaluate antiplatelet antibodies (see Chapter 71). However, most of these are not clinically reliable, and a diagnosis of IMT can be made only after other causes of thrombocytopenia have been excluded, regardless of the results of the antiplatelet antibody tests.

Abdominal radiographs and ultrasonograms may reveal an enlarged spleen not evident during physical examination. Diffuse splenomegaly (splenic sequestration of platelets) may be the cause of the thrombocytopenia, or it may reflect work hypertrophy (mononuclear phagocytic system hyperplasia) and extramedullary hematopoiesis in a dog with IMT. Splenic nodules are usually an incidental finding in dogs with thrombocytopenia and may represent extramedullary hematopoiesis or hyperplasia; FNA of the nodules should establish a cytologic diagnosis. Despite the low platelet counts, clinically relevant bleeding is extremely rare.

Often a specific diagnosis of IMT is obtained only after a therapeutic trial with corticosteroids (see later and Chapters 72 and 73) results in resolution of the thrombocytopenia. If the clinician is in doubt regarding whether the thrombocytopenia is caused by a vector-borne diseases or IMT (in dogs), immunosuppressive doses of corticosteroids can be administered in conjunction with doxycycline (5-10 mg/kg PO q12-24h) until serologic or PCR test results become available. This combination of agents has no deleterious effects on dogs with vector-borne diseases, but not all of them are doxycycline responsive.

Blood or blood components should be transfused as needed (see Chapter 82). However, the transfusion of WFB, platelet-rich plasma, or platelets rarely, if ever, results in normalization of the platelet count or even in increases in the platelet count to safe levels. In addition, in most dogs, platelet transfusions are cost-prohibitive. Symptomatic prohemostatic treatment with aminocaproic or tranexamic acid, or *Yunnan baiyao* can be used in patients with life-threatening bleeding.

Immune-Mediated Thrombocytopenia

IMT is the most common cause of spontaneous bleeding in dogs but is rare in cats. It affects primarily middle-aged female dogs; Cocker Spaniels and Old English Sheepdogs are overrepresented. The clinical signs are those of a primary hemostatic defect and include petechiae, ecchymoses, and mucosal bleeding. As discussed earlier, a bleeding score for thrombocytopenic dogs was proposed for dogs (Makielski et al., 2018). Acute collapse may occur if bleeding is pronounced; if the anemia is mild, most dogs are fairly asymptomatic. IMT is acute or peracute in onset in most dogs. During physical examination, signs of primary hemostatic bleeding (e.g., petechiae, ecchymoses, mucosal bleeding), with or without splenomegaly, may be found.

The complete blood count (CBC) in dogs with IMT is characterized by thrombocytopenia with or without anemia, depending on the degree of spontaneous bleeding and presence or absence of concurrent IHA; the anemia can be regenerative or nonregenerative, depending on the time of onset of the bleeding. Mature leukocytosis may also be present. However, as a general rule, in dogs with IMT hematologic changes are limited to the thrombocytopenia. If IHA is associated with IMT (i.e., Evans syndrome), a Coombs-positive regenerative anemia with spherocytosis or autoagglutination is present. Bone marrow cytologic studies typically reveal megakaryocytic hyperplasia, although megakaryocytic hypoplasia with free megakaryocyte nuclei is occasionally present. In addition to the thrombocytopenia, the bleeding time is the only other abnormal test result (ACT, aPTT, OSPT, FDP–D-dimer, and fibrinogen concentration are normal). An inverse linear correlation is usually present between the platelet count and BMBT (i.e., a longer BMBT with lower platelet counts). Ideally, vector-borne diseases and drug-induced thrombocytopenia should be ruled out before establishing a definitive diagnosis of IMT.

My approach is as follows: If the index of suspicion for IMT is high—that is, a fairly asymptomatic dog with spontaneous primary hemostatic bleeding and thrombocytopenia as the sole hematologic abnormality—I institute a therapeutic trial with immunosuppressive doses of corticosteroids (equivalent to 2-8 mg/kg/day of prednisone). Responses are usually seen within 24 to 96 hours. No clinical evidence exists that dexamethasone is more effective than prednisone in controlling IMT. In my experience, acute gastrointestinal (GI) tract ulceration is considerably more prevalent in dogs

receiving dexamethasone than in those receiving prednisone. Because an acute upper GI tract bleed is usually catastrophic in a dog with thrombocytopenia, prednisone is my drug of choice. H_2 antihistamines such as famotidine (0.5-1 mg/kg PO q12-24h) or proton pump inhibitors (omeprazole 0.5-1 mg/kg, PO, q24h) should be used in combination with the corticosteroids.

FWB, stored blood, or packed RBCs should be administered as needed to maintain adequate oxygen-carrying capacity (see Chapter 82, "Transfusion Therapy"). In my experience, in addition to immunosuppressive doses of corticosteroids, cyclophosphamide given intravenously (IV) or PO in a single dose of 200 to 300 mg/m^2 is effective for inducing remission. However, it should not be used as a maintenance agent because it may result in sterile hemorrhagic cystitis when used on a long-term basis. Vincristine at a dose of 0.5 mg/m^2 given IV traditionally has been recommended for dogs with IMT. This drug stimulates megakaryocyte endomitosis, resulting in early platelet release from the bone marrow. However, because vinca alkaloids bind to tubulin, the platelets released prematurely are not fully functional (tubulin is responsible for platelet aggregation), and the patients may have further bleeding before the platelet count increases. As discussed in Chapters 72 and 82, human intravenous immunoglobulin (0.5-1 g/kg IV, single dose) has been used successfully in dogs with refractory or life-threatening IMT. Transfusion of platelet concentrates may be indicated, but platelet numbers rarely increase significantly given that the thrombocytopenia is due to peripheral consumption. In a retrospective study (Ng et al., 2016), the transfusion of cryopreserved platelets to 43 thrombocytopenic dogs had no influence on survival.

Failure to induce remission, which normalizes the platelet count, is usually the result of insufficient drug (low doses or the need for a second agent), insufficient duration of therapy (the drugs have not yet had time to become effective), or an incorrect diagnosis. In the event of one of these, the treatment protocol can easily be amended, with the thrombocytopenia usually resolving as a result. Azathioprine (50 mg/m^2 PO q24-48h) is effective in maintaining remission but is not a good agent for inducing remission. In some dogs azathioprine is better tolerated than long-term corticosteroid therapy, although close hematologic monitoring is recommended given its myelosuppressive properties and low potential for hepatotoxicity. See Chapters 72 and 73 for additional information and drug dosages.

The prognosis is good in most dogs with IMT, although they may require lifelong treatment. Dogs with refractory IMT can be successfully treated with pulse-dose cyclophosphamide, human immunoglobulin, mycophenolate mofetil, or splenectomy.

IMT has become more prevalent in cats over the past few years. The typical clinical presentation is different from dogs in that most cats have chronic thrombocytopenia that does not lead to spontaneous bleeding. A platelet count of 10,000 to 30,000/µL is relatively common in an otherwise healthy cat without spontaneous bleeding. As discussed earlier, in thrombocytopenic dogs and cats, it is imperative to determine whether the patient has platelet aggregates by evaluating a blood smear or the graphics from the analyzer (see Fig. 87.1). I have followed up several of these cats for months to years, and their platelet counts do not increase markedly with treatment, questioning the diagnosis of IMT. Interestingly, a high proportion of these cats also have regenerative or nonregenerative anemia, neutropenia, lymphocytosis, or combinations thereof, so an infectious process such as anaplasmosis or ehrlichiosis cannot be excluded. The cytopenias may resolve for no apparent reason, only to have a decrease in another cell line months later. Because most of these cats do not bleed, the clinician should be aware that increasing drug dosages or adding drugs may cause more problems than monitoring the platelet count. My treatment of choice for cats with IMT or immune-mediated cytopenias is a combination of dexamethasone (4 mg total dose, q1-2 wk) and chlorambucil (20-30 mg/m^2 PO q2wk). I have also successfully used human intravenous immunoglobulin G in a limited number of cats with immune-mediated cytopenias. See Chapter 73 for more discussion of IMT.

PLATELET DYSFUNCTION

The presence of primary hemostatic bleeding in a patient with a normal platelet count is highly suggestive of a platelet dysfunction syndrome, although vasculopathies and enhanced fibrinolysis should also be considered. Platelet dysfunction syndromes can be congenital or acquired (Box 87.5); however, they rarely result in spontaneous bleeding. More often a prolonged BMBT is noted preoperatively in



BOX 87.5

Platelet Function Defects in Dogs and Cats

Hereditary

vWD (many breeds)
Macrothrombocytopenia (Cavalier King Charles Spaniel)
Glanzmann's thromboasthenic thrombopathia (Otterhound, Great Pyrenees)
Canine thrombopathia (Basset Hounds, Foxhounds, Spitz, German Shepherd Dogs)
Collagen deficiency diseases or Ehlers-Danlos syndrome (many breeds)
Scott syndrome (lack of platelet procoagulant activity; German Shepherd Dogs)

Acquired

Drugs (prostaglandin inhibitors, antibiotics, phenothiazines, vaccines)
Secondary to diseases (myeloproliferative disorders, systemic lupus erythematosus, renal disease, liver disease, dysproteinemias)

vWD, von Willebrand disease.
Modified from Boudreaux MK: Inherited intrinsic platelet disorders. In Weiss DJ, Wardrop KJ, editors: *Schalm's veterinary hematology*, ed 6, Ames, Iowa, 2010, Wiley-Blackwell, p 619.

TABLE 87.4

Classification of von Willebrand Disease in Dogs

TYPE	DEFECT	BREEDS
1	Low concentration of normal vWF	Airedale, Akita, Bernese Mountain dog, Dachshund, Doberman Pinscher, German Shepherd, Golden Retriever, Greyhound, Irish Wolfhound, Kerry Blue Terrier, Manchester Terrier, Miniature Pinscher, Papillon, Pembroke Welsh Corgi, Poodles, Schnauzer, other pure breeds and mixed-breed dogs
2	Low concentration of abnormal vWF	German Shorthaired Pointer, German Wirehaired Pointer
3	Absence of vWF	Familial: Dutch Kooiker, Scottish Terrier, Shetland Sheepdog Sporadic: Dutch Kooiker, Scottish Terrier, Shetland Sheepdog; sporadic cases Border Collie, Chesapeake Bay Retriever, Cocker Spaniel, Eskimo dog, Labrador Retriever, Maltese, Pitbull, mixed breeds

vWD, von Willebrand disease; *vWF,* von Willebrand factor.
Modified from Brooks MB, Catalfamo JL: Von Willebrand disease. In Weiss DJ, Wardrop KJ, editors: *Schalm's veterinary hematology,* ed 6, Ames, Iowa, 2010, Wiley-Blackwell, p 612.

an otherwise healthy animal, or the animal has a family history of bleeding or pronounced bleeding during a previous surgery. Congenital platelet dysfunction syndromes are rare, with the notable exception of vWD. Some authors classify vWD among the congenital clotting factor deficiencies; however, because its clinical manifestations are those of a primary hemostatic defect, I include it in this section. Acquired platelet function disorders are more common; clinically they are mainly secondary to monoclonal gammopathies, ehrlichiosis, uremia, retroviral infections, or drug therapy.

von Willebrand Disease

vWD is the most common inherited bleeding disorder in humans and dogs but is rare in cats. The term *von Willebrand syndrome* (vWS) is reserved for an acquired vWF deficiency. vWD can be classified into three types (Table 87.4). Dogs with the disease typically have a decreased concentration or activity (type 1 vWD), absence of circulating vWF (type 3 vWD), or low to normal concentrations of an abnormal vWF (type 2 vWD), which result in mild (if any) spontaneous bleeding or, more likely, prolonged surgical bleeding. In dogs vWD can be inherited as an autosomal dominant trait with incomplete penetrance or, more rarely, an autosomal recessive trait (see later). This disorder has been reported to occur in more than 50 breeds of dogs but is more common in Doberman Pinschers, German Shepherd Dogs, Poodles, Golden Retrievers, and Shetland Sheepdogs. In these breeds the defect is inherited as an autosomal dominant trait with incomplete penetrance. In Scottish Terriers and Shetland Sheepdogs, it can be inherited as an autosomal recessive trait; homozygous dogs have no detectable vWF concentrations and are usually severely affected. Type 1 vWD has been purportedly reported to occur in association with clinical hypothyroidism in dogs; however, most scientifically controlled studies have failed to prove an association between

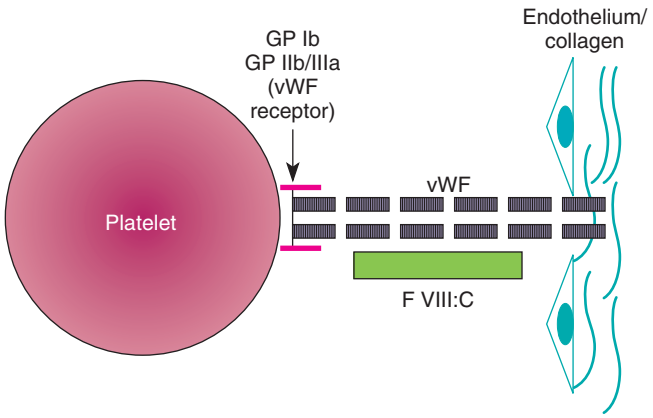


FIG 87.4
Interaction between vWF, platelet, and subendothelial surfaces. *F VIII:C,* Factor VIII coagulant; *GP,* glycoprotein; *vWF,* von Willebrand factor.

vWD and hypothyroidism in dogs. Type 2 vWS has been reported in dogs with aortic valvular disease; in those dogs, the high shear associated with turbulent flow across the valve resulted in selective depletion of high-molecular-weight vWF multimers (Tarnow et al., 2005).

In humans vWF is produced by megakaryocytes and endothelial cells, circulates in plasma complexed to factor VIII coagulant (factor VIII C), and is one of the major adhesive proteins in the body. In the dog, platelets do not contribute as much vWF to plasma as in humans. vWF is mainly responsible for causing platelets to adhere to the subendothelial structures (e.g., collagen) in areas of high shear once endothelial cell damage has occurred, thus initiating the formation of the primary hemostatic plug (Fig. 87.4). The vWF molecule circulates coiled; it uncoils at the site of endothelial damage, binds to the subendothelium and then to the platelet receptors, and the platelets are reeled in to the site of

injury. As a consequence, vWD is usually characterized by primary hemostatic defects (e.g., petechiae, ecchymoses, mucosal bleeding). However, most dogs with vWD do not bleed spontaneously but bleed excessively during or after surgery; excessive bleeding during teething or estrus can also occur, but petechiae and ecchymoses are rare. Most dogs with vWD and spontaneous bleeding seen at our clinic are brought in for the evaluation of diffuse oropharyngeal or vaginal bleeding. People with vWD can also have low circulating concentrations of factor VIII, leading to spontaneous secondary hemostatic bleeding (i.e., the clinical findings of hemophilia A); however, this is extremely rare in dogs. Perinatal death, abortions, or stillbirths are common in litters with vWD.

The hemostasis screen results and platelet counts are normal in most dogs with vWD. However, the results of a PFA-100 test or BMBT usually assist in establishing a diagnosis. As a general rule, the PFA-100 closure time or BMBT is prolonged if the vWF concentration or activity is low. The BMBT may be the most cost-effective method for screening dogs for vWD, although its results are not foolproof. It can be done before surgery in breeds at risk or if the owner or breeder is interested in determining whether the dog is likely to have this disorder. However, a normal bleeding time does not necessarily rule out vWD. At our clinic we routinely use the PFA-100 before surgery in dogs at high risk for vWD so that appropriate therapy can be instituted before or during surgery. A diagnosis of vWD can be confirmed by quantifying vWF in specialized veterinary coagulation laboratories. Genetic testing for vWD in specific breeds is available through commercial diagnostic laboratories (VetGen; https://www.vetgen.com/canine-vWD1.html).

Most dogs with type 1 vWD can be successfully treated before surgery or during a bleeding episode with desmopressin acetate (DDAVP), which causes a massive release of vWF from the endothelial cells and results in shortening of the BMBT and the PFA-100 closure times within 30 minutes of administration. A single 1-µg/kg dose of DDAVP (intranasal preparation) given subcutaneously consistently lessens bleeding in dogs with type 1 vWD despite modest increases in vWF concentration. DDAVP is not effective in dogs with types 2 or 3 vWD because these dogs have an abnormal (i.e., nonfunctional) vWF or lack vWF. Cryoprecipitate is the blood component of choice for dogs with vWD; a unit of cryoprecipitate is defined as the volume obtained from a unit of FFP (see Chapter 82). We use a dosage of 1 U cryoprecipitate/10 kg of body weight; therefore a Doberman Pinscher typically receives 3 U. If cryoprecipitate is not available, FFP or WFB can be used. DDAVP can also be administered to the blood donor dog 1 hour before blood is collected to maximize the yield of vWF. Systemic prohemostatic agents such as aminocaproic or tranexamic acids, and *Yunnan baiyao* can also be used in these patients. The use of topical hemostatic agents such as fibrin, collagen, or methacrylate is also indicated to control the local bleeding. As is the case in dogs with other inheritable disorders, dogs with congenital vWD should not be bred.

Other Congenital Platelet Function Defects

Platelet function defects leading to spontaneous primary hemostatic bleeding have been reported in at least three breeds of dogs (Otterhounds, Foxhounds, and Basset Hounds). The clinical signs and clinicopathologic abnormalities are similar to those seen in dogs with vWD, but the vWF concentrations are normal or high. A syndrome of spontaneous and postoperative bleeding resembling Scott syndrome in humans from a lack of platelet procoagulant activity has been well characterized in German Shepherd Dogs (Jandrey et al., 2012).

SECONDARY HEMOSTATIC DEFECTS

Dogs with secondary hemostatic defects are usually evaluated because of collapse, exercise intolerance, dyspnea, abdominal distention, lameness, subcutaneous bruising, or masses. The collapse and exercise intolerance are usually caused by anemia resulting from intracavitary bleeding, as are the dyspnea and abdominal distention. The lameness is usually caused by hemarthrosis, and the masses or lumps usually represent hematomas. Cats and dogs with secondary hemostatic disorders do not have petechiae or ecchymoses, or mucosal bleeding (e.g., melena, epistaxis) is rarely seen. In general, the severity of the bleeding is directly related to the severity of the deficiency of the clotting factor(s). Liver disease and rodenticide poisoning leading to vitamin K deficiency are the two most common causes of secondary hemostatic defects seen at our clinic; however, the former is rarely associated with spontaneous bleeding. As noted, these disorders are more common in dogs than in cats and are far less common than primary hemostatic defects.

CONGENITAL CLOTTING FACTOR DEFICIENCIES

Congenital clotting factor deficiencies, as well as the breeds affected, are listed in Box 87.3. They are relatively common in dogs but are rare in cats. Most genetic mutations leading to these defects have been well characterized, and some laboratories now offer genetic testing for congenital coagulopathies. Hemophilia A and B are sex-linked traits; the modes of inheritance of other coagulopathies vary. In affected animals, the severity of the bleeding is usually inversely proportional to the concentration of the individual clotting factor affected (e.g., bleeding is more severe in association with a very low factor activity). Clinical signs usually include spontaneous hematoma formation, which the owners may describe as lumps, and bleeding into body cavities, as well as signs compatible with so-called fading puppy syndrome and protracted umbilical cord bleeding after birth. Abortions or stillbirths in the litter are common. Petechiae and ecchymoses are not present in dogs with congenital clotting factor deficiencies. Cats with congenital clotting factor deficiency usually do not bleed spontaneously but have intraoperative or delayed postoperative bleeding.

Carriers of the defect may be asymptomatic but usually have prolonged clotting times in vitro. Certain factor deficiencies (so-called contact factors), including factors XII and XI, Fletcher factor (prekallikrein), and HMWK, are also found in otherwise asymptomatic animals (i.e., no excessive bleeding) with a markedly prolonged aPTT. However, massive and often life-threatening postoperative bleeding starting 24 to 36 hours after surgery is common in dogs with factor XI deficiency.

Most dogs and cats with congenital coagulopathies are treated with supportive and transfusion therapies; no other treatments appear to be beneficial, but anecdotally, aminocaproic acid may help control bleeding. There is ongoing research on gene therapy in canine models of hemophilia and other inherited coagulopathies. As with animals with other congenital defects, dogs and cats with coagulopathies should not be bred.

VITAMIN K DEFICIENCY

Vitamin K deficiency in small animals usually results from the ingestion of vitamin K antagonists (e.g., warfarin, diphacinone, brodifacoum, bromadiolone), although it can also occur as a consequence of malabsorption in dogs and cats with obstructive cholestasis, infiltrative bowel disease, or liver disease. Four clotting factors are vitamin K–dependent: factors II, VII, IX, and X. Proteins C and S, two natural anticoagulants, are also vitamin K–dependent. Because of its clinical relevance, the following discussion focuses only on rodenticide poisoning, which is relatively common in dogs and extremely rare in cats.

Most dogs with toxicity are evaluated because of acute collapse and a possible history of rodenticide ingestion. Coughing, thoracic pain, and dyspnea are also common. These dogs usually have clinical signs compatible with secondary bleeding, such as hematomas and bleeding into body cavities. The most common site of bleeding in dogs evaluated at our clinic is the thorax; some dogs have superficial skin bruising in areas of friction, such as the axilla or groin. Other abnormalities include pale mucous membranes, anemia (usually regenerative if sufficient time has elapsed since the acute bleeding episode), and hypoproteinemia. Sudden death may occur as a result of central nervous system or pericardial hemorrhage.

If the rodenticide has been ingested minutes to hours before presentation, induced vomiting and the administration of activated charcoal may eliminate or neutralize most of it. If the ingestion is questionable and no clinical signs of coagulopathy are present (e.g., hemothorax, hemoabdomen, bruising), determination of the OSPT is recommended. Because factor VII is the shortest lived vitamin K–dependent protein (circulating half-life, 4-6 hours), the OSPT is usually prolonged before spontaneous bleeding becomes evident.

The typical hemostasis screen in a dog with symptomatic vitamin K deficiency reveals marked prolongation of the OSPT and aPTT; this is one of the few clinical situations in which the OSPT is typically longer than the aPTT. The FDP test is positive in more than half of affected dogs and mild thrombocytopenia is present (70,000-125,000/μL), which is likely caused by an excessive consumption of platelets from protracted bleeding.

These animals usually require immediate transfusions of WFB or FFP (or cryopoor plasma) to replenish the coagulation factors (and packed RBCs if the animal is anemic). It may take 8 to 12 hours before vitamin K therapy appreciably shortens the OSPT and subsequently decreases bleeding.

Vitamin K is available in several forms, but vitamin K_1 is the most effective. It is available for oral or parenteral use. Intravenous administration of vitamin K is not recommended because of the risk of anaphylactic reactions or Heinz body formation; intramuscular injections in a dog with a coagulopathy usually result in hematoma formation. Subcutaneous administration of vitamin K_1 with a 25-gauge needle (loading dose 5 mg/kg, followed in 8 hours by 2.5 mg/kg subcutaneously [SC] q8h) is preferred if the patient is properly hydrated. Administration of oral loading doses of vitamin K_1 has been advocated for the treatment of dogs with rodenticide poisoning (5 mg/kg with a fatty meal, then 2.5 mg/kg q8-12h); this is my preferred treatment. Because vitamin K is lipid-soluble, its absorption is enhanced if given with fatty meals. Animals with cholestatic or malabsorptive syndromes may require continued subcutaneous injections of vitamin K. In critical cases the OSPT should be monitored every 8 hours until it normalizes.

If the anticoagulant is known to be warfarin or another first-generation hydroxycoumarin, 1 week of oral vitamin K_1 is usually sufficient to reverse the coagulopathy. However, if it is indanedione or any of the second- or third-generation anticoagulants, oral vitamin K_1 therapy must be maintained for at least 3 weeks and possibly as long as 6 weeks. Most currently available rodenticides contain second- and third-generation anticoagulants. If the rodenticide ingested is unknown, the animal should be treated for 1 week, at which time vitamin K treatment is discontinued. An OSPT is then determined within 24 to 48 hours of the last dose. If the OSPT is prolonged, therapy should be reinstituted and maintained for 2 more weeks and the OSPT reevaluated at the end of this period.

MIXED (COMBINED) HEMOSTATIC DEFECTS

DISSEMINATED INTRAVASCULAR COAGULATION

DIC, previously called consumptive coagulopathy or defibrination syndrome, is a complex syndrome in which excessive intravascular coagulation leads to multiple-organ microthrombosis (multiple organ failure [MOF]) and paradoxic bleeding caused by the inactivation or excessive consumption of platelets and clotting factors as a result of enhanced fibrinolysis. DIC is not a specific disorder but rather a common pathway in a variety of disorders. Moreover, DIC constitutes a dynamic phenomenon in which the patient's status and the results of coagulation tests change markedly,

rapidly, and repeatedly during treatment. This syndrome is relatively common in dogs and cats.

Pathogenesis

Several general mechanisms can lead to the activation of intravascular coagulation and therefore to the development of DIC, including the following:

- Endothelial damage
- Platelet activation
- Release of tissue procoagulants

Endothelial damage commonly results from electrocution or heat stroke, although it may also play a role in sepsis-associated DIC. Platelets can be activated by a variety of stimuli, but mainly they are activated by viral infections (e.g., FIP in cats) or sepsis. Tissue procoagulants (likely TF) are released in several common clinical conditions, including trauma, hemolysis, pancreatitis, bacterial infections, acute hepatitis, and possibly some neoplasms (e.g., HSA). TF is ubiquitous and is expressed in almost every cell membrane, except for inactive or resting endothelial cells; therefore exposure of any cell membrane to circulating blood activates the extrinsic system.

The best way to understand the pathophysiologic process of DIC is to consider the entire vascular system as a single, giant blood vessel and the pathogenesis of the disorder as an exaggeration of the normal hemostatic mechanisms. Once the coagulation cascade has been activated in this giant vessel (i.e., it is widespread within the microvasculature in the body), several events take place. Although they are described sequentially, most of them actually occur simultaneously, and the intensity of each varies with time, thus making for an extremely dynamic process.

First, the primary and secondary hemostatic plugs are formed (see p. 1387). Because this is happening in thousands or tens of thousands of small vessels simultaneously, multiple thrombi form in the microcirculation. If this process is left unchecked, ischemia (resulting in MOF) eventually develops. During this excessive intravascular coagulation, platelets are consumed and destroyed in large quantities, leading to thrombocytopenia. Second, the fibrinolytic system is activated systemically, resulting in clot lysis and the inactivation (or lysis) of clotting factors and impaired platelet function. Third, AT, proteins C and S, and other natural anticoagulant systems are consumed in an attempt to halt intravascular coagulation, leading to exhaustion of these systems. Fourth, the formation of fibrin strands within the microcirculation leads to the development of hemolytic anemia and further compounds the thrombocytopenia as the RBCs are sheared by these fibrin strands (i.e., fragmented RBCs or schistocytes).

When all these events are considered, it is easy to understand the following: (1) why an animal with multiple organ thrombosis caused by excessive intravascular coagulation and the depletion of natural anticoagulants is bleeding spontaneously (as a result of thrombocytopenia, impaired platelet function, and inactivation of clotting factors); and (2) why one of the therapeutic approaches that appears to be beneficial in halting the bleeding in dogs and cats with DIC is to administer heparin or other anticoagulants paradoxically (i.e., if sufficient AT is available, heparin halts intravascular coagulation, which in turn decreases activation of the fibrinolytic system, thus releasing its inhibitory effect on the clotting factors and platelet function).

In addition to the events just described, impaired tissue perfusion results in the development of secondary enhancers of DIC, including hypoxia; lactic acidosis; hepatic, renal, and pulmonary dysfunction; and the release of myocardial depressant factor. The function of the mononuclear-phagocytic system also is impaired so that FDPs and other by-products, as well as bacteria absorbed from the intestine, cannot be cleared from the circulation. These factors also must be dealt with therapeutically (see p. 1403).

The prevalence of primary disorders associated with DIC in 50 dogs and 21 cats evaluated by the author is depicted in Table 87.5. Neoplasia (primarily HSA), liver disease, and immune-mediated blood diseases were the most common disorders associated with DIC in dogs, whereas liver disease (primarily hepatic lipidosis), neoplasia (mainly lymphoma), and FIP were the disorders most frequently associated with DIC in cats.

In my experience, symptomatic DIC in dogs (i.e., that associated with bleeding) is most commonly associated with HSA, followed by sepsis, pancreatitis, hemolytic anemia, gastric dilation-volvulus, and liver disease. Symptomatic DIC is extremely rare in cats but hemostatic evidence of DIC is common, accounting for approximately two thirds of the abnormal hemostatic profiles in this species. As noted, DIC is common in cats with liver disease, hypertrophic cardiomyopathy, sepsis, malignant neoplasms, or FIP. We have also observed symptomatic DIC in two cats receiving methimazole. The pathogenesis of DIC in dogs with HSA appears to be complex and multifactorial; the major mechanism triggering intravascular coagulation in dogs with this neoplasm was thought to be the abnormal irregular endothelium in the neoplasm (i.e., exposure to subendothelial collagen and the activation of coagulation). However, some canine HSAs appear to synthesize a cancer procoagulant because dogs with small HSAs can have severe DIC, whereas some dogs with widely disseminated HSA have normal hemostasis.

Clinical Features

Dogs with DIC can have several clinical presentations; the two common forms are chronic silent (subclinical) and acute (fulminant) DIC. In the chronic silent form, the patient does not have evidence of spontaneous bleeding, but clinicopathologic evaluation of the hemostatic system reveals abnormalities compatible with this syndrome (see later). This form of DIC appears to be common in dogs with malignancy and other chronic disorders. The acute form may represent a true acute phenomenon (e.g., after heat stroke, electrocution, or acute pancreatitis) or, more commonly, it represents acute decompensation of a chronic silent process (e.g., HSA).

TABLE 87.5

Primary Disorders Associated With Disseminated Intravascular Coagulation*

DISEASE	DOGS (%)	CATS (%)
Neoplasia	18	29
HAS	8	5
Carcinoma	4	10
LSA	4	14
HA	2	0
Liver disease	14	33
Cholangiohepatitis	4	0
Lipidosis	0	24
PSS	4	0
Cirrhosis	2	0
Unspecified	4	10
Pancreatitis	4	0
Immune-mediated diseases	10	0
IHA	4	0
IMT	2	0
Evans syndrome	2	0
IMN	2	0
Infectious diseases	10	19
FIP	0	19
Sepsis	8	0
Babesiosis	2	2
Rodenticide†	8	0
GDV	6	0
HBC	4	0
Miscellaneous	18	19

FIP, feline infectious peritonitis; *GDV,* gastric dilation-volvulus; *HA,* hemangioma; *HBC,* hit by car; *HSA,* hemangiosarcoma; *IHA,* immune-mediated hemolytic anemia; *IMN,* immune-mediated neutropenia; *IMT,* immune-mediated thrombocytopenia; *LSA,* lymphoma; *PSS,* portosystemic shunt.

*In 50 dogs and 21 cats evaluated at The Ohio State University Veterinary Teaching Hospital.

†The results of hemostasis profiles in dogs with rodenticide toxicity mimic those seen in disseminated intravascular coagulation (DIC).

From Couto CG: Disseminated intravascular coagulation in dogs and cats, *Vet Med* 94:547, 1999. This table originally appeared in the June 1999 issue of *Veterinary Medicine*. It is reprinted here by permission of Thomson Veterinary Healthcare Communications, 8033 Flint, Lenexa, Kan 66214; (913) 492-4300; fax: (913) 492-4157; www.vetmedpub.com. All rights reserved.

Acute DIC is extremely rare in cats. Regardless of the pathogenesis, dogs with acute DIC often are brought in because of profuse spontaneous bleeding and constitutional signs attributable to anemia or parenchymal organ thrombosis (MOF). The clinical signs of bleeding indicate both primary bleeding (e.g., petechiae, ecchymoses, mucosal bleeding) and secondary bleeding (blood in body cavities); diffuse intraoperative bleeding is frequently the first sign detected by the clinician. Clinical and clinicopathologic evidence of organ dysfunction is also present. Most cats with DIC seen at our clinic do not have evidence of spontaneous bleeding; clinical signs in these cats are those associated with the primary disease.

In a recent retrospective study of 50 dogs with DIC conducted in our clinic, only 26% had evidence of spontaneous bleeding, whereas only one of 21 cats with DIC had evidence of spontaneous bleeding. Most patients were presented for evaluation of their primary problem and were not bleeding spontaneously; DIC was diagnosed as part of the routine clinical evaluation.

Diagnosis

Several hematologic findings help support a presumptive clinical diagnosis of DIC. These include a regenerative hemolytic anemia (although occasionally, because the patient has a chronic disorder such as cancer, the anemia is nonregenerative), hemoglobinemia (caused by intravascular hemolysis), RBC fragments or schistocytes, thrombocytopenia, neutrophilia with a left shift and toxic changes, and rarely neutropenia. Most of these features are evident with the evaluation of a spun hematocrit and blood smear.

Serum biochemical abnormalities in patients with DIC include hyperbilirubinemia from hemolysis or hepatic thrombosis, azotemia and hyperphosphatemia if severe renal microembolization has occurred, increase in liver enzyme activities caused by hypoxia or hepatic microembolization, decreased total carbon dioxide content caused by metabolic acidosis, and panhypoproteinemia if the bleeding is severe enough. Another manifestation of MOF is the development of multifocal ventricular premature contractions resulting in a tachyarrhythmia and easily visualized in an electrocardiogram.

Urinalysis usually reveals hemoglobinuria and bilirubinuria and occasionally proteinuria and cylindruria. Urine samples in dogs with acute DIC should not be obtained by cystocentesis because severe intravesical or intramural bleeding may result.

Hemostatic abnormalities in dogs with DIC include thrombocytopenia, prolongation of the OSPT or aPTT (>25% of the concurrent control), normal or low fibrinogen concentration, positive FDP or D-dimer test, and decreased AT concentration. Using a TEG, fibrinolysis can be enhanced in these animals. At our clinic, DIC is diagnosed if the patient has four or more of the hemostatic abnormalities just described, particularly if schistocytes are present.

The hemostatic abnormalities in 50 dogs and 21 cats with DIC evaluated in our clinic are listed in Table 87.6. In dogs thrombocytopenia, prolongation of the aPTT, anemia, and schistocytosis were common; in contrast with previous descriptions of the syndrome in dogs, regenerative anemia, prolongation of the OSPT, and hypofibrinogenemia were not. In cats prolongation of the aPTT and/or OSPT, schistocytosis, and thrombocytopenia were common,

TABLE 87.6

Hemostatic Abnormalities*

ABNORMALITY	DOGS (%)	CATS (%)
Thrombocytopenia	90	57
Prolonged aPTT	88	100
Schistocytosis	76	67
Positive FDP	64	24
Prolonged OSPT	42	71
Hypofibrinogenemia	14	5

aPTT, Activated partial thromboplastin time; *FDP,* fibrin degradation product; *OSPT,* one-stage prothrombin time.
*In 50 dogs and 21 cats with disseminated intravascular coagulation (DIC) evaluated at The Ohio State University Veterinary Teaching Hospital.
From Couto CG: Disseminated intravascular coagulation in dogs and cats, *Vet Med* 94:547, 1999.

whereas the presence of FDPs and hypofibrinogenemia were rare.

Estrin et al. (2006) have described clinical and clinicopathologic findings in 46 cats with DIC. Spontaneous bleeding was present in 15% of the cats; 43 of 46 cats died or were euthanized. The most common underlying disorders were lymphoma, other forms of neoplasia, pancreatitis, and sepsis. The median PT of nonsurvivors was more prolonged than in survivors ($P = 0.005$). DIC in cats can result from a variety of neoplastic, infectious, and inflammatory disorders and is associated with a high case fatality rate.

Treatment

Once a diagnosis of DIC has been established, or even if the degree of suspicion is high that DIC is present, treatment should be instituted without delay. Unfortunately, no controlled clinical trials have been performed in veterinary medicine evaluating the effects of different treatments in dogs or cats with DIC, so this discussion reflects my personal recommendations for the treatment of dogs with this disorder (Box 87.6).

Unquestionably, removing or eliminating the precipitating cause constitutes the main therapeutic goal in patients with DIC, but this is not always possible. Conditions in which the precipitating causes can be eliminated or ameliorated include a primary HSA (surgical excision), disseminated or metastatic HSA (chemotherapy), sepsis (appropriate antimicrobial treatment), and IHA (immunosuppressive treatment). In most other situations (e.g., electrocution, heat stroke, pancreatitis), the cause can rarely be eliminated within a short time. Therefore the treatment of dogs with DIC is aimed at the following:

- Halting intravascular coagulation
- Maintaining good parenchymal organ perfusion
- Preventing secondary complications

BOX 87.6

Treatment of Dogs and Cats With Disseminated Intravascular Coagulation

1. Eliminate the precipitating cause.
2. Halt intravascular coagulation:
   Heparin
   - Minidose: 5-10 IU/kg SC q8h
   - Low dose: 50-100 IU/kg SC q8h
   - Intermediate dose: 300-500 IU/kg, SC or IV, q8h
   - High dose: 750-1000 IU/kg, SC or IV, q8h

   Blood or blood products (provide AT, other anticoagulants, and clotting factors)
3. Maintain parenchymal organ perfusion:
   Aggressive fluid therapy
4. Prevent secondary complications:
   Oxygen
   Correction of acid-base imbalance
   Antiarrhythmics
   Antibiotics

AT, Antithrombin.

Of note, if blood and blood products were available in an unlimited supply, as is the case in most human hospitals, small animal patients with DIC would not die of hypovolemic shock. Most dogs with DIC die of pulmonary or renal dysfunction. At our clinic, so-called DIC lungs (i.e., intrapulmonary hemorrhages with alveolar septal microthrombi) appear to be a common cause of death in these patients.

Halting Intravascular Coagulation

I use a dual approach to halt intravascular coagulation—the administration of heparin and blood or blood products. As noted, heparin is a co-factor for AT and therefore is not effective in preventing the activation of coagulation unless AT activity in the plasma is sufficient. Because AT activity in animals with DIC is usually low as a result of consumption and possibly inactivation, the patient should be provided with sufficient quantities of this anticoagulant. The most cost-efficient way of achieving this is to administer FFP. The old adage that administering blood or blood products to a dog with DIC is analogous to "adding logs to a fire" has not been true, in my experience. Therefore blood or blood products should never be withheld based solely on this.

Heparin has been used historically to treat DIC in humans and dogs. However, controversy still exists regarding whether it is beneficial. In my experience, the survival rate in dogs with DIC seems to have increased since I started using heparin and blood products. Although this can also be attributed to improvement in patient care, I believe that heparin is beneficial in such patients and indeed may be responsible for the increased survival rate.

Sodium heparin is given in a wide range of doses. Following are the four traditional dose ranges:

- Minidose: 5 to 10 IU/kg SC q8h
- Low dose: 50 to 100 IU/kg SC q8h
- Intermediate dose: 300 to 500 IU/kg, SC or IV, q8h
- High dose: 750 to 1000 IU/kg, SC or IV, q8h

I use low-dose heparin in combination with the transfusion of blood or blood components. The rationale is that this dose of heparin does not prolong the ACT or aPTT in normal dogs (a minimum of 150-250 IU/kg q8h is required to prolong the aPTT in normal dogs), and it appears to be biologically active in these animals, given that some of the clinical signs and hemostatic abnormalities are reversed in animals receiving this dosage. The fact that it does not prolong the aPTT or ACT is extremely helpful in dogs with DIC. For example, if a dog with DIC is receiving intermediate-dose heparin, it is impossible to predict, on the basis of hemostatic parameters, whether a prolongation of the aPTT is caused by excessive heparin administration or progression of this syndrome. As laboratory tests for the determination of heparin levels become widely available, this may become a moot point. Until then, my clinical impression is that if an animal with DIC receiving minidose or low-dose heparin shows a prolonged ACT or aPTT, the intravascular coagulation is deteriorating and a treatment change is necessary. The use of low-molecular-weight heparin in dogs with DIC has been investigated. In an experimental model of DIC in Beagles, high doses of low-molecular-weight heparin resulted in resolution of the clinicopathologic abnormalities associated with DIC (Mischke et al., 2005).

I recently used cryoprecipitate infusions to treat five dogs with DIC successfully; three had hemangiosarcoma and two had gastric dilation-volvulus (GDV). Lepirudin, a novel leech recombinant AT, has proved beneficial in preventing MOF in an experimental model of sepsis with enteric organisms in Greyhounds. However, this treatment is currently cost-prohibitive.

If evidence of severe microthrombosis is present (e.g., marked azotemia, lactic acidosis, increase in liver enzyme levels, multifocal ventricular premature contractions), dyspnea, or hypoxemia, intermediate- or high-dose heparin can be used, with the goal of prolonging the ACT to 2 to 2.5 times the baseline value, or normal if the baseline time was already prolonged. TEG can also be used to monitor heparinization. If overheparinization occurs, protamine sulfate can be administered by slow intravenous infusion (1 mg for each 100 IU of the last dose of heparin; 50% of the calculated dose is given 1 hour after the heparin and 25% 2 hours after the heparin). The remainder of the dose can be administered if clinically indicated. Protamine sulfate should be administered with caution because it can be associated with acute anaphylaxis in dogs. Once improvement in the clinical and clinicopathologic parameters has been achieved, the heparin dose should be tapered gradually, over 1 to 3 days, to prevent rebound hypercoagulability, a phenomenon commonly observed in humans.

Aspirin and other antiplatelet agents can also be given to prevent platelet activation and thus halt intravascular coagulation. Doses of 0.5 to 10 mg/kg of aspirin given orally every 12 hours in dogs and every third day in cats have been recommended, although in my experience aspirin is rarely of clinical benefit. If it is used, the patient should be closely watched for severe GI tract bleeding, because this NSAID can cause gastroduodenal ulceration, which could be catastrophic in a dog with a severe coagulopathy such as DIC.

Maintaining Good Parenchymal Organ Perfusion

Good parenchymal organ perfusion is best achieved with aggressive fluid therapy consisting of crystalloids or plasma expanders such as dextran (see Table 87.6). The purpose of this therapy is to dilute out the clotting and fibrinolytic factors in the circulation, flush out microthrombi from the microcirculation, and maintain the precapillary arterioles patent so that blood is shunted to areas in which oxygen exchange is efficient. However, care should be taken not to overhydrate an animal with compromised renal or pulmonary function.

Preventing Secondary Complications

As noted, numerous complications occur in dogs with DIC. Attention should be directed toward maintaining oxygenation by oxygen mask, cage, or nasopharyngeal catheter, correcting acidosis, eliminating cardiac arrhythmias, and preventing secondary bacterial infections. The ischemic GI mucosa no longer functions as an effective barrier to microorganisms, bacteria are absorbed and cannot be cleared by the hepatic mononuclear-phagocytic system, and sepsis occurs.

Prognosis

The prognosis for dogs and cats with DIC is still grave. Despite the numerous acronyms for DIC coined over the past few decades (e.g., "death is coming," "dead in cage," "dog in cooler"), most patients recover with appropriate treatment if the inciting cause can be controlled. In the retrospective study of DIC in dogs conducted at OSU-VTH, the mortality rate was 54%; however, the mortality rate in dogs with minor changes in the hemostasis screen (fewer than three abnormalities) was 37%, whereas in dogs with severe hemostatic abnormalities (more than three hemostatic abnormalities) it was 74%. In addition, marked prolongation of the aPTT and marked thrombocytopenia were negative prognostic factors. The median aPTT in dogs that survived was 46% over the controls, whereas it was 93% over the controls in dogs that did not survive. Similarly, the median platelet count in dogs that survived was 110,000/μL, and in dogs that did not survive it was 52,000/μL.

THROMBOSIS

Thrombotic and thromboembolic disorders appear to be considerably less common in cats and dogs than in humans. Several situations can result in thrombosis or TE, including stasis of blood, activation of intravascular coagulation in an area of abnormal or damaged endothelium, decreased activity of natural anticoagulants, and decreased or impaired fibrinolysis. Thrombosis has been recognized clinically as associated with cardiomyopathy, hyperadrenocorticism, protein-losing enteropathy and nephropathy, and IHA. A syndrome of aortoiliac thrombosis has been recognized primarily in Cavalier King Charles Spaniels, Greyhounds, and other sighthound breeds (Goncalves et al., 2008; Lake-Bakaar et al., 2012).

Diagnosing TE is not an easy task. Clinical signs are variable and include signs associated with parenchymal organ ischemia (e.g., dyspnea from pulmonary TE, high liver enzyme activities in patients with hepatic TE, intermittent rear limb claudication in dogs with aortic thrombosis). A positive D-dimer test has been reported to be associated with TE disease in dogs, but that is not my experience. TEG is a rapid and sensitive test to diagnose TE disease in some dogs (Fig. 87.5); however, in a large proportion of dogs with overt thrombosis, the TEG tracings are normal.

Stasis of blood and possibly an irregular endothelial surface appear to be the major causes in cats with aortic (iliac) TE secondary to hypertrophic cardiomyopathy. Arterial pathology and high blood viscosity associated with a high hematocrit are suspected in Greyhounds and other sighthounds. Decreased activity of the natural anticoagulant AT plays a major role in the thrombosis seen in dogs with protein-losing nephropathy or protein-losing enteropathy; in addition, humans with hypertension frequently have a high concentration of PAI-1, which in turn inhibits fibrinolysis, thus resulting in a net procoagulant effect. This mechanism may also be important in dogs with protein-losing nephropathy and hypertension. The decreased AT activity stems from the fact that this is a relatively small molecule (≈60 kDa) that is easily lost in the urine or gut contents in dogs with either of these two disorders. The thrombosis commonly seen in dogs with hyperadrenocorticism is likely related to the induction of PAI-1 synthesis by corticosteroids (corticosteroids inhibit fibrinolysis). An increased risk for TE has been recognized in dogs with IHA. Although the pathogenesis of these disorders is obscure, the release of procoagulants from the lysed RBCs has been postulated as a cause; sludging of autoagglutinated RBCs in the microcirculation is also likely to contribute to this procoagulant state.

Dogs and cats at high risk for thrombosis or TE should receive anticoagulants. The two drugs commonly used in cats and dogs at risk for this condition are aspirin and heparin. Coumarin derivatives are commonly used in humans, but in dogs and cats they can result in excessive bleeding. In recent reports of human AT deficiency, anabolic steroids such as stanozolol have also been suggested to decrease the risk of thrombotic disorders because of their stimulatory effect on the fibrinolytic system. The recognition and management of pulmonary TE are discussed in Chapter 22.

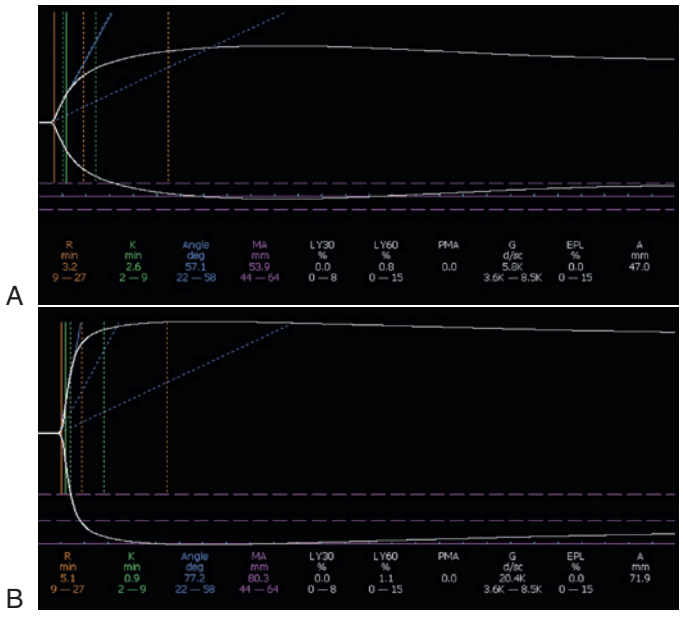


FIG 87.5
(A) Thromboelastograph Hemostasis Analyzer system (TEG) tracing in a normal dog. The maximum amplitude (MA) provides information on the strength of the clot and is within the reference range (53.9 mm). **(B)** TEG tracing in a dog with hypercoagulability. Note that the MA is 80.3 mm.

Suggested Readings

Barr JW, McMichael M. Inherited disorders of hemostasis in dogs and cats. *Top Companion Anim Med*. 2012;27:53.

Boudreaux MK. Inherited intrinsic platelet disorders. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. ed 6. Ames, Iowa: Wiley-Blackwell; 2010:619.

Brooks MB, Catalfamo JL. Von Willebrand disease. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. ed 6. Ames, Iowa: Wiley-Blackwell; 2010:612.

Brooks MB. Hereditary coagulopathies. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. ed 6. Ames, Iowa: Wiley-Blackwell; 2010:661.

Callan MB, Giger U. Effect of desmopressin acetate administration on primary hemostasis in Doberman Pinschers with type-1 von Willebrand disease as assessed by a point-of-care instrument. *Am J Vet Res*. 1700;63:2002.

Couto CG. Disseminated intravascular coagulation in dogs and cats. *Vet Med*. 1999;94:547.

Couto CG, et al. Evaluation of platelet aggregation using a point-of-care instrument in retired racing Greyhounds. *J Vet Intern Med*. 2006;20:365.

Estrin MA, et al. Disseminated intravascular coagulation in cats. *J Vet Intern Med*. 2006;20:1334.

Fletcher DJ, et al. Evaluation of tranexamic acid and ε-aminocaproic acid concentrations required to inhibit fibrinolysis in plasma of dogs and humans. *Am J Vet Res*. 2014;75:731.

Frederick J, et al. The effects of oral administration of Yunnan Baiyao on blood coagulation in beagle dogs as measured by kaolin-activated thromboelastography and buccal mucosal bleeding times. *Can J Vet Res*. 2017;81:41.

Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. 2008;359:938.

Goncalves R, et al. Clinical and neurological characteristics of aortic thromboembolism in dogs. *J Small Anim Pract*. 2008;49:178.

Grindem CB, et al. Epidemiologic survey of thrombocytopenia in dogs: a report on 987 cases. *Vet Clin Pathol*. 1991;20:38.

Jandrey KE, et al. Clinical characterization of canine platelet procoagulant deficiency (Scott syndrome). *J Vet Intern Med*. 2012;26:1402.

Kelmer E, et al. Effects of intravenous administration of tranexamic acid on hematological, hemostatic, and thromboelastographic analytes in healthy adult dogs. *J Vet Emerg Crit Care (San Antonio)*. 2015;25:495.

Kraus KH, et al. Effect of desmopressin acetate on bleeding times and plasma von Willebrand factor in Doberman Pinscher dogs with von Willebrand's disease. *Vet Surg*. 1989;18:103.

Lake-Bakaar GA, et al. Aortic thrombosis in dogs: 31 cases (2000-2010). *J Am Vet Med Assoc*. 2012;241:910.

Lara García A, et al. Postoperative bleeding in retired racing Greyhounds. *J Vet Intern Med*. 2008;22:525.

Levi M, et al. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145:24.

Makielski KM, et al. Development and implementation of a novel immune thrombocytopenia bleeding score for dogs. *J Vet Intern Med*. 2018;32:1041.

Marin LM, et al. Retrospective evaluation of the effectiveness of epsilon aminocaproic acid for the prevention of postamputation bleeding in retired racing Greyhounds with appendicular bone tumors: 46 cases (2003-2008). *J Vet Emerg Crit Care (San Antonio)*. 2012a;22:332.

Marin LM, et al. Epsilon aminocaproic acid for the prevention of delayed postoperative bleeding in retired racing Greyhounds undergoing gonadectomy. *Vet Surg*. 2012b;41:594.

Mischke R, et al. Efficacy of low-molecular-weight heparin in a canine model of thromboplastin-induced acute disseminated intravascular coagulation. *Res Vet Sci*. 2005;79:69.

Morales F, et al. Effects of 2 concentrations of sodium citrate on coagulation test results, von Willebrand factor concentration, and platelet function in dogs. *J Vet Intern Med*. 2007;21:472.

Murphy LA, et al. Use of Yunnan Baiyao and epsilon aminocaproic acid in dogs with right atrial masses and pericardial effusion. *J Vet Emerg Crit Care (San Antonio)*. 2017;27:121.

Nelson OL, Andreasen C. The utility of plasma D-dimer to identify thromboembolic disease in dogs. *J Vet Intern Med*. 2003;17:830.

Ng ZY, et al. Cryopreserved platelet concentrate transfusions in 43 dogs: a retrospective study (2007-2013). *J Vet Emerg Crit Care (San Antonio)*. 2016;26:720.

Nielsen LN, et al. Prolonged activated prothromboplastin time and breed specific variation in haemostatic analytes in healthy adult Bernese Mountain dogs. *Vet J*. 2011a;190:150.

Nielsen LN, et al. The presence of antiphospholipid antibodies in healthy Bernese Mountain dogs. *J Vet Intern Med*. 2011b;25:1258.

Peterson JL, et al. Hemostatic disorders in cats: a retrospective study and review of the literature. *J Vet Intern Med*. 1995;9:298.

Ralph AG, Brainard BM. Update on disseminated intravascular coagulation: when to consider it, when to expect it, when to treat it. *Top Companion Anim Med*. 2012;27:65.

Ramsey CC, et al. Use of streptokinase in four dogs with thrombosis. *J Am Vet Med Assoc*. 1996;209:780.

Riond B, et al. Effective prevention of pseudothrombocytopenia in feline blood samples with the prostaglandin I2 analogue Iloprost. *BMC Vet Res*. 2015;11:1.

Sheafor S, et al. Clinical approach to the dog with anticoagulant rodenticide poisoning. *Vet Med*. 1999;94:466.

Stokol T. Plasma D-dimer for the diagnosis of thromboembolic disorders in dogs. *Vet Clin North Am Small Anim Pract*. 2003;33:1419.

Tansey C, et al. A prospective evaluation of oral Yunnan Baiyao therapy on thromboelastographic parameters in apparently healthy dogs. *J Vet Emerg Crit Care (San Antonio)*. 2018;28:221.

Tarnow I, et al. Dogs with heart diseases causing turbulent high-velocity blood flow have changes in platelet function and von Willebrand factor multimer distribution. *J Vet Intern Med*. 2005;19:515.

Urban R, et al. Hemostatic activity of canine frozen plasma for transfusion using thromboelastography. *J Vet Intern Med*. 2013;in press.

Wiinberg B, et al. Validation of human recombinant tissue factor-activated thromboelastography on citrated whole blood from clinically healthy dogs. *Vet Clin Pathol*. 2005;34:389.

CHAPTER 88

Lymphadenopathy and Splenomegaly



APPLIED ANATOMY AND HISTOLOGY

The lymph nodes and spleen constitute the main source of immunologic and mononuclear-phagocytic (MP) cells in the body. Because these lymphoid structures are in a constant dynamic state, they continuously reshape and change in size in response to antigenic stimuli. In general, the response of the cells within a lymph node to different stimuli is similar to that occurring in the spleen. However, the spleen responds primarily to bloodborne antigens (mainly nonopsonized organisms), whereas the lymph nodes respond to antigens arriving through the afferent lymphatics (i.e., local tissue response). The response of the lymph nodes and spleen to different stimuli is briefly reviewed in this chapter.

Lymph nodes are reniform, encapsulated, well-developed structures responsible for filtering lymph and participating in immunologic reactions. Fig. 88.1 depicts the basic microscopic anatomy of a lymph node in a carnivore. It is composed of a capsule, subcapsular spaces, cortex, paracortex, and medulla. Each of these areas has specific functions. The capsule surrounds and supports all other structures within the node (stroma). The subcapsular spaces (or sinuses) contain mainly MP cells responsible for "filtering" particles arriving through the afferent lymphatics and presenting the antigens to the lymphoid cells. The cortex contains mainly B-cell areas in the germinal centers; when properly stimulated, the primary follicles turn into secondary follicles, containing primarily early lymphoid cells in the center. The paracortex is composed primarily of T cells and is therefore involved in cell-mediated immunity. The medulla contains the medullary cords, in which the committed B cells persist and may expand to solid areas of plasma cells in response to antigenic stimulation. Between the medullary cords, the medullary sinuses form an endothelial sieve containing varying numbers of MP cells, which screen the efferent lymph. The lymph flows from the medulla to the efferent lymphatics in the hilus.

An understanding of the different histologic and functional characteristics of these anatomic areas aids in understanding the pathogenesis of lymphadenopathy. For example, a lymph node reacting to a bacterial infection has primarily B-cell hyperplasia characterized by increased numbers of secondary follicles. This histologic-functional compartmentalization should be kept in mind when interpreting cytologic or histopathologic lymph node specimens.

Recently, Suami et al. described lymphatic territories (lymphosomes), areas that drain specific lymph nodes and are useful when identifying sentinel lymph nodes during oncologic surgery (Suami et al., 2013).

FUNCTION

The two main functions of the lymph nodes are to filter particulate material and participate in immunologic processes. Particulate material is filtered as lymph flows through the areas rich in MP cells while it moves from the afferent to the efferent lymphatics. During this transit, particulate material is taken up and processed by the MP or antigen-processing (AP) cells and presented to the lymphoid cells to elicit a humoral or cellular immune response.

The spleen has multiple functions, including extramedullary hematopoiesis, filtration and phagocytosis, remodeling of red blood cells (RBCs), removal of intraerythrocytic inclusions, storage of RBCs and platelets, metabolizing of iron, and immunologic functions. The canine spleen also stores reticulocytes and releases them into circulation in response to catecholamine release (Horvath et al., 2014). Because of its nonsinusal nature, the feline spleen is less efficient at removing intracellular inclusions than its canine counterpart.

LYMPHADENOPATHY

Etiology and Pathogenesis

In this chapter, lymphadenopathy is defined as lymph node enlargement. According to the distribution, the following terms are used to characterize lymphadenopathy. *Solitary lymphadenopathy* refers to the enlargement of a single lymph

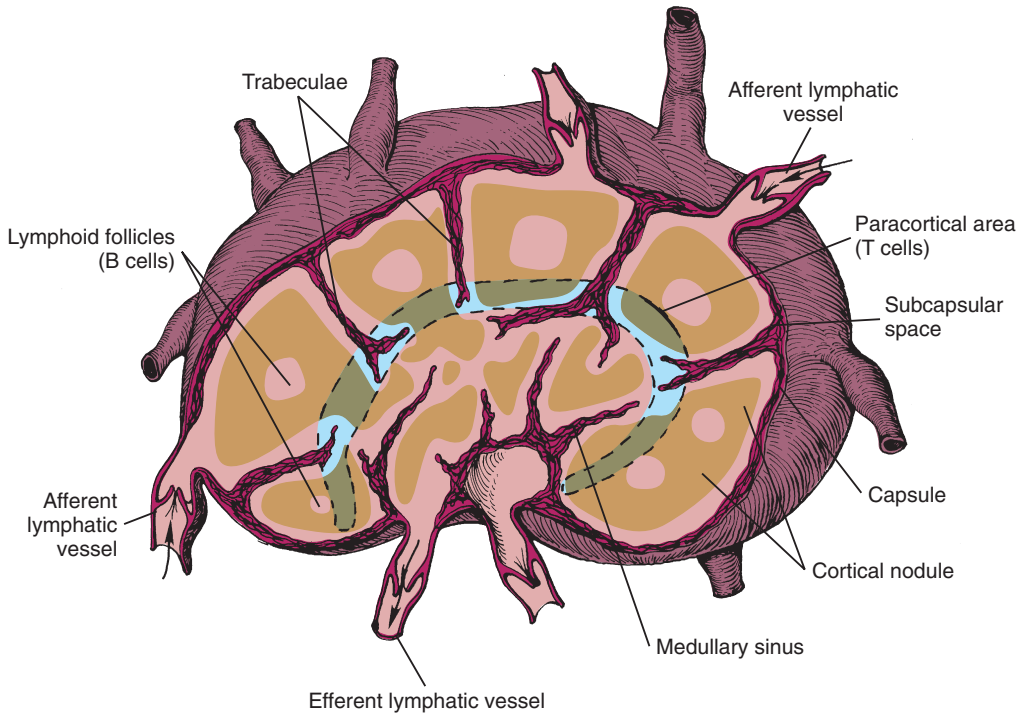


FIG 88.1
Microscopic anatomy of a typical lymph node in a carnivore. (From Couto CG: Diseases of the lymph nodes and spleen. In Ettinger SJ, editor: *Textbook of veterinary internal medicine—diseases of the dog and cat,* ed 3, Philadelphia, 1989, WB Saunders.)

node. *Regional lymphadenopathy* is the enlargement of a chain of lymph nodes draining a specific anatomic area. *Generalized lymphadenopathy* is a multicentric lymph node enlargement affecting more than one anatomic area. Lymphadenopathies can also be classified as superficial or deep (or visceral) according to their anatomic location.

Lymph nodes enlarge as a consequence of the proliferation of normal cells that normally reside in the node, or infiltration with normal or abnormal cells. Rarely lymph nodes enlarge as a result of vascular changes (e.g., hyperemia, congestion, neovascularization, edema).

When normal cells proliferate within a lymph node in response to antigenic stimuli (e.g., vaccination, infection), the term *reactive lymphadenopathy* (or lymph node hyperplasia) is used. Lymphoid and MP-AP cells proliferate in response to immunologic and infectious stimuli, although occasionally a clinician evaluates a dog or cat in which a cause for the reactive lymphadenopathy cannot be identified. Because these lymphoid structures are usually presented with many antigens simultaneously, the cell proliferation that occurs in reactive lymphadenopathies is polyclonal; that is, a wide variety of morphologic types of lymphoid and MP-AP cell types are present in a cytologic or histopathologic specimen.

When polymorphonuclear leukocytes or macrophages predominate in the cellular infiltrate, the term *lymphadenitis* is used. This is usually, but not always, a result of infectious processes. Depending on the predominant cell type in the infiltrate, lymphadenitides are classified as suppurative (neutrophils predominate), granulomatous (macrophages predominate), pyogranulomatous (macrophages and neutrophils predominate), or eosinophilic (eosinophils predominate). A focal area of suppurative inflammation with marked liquefaction (i.e., pus) is referred to as a lymph node abscess. The agents that commonly cause the different types of lymphadenitis are listed in Table 88.1.

Infiltrative lymphadenopathies usually result from the displacement of normal lymph node structures by neoplastic cells and, infrequently, from extramedullary hematopoiesis. Neoplasms affecting the lymph nodes can be primary hematopoietic tumors or secondary (metastatic) neoplasms. Lymph node infiltration by hematopoietic malignancies (i.e., lymphoma) constitutes one of the most common causes of generalized lymphadenopathy in dogs (see Table 88.1).

Clinical Features

From a clinical standpoint, familiarization with the location and palpation characteristics of normal lymph nodes, which should always be evaluated during a routine physical examination, is important. The following lymph nodes are palpable in normal dogs and cats: mandibular, prescapular (or superficial cervical), axillary (in approximately half of animals), superficial inguinal, and popliteal (Fig. 88.2). Lymph nodes that are palpable only when markedly enlarged include the facial, retropharyngeal, mesenteric, and iliac (sublumbar) lymph nodes.

TABLE 88.1

Classification of Lymphadenopathies in Dogs and Cats

TYPE	SPECIES
Proliferative and Inflammatory Lymphadenopathies	
Infectious	
Bacterial	
Actinomyces spp.	D, C
Borrelia burgdorferi	D
Brucella canis	D
Corynebacterium spp.	C
Mycobacterium spp.	D, C
Nocardia spp.	D, C
Streptococci	D, C
Contagious streptococcal lymphadenopathy	C
Yersinia pestis	C
Bartonella spp.	D, C
Localized bacterial infection	D, C
Septicemia	D, C
Rickettsial	
Ehrlichiosis	D, C
Anaplasmosis	D, C
RMSF	D
Salmon poisoning	D
Fungal	
Aspergillosis	D, C
Blastomycosis	D, C
Coccidioidomycosis	D
Cryptococcosis	D, C
Histoplasmosis	D, C
Phaeohyphomycosis	D, C
Phycomycosis	D, C
Sporotrichosis	D, C
Pneumocystis spp.	D
Other mycoses	D, C
Algal	
Protothecosis	D, C
Parasitic	
Babesiosis	D
Cytauxzoonosis	C
Demodicosis	D, C
Hepatozoonosis	D
Leishmaniasis	D
Neospora caninum	D
Toxoplasmosis	D, C
Trypanosomiasis	D
Viral	
Canine viral enteritides	D
Feline immunodeficiency virus	C
Feline infectious peritonitis	C
Feline leukemia virus	C
Infectious canine hepatitis	D
Noninfectious	
Dermatopathic lymphadenopathy	D, C
Drug reactions	D, C
Idiopathic	D, C
Distinctive peripheral lymph node hyperplasia	C
Plexiform vascularization of lymph nodes	C
Immune-mediated disorders	
Systemic lupus erythematosus	D, C
Rheumatoid arthritis	D
Immune-mediated polyarthritides	D, C
"Puppy strangles" (juvenile cellulitis)	D
Other immune-mediated disorders	D, C
Localized inflammation	D, C
Postvaccinal	D, C
Infiltrative Lymphadenopathies	
Neoplastic	
Primary hemolymphatic neoplasms	
Leukemias	D, C
Lymphomas	D, C
Malignant histiocytosis	D, C
Multiple myeloma	D, C
Systemic mast cell disease	D, C
Metastatic neoplasms	
Carcinoma	D, C
Malignant melanoma	D
Mast cell tumor	D, C
Sarcoma	D, C
Nonneoplastic	
Eosinophilic granuloma complex	C, D
Mast cell infiltration (nonneoplastic)	D, C

C, Cats; *D,* dogs; *RMSF,* Rocky Mountain spotted fever.
Modified from Hammer AS, et al.: Lymphadenopathy. In Fenner NR, editor: *Quick reference to veterinary medicine,* ed 2, Philadelphia, 1991, JB Lippincott.

When evaluating dogs and cats with lymphadenopathy or diffuse splenomegaly, the clinician can glean important information from the history. Certain diseases are prevalent in certain breeds, such as mycobacterial infections in Basset Hounds and Schnauzers; histiocytic neoplasms in Bernese Mountain dogs, Rottweilers, Labradors, Golden Retrievers, and Flat Coated retrievers; others have a defined geographic or seasonal prevalence, including leishmaniasis in the Mediterranean region of Europe, salmon poisoning in the Pacific Northwest, and some systemic mycoses, such as histoplasmosis in the Ohio River Valley. Systemic (constitutional) clinical signs are usually present in dogs with systemic

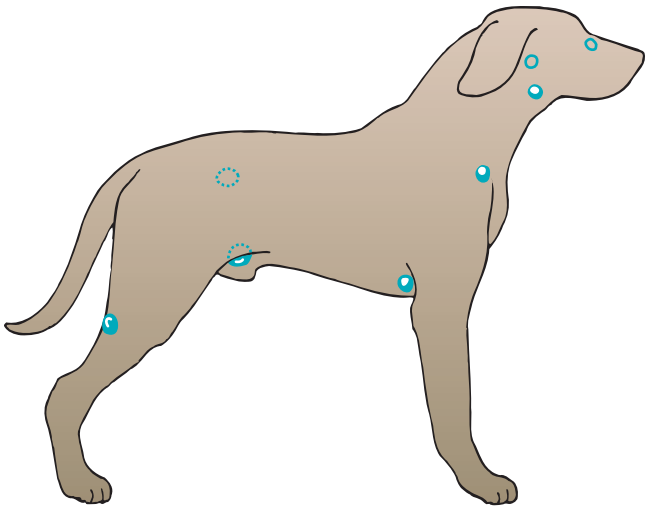


FIG 88.2
Anatomic distribution of clinically relevant lymph nodes in a dog. The nodes are in the same general location in cats. The lymph nodes depicted by the *darkened circles* include, from cranial to caudal, the mandibular, prescapular, axillary, superficial inguinal, and popliteal lymph nodes. The lymph nodes depicted by the *open circles* include, from cranial to caudal, the facial, retropharyngeal, and iliac or sublumbar lymph nodes. (From Couto CG: Diseases of the lymph nodes and spleen. In Ettinger SJ, editor: *Textbook of veterinary internal medicine—diseases of the dog and cat,* ed 3, Philadelphia, 1989, WB Saunders.)

TABLE 88.2

Correlation Between Clinical Presentation and Cause in Dogs and Cats With Lymphadenopathy*

	SOLITARY OR REGIONAL	
GENERALIZED	**SUPERFICIAL**	**INTRACAVITARY**
Lymphoma	Abscess	Histoplasmosis (A, T)
Histoplasmosis	Periodontal disease	Blastomycosis (T)
Blastomycosis	Paronychia	Apocrine gland adenocarcinoma (A)
Postvaccinal	Deep pyoderma	Primary lung tumors (T)
Anaplasmosis	Demodicosis	Lymphoma (A, T)
Ehrlichiosis	Mast cell tumor	Mast cell tumor (A)
Leukemias	Malignant melanoma	Prostatic adenocarcinoma (A)
Malignant histiocytosis	Eosinophilic granuloma complex	Malignant histiocytosis (A, T)
Systemic lupus erythematosus	Lymphoma	Lymphomatoid granulomatosis (T)
Other		Tuberculosis (A, T)

A, Abdomen; *T,* thorax.
*In the midwestern United States (in relative order of importance).

mycoses, salmon poisoning, Rocky Mountain spotted fever (RMSF), anaplasmosis, ehrlichiosis, bartonellosis, leishmaniasis, or acute leukemia, and in some dogs and cats with immune-mediated diseases. Clinical signs are rare or can be absent in dogs and cats with chronic lymphocytic leukemia, anaplasmosis, most lymphomas, and reactive lymphadenopathies occurring after vaccination; cats with idiopathic reactive lymphadenopathy (see later) are usually asymptomatic.

Clinical signs in dogs and cats with lymphadenopathy or splenomegaly are vague and nonspecific and are usually related to the primary disease rather than the organ enlargement. They include anorexia, weight loss, weakness, abdominal distention, vomiting, diarrhea, polyuria-polydipsia (PU-PD; in dogs with lymphoma-associated hypercalcemia), or a combination of these. Enlarged lymph nodes can occasionally result in obstructive or compressive signs (e.g., dysphagia resulting from enlarged retropharyngeal nodes, coughing resulting from enlarged tracheobronchial nodes; see Fig. 79.7).

The distribution of the lymphadenopathy is also of diagnostic relevance. In patients with solitary or regional lymphadenopathy, the area drained by the lymph node(s) should be examined meticulously because the primary lesion is generally found there. As discussed earlier, Suami et al. recently published an excellent review of lymphatic territories. Most cases of superficial solitary or regional lymphadenopathy in dogs and cats result from localized inflammatory or infectious processes or from metastatic neoplasia (less commonly), whereas most cases of deep (e.g., intraabdominal, intrathoracic) solitary or regional lymphadenopathy result from metastatic neoplasia or systemic infectious diseases (e.g., systemic mycoses). Recently, cyst-like lesions of intraabdominal lymph nodes in patients with both nonneoplastic (70%) or neoplastic (30%) lesions were described (Liotta et al., 2017). Idiopathic mesenteric purulent lymphadenopathy was also recently described in dogs (Salavati Schmitz, 2016). Most cases of generalized lymphadenopathy are caused by systemic fungal or bacterial infections (dogs), nonspecific hyperplasia (mainly cats), or lymphoma (dogs; Table 88.2).

The characteristics of the lymph nodes on palpation are also important. In most dogs and cats with lymphadenopathy, regardless of the distribution, the lymph nodes are firm, irregular, and painless; their temperature is normal to the touch (cold lymphadenopathies); and they do not adhere to the surrounding structures. However, in patients with lymphadenitis, the lymph nodes may be softer than usual and more tender and warmer than normal; they may also adhere to surrounding structures (fixed lymphadenopathy). Fixed lymphadenopathies may also be the presenting feature in dogs and cats with metastatic lesions, lymphomas with extracapsular invasion, or certain infectious diseases (e.g., mycobacteriosis).

The size of the affected lymph nodes is also important. Massive lymphadenopathy—lymph node size 5 to 10 times normal—occurs almost exclusively in dogs with lymphoma, malignant histiocytosis (Fig. 88.3), or infectious lymphadenitis (lymph node abscess formation; hilar lymphadenopathy in dogs with histoplasmosis). In cats, the

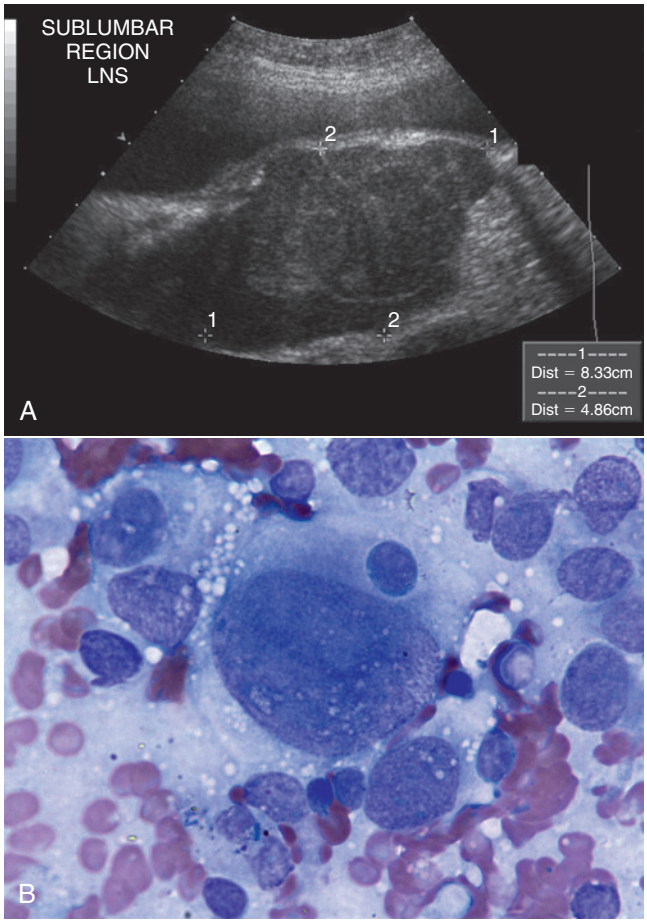


FIG 88.3
(A) Ultrasonographic image of massive sublumbar (iliac) lymphadenopathy in a Great Pyrenees with malignant histiocytosis. **(B)** Cytologic evaluation revealed a pleomorphic population of round cells exhibiting cytophagia (Diff-Quik stain; ×1000).

syndrome of distinctive lymph node hyperplasia usually results in massive lymphadenopathy (Fig. 88.4). Rarely metastatic lymph nodes exhibit this degree of enlargement; the main example of massive metastatic lymphadenopathy is the apocrine gland adenocarcinoma metastases to the sublumbar lymph nodes. Recognizing that lymph nodes of normal size may contain metastatic neoplasia is important; this is relatively common in dogs with mast cell tumors, where a node that is normal on palpation may contain large numbers of metastatic mast cells. Dogs with salmon poisoning may also have marked generalized lymphadenopathy as the presenting feature, preceded by or in conjunction with bloody diarrhea. Mild to moderate lymph node enlargement (two to four times the normal size) occurs mostly in a variety of reactive and inflammatory lymphadenopathies (e.g., ehrlichiosis, bartonellosis, anaplasmosis, RMSF, systemic mycoses, leishmaniasis, immune-mediated diseases, skin diseases) and in leukemias.

As noted, the area draining the enlarged lymph node(s) should always be thoroughly examined (Suami et al., 2013),



FIG 88.4
Massive mandibular lymphadenopathy in a young feline leukemia virus–positive cat with idiopathic reactive lymphadenopathy. The lymphadenopathy resolved with supportive care.

paying particular attention to the skin, subcutis, and bone. In dogs and cats with generalized lymphadenopathy, evaluation of other hemolymphatic organs, such as the spleen, liver, and bone marrow is important.

SPLENOMEGALY

Etiology and Pathogenesis

Splenomegaly is defined as a localized or diffuse splenic enlargement. The term *localized splenomegaly* (or splenic mass) refers to a localized palpable enlargement of the spleen. Diffuse splenic enlargement occurs as a consequence of the proliferation of normal cells or infiltration with normal or abnormal cells. Rarely diffuse splenic enlargement can occur as a result of vascular changes (e.g., hyperemia, congestion). Focal splenomegaly is more common in dogs, and diffuse splenomegaly is more common in cats.

Diffuse splenomegaly is classified into four major categories in terms of its pathogenesis—lymphoreticular hyperplasia, inflammatory (e.g., splenitis), infiltration with abnormal cells (e.g., lymphoma) or substances (e.g., amyloidosis), and congestion (Table 88.3).

The spleen commonly reacts to bloodborne antigens and RBC destruction with hyperplasia of the MP-AP and lymphoid components. This hyperplasia has been referred to as work hypertrophy because it usually results in varying degrees of splenic enlargement. Hyperplastic splenomegaly is relatively common in dogs with ehrlichiosis, leishmaniasis, bacterial endocarditis, systemic lupus erythematosus, or chronic bacteremic disorders such as diskospondylitis and brucellosis, and in cats with mycoplasmosis or immune-mediated cytopenias.

RBC phagocytosis by the splenic MP system in humans can lead to hyperplasia of this cell population, resulting in

TABLE 88.3

Pathogenetic Classification of Splenomegaly in Dogs and Cats

TYPE	SPECIES
Inflammatory and Infectious Splenomegaly	
Suppurative splenitis	
Penetrating abdominal wounds	D, C
Migrating foreign bodies	D, C
Bacterial endocarditis	D, C
Septicemia	D
Splenic torsion	D
Toxoplasmosis	D, C
Infectious canine hepatitis (acute)	D
Mycobacteriosis (i.e., tuberculosis)	D, C
Necrotizing splenitis	
Splenic torsion	D
Splenic neoplasia	D
Salmonellosis	D, C
Eosinophilic splenitis	
Eosinophilic gastroenteritis	D, C
Hypereosinophilic syndrome	C, D
Lymphoplasmacytic splenitis	
Infectious canine hepatitis (chronic)	D
Ehrlichiosis/Anaplasmosis (chronic)	D, C
Pyometra	D, C
Brucellosis	D
Hemobartonellosis	D, C
Bartonellosis	D, C
Leishmaniasis	D, C
Granulomatous splenitis	
Histoplasmosis	D, C
Mycobacteriosis (i.e., tuberculosis)	D, C
Pyogranulomatous splenitis	
Blastomycosis	D, C
Sporotrichosis	D
Feline infectious peritonitis	C
Mycobacteriosis (i.e., tuberculosis)	D, C
Bartonellosis	D, C
Hyperplastic Splenomegaly	
Bacterial endocarditis	D
Brucellosis	D
Discospondylitis	D
Systemic lupus erythematosus	D, C
Hemolytic disorders (see text)	D, C
Congestive Splenomegaly	
Pharmacologic (see text)	D, C
Portal hypertension	D, C
Splenic torsion	D
Infiltrative Splenomegaly	
Neoplastic	
Acute and chronic leukemias	D, C
Systemic mastocytosis	D, C
Malignant histiocytosis	D, C
Lymphoma	D, C
Multiple myeloma	D, C
Metastatic neoplasia	D, C (rare)
Nonneoplastic	
EMH	D, C
Hypereosinophilic syndrome	C, D
Amyloidosis	D

C, Cats; *D,* dogs; *EMH,* extramedullary hematopoiesis.
Modified from Couto CG: Diseases of the lymph nodes and the spleen. In Ettinger S, editor: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, WB Saunders.

splenomegaly. The same seems to occur in dogs and cats with certain hemolytic disorders, including immune-mediated hemolytic anemia, drug-induced hemolysis, pyruvate kinase deficiency anemia, phosphofructokinase deficiency anemia, familial nonspherocytic hemolysis in Poodles and Beagles, Heinz body hemolysis, and mycoplasmosis. Rarely an area of focal splenomegaly is diagnosed histopathologically as hyperplasia (i.e., nodular hyperplasia) after performing a splenectomy.

As in the lymph nodes, if polymorphonuclear leukocytes or macrophages predominate in the cellular infiltrate, the term *splenitis* is used. The infiltrates are also classified according to the cell type as suppurative, granulomatous, pyogranulomatous, or eosinophilic. Splenic abscesses can also form, often in association with a perforation by a foreign body. Necrotizing splenitis caused by gas-forming anaerobes can occur in dogs in association with splenic torsion or neoplasia. Lymphoplasmacytic splenitis cannot be distinguished cytologically from splenic hyperplasia. The causative agents for different types of splenitis are listed in Table 88.3. In a recent study of 33 dogs with splenitis in Italy (Ferri et al., 2016), most dogs had purulent (suppurative; 27%) or pyogranulomatous (24%) splenitis. In most dogs with purulent splenitis, bacteria could be identified when

using Gram stain. Most dogs with pyogranulomatous splenitis had leishmaniasis.

Infiltrative splenomegalies are also common in small animals. Marked splenomegaly is a common finding in dogs and cats with acute and chronic leukemias, although it is more common in dogs; in dogs and cats with systemic mastocytosis; and in dogs with malignant histiocytosis. In addition, diffuse neoplastic infiltration of the spleen commonly occurs in dogs and cats with lymphoma or multiple myeloma. Diffuse splenomegaly may be the only physical examination and imaging finding in cats with monoclonal gammopathies; fine-needle aspiration (FNA) of the spleen reveals diffuse infiltration with plasma cells and is a common presentation for myeloma in this species. Metastatic splenic neoplasms usually result in focal splenomegaly but are rare.

Nonneoplastic causes of infiltrative splenomegaly are uncommon, with the exception of extramedullary hematopoiesis (EMH), which is more common in dogs than in cats. Because the spleen retains its fetal hematopoietic potential during adult life, a variety of stimuli—such as anemia, severe splenic or extrasplenic inflammation, neoplastic infiltration of the spleen, bone marrow hypoplasia, and splenic congestion—may cause the spleen to resume its fetal hematopoietic function and produce RBCs, white blood cells, and platelets. Finding EMH by percutaneous FNA of the spleen is the norm in dogs and cats with diffuse or focal splenomegaly; the presence of hematopoietic blasts may lead to an erroneous diagnosis of lymphoma in some of these patients. I have also observed splenic EMH in dogs with pyometra, immune-mediated hemolysis, immune-mediated thrombocytopenia, several infectious diseases, and a variety of malignant neoplasms as well as in seemingly healthy dogs. Another disorder that commonly results in prominent infiltrative splenomegaly is the hypereosinophilic syndrome of cats (and some dogs, such as Rottweilers), a disease characterized by peripheral blood eosinophilia, bone marrow hyperplasia of the eosinophil precursors, and multiple-organ infiltration by mature eosinophils (see Chapter 85).

The canine and feline spleens have a great capacity to store blood, and under normal circumstances they store between 10% and 20% of the total blood volume. However, tranquilizers and barbiturates can cause splenic blood pooling because of relaxation of the smooth muscle of the splenic capsule, leading to congestive splenomegaly. The blood that has pooled in an enlarged spleen can account for up to 30% of the total blood volume. Anesthetics rarely used these days, such as halothane, also may result in marked decreases of 10% to 20% in the packed cell volume and plasma protein concentration in dogs as a result of the same mechanism.

Portal hypertension can lead to congestive splenomegaly; however, such splenic congestion does not appear to be as common in dogs and cats as it is in humans. Causes of portal hypertension that may lead to splenomegaly in small animals include right-sided congestive heart failure, obstruction of the caudal vena cava as a result of congenital malformations, neoplasia, heartworm disease, and intrahepatic obstruction of the vena cava. Splenic vein thrombosis is a common incidental finding in dogs; it is usually associated with the administration of corticosteroids and is typically of no clinical relevance. Ultrasonographic evaluation in these patients usually reveals markedly distended splenic, portal, or hepatic veins or thrombi.

A relatively common cause of congestive splenomegaly in dogs is splenic torsion (DeGroot et al., 2016). Torsion of the spleen, by itself or in association with gastric dilation-volvulus syndrome, commonly results in marked splenomegaly caused by congestion. Splenic torsion can occur independently of gastric dilation-volvulus syndrome. Most affected dogs are large, deep-chested breeds, primarily Great Danes, Chows, and German Shepherd Dogs. Clinical signs can be acute or chronic. Dogs with acute splenic torsion are usually evaluated because of acute abdominal pain and distention, vomiting, depression, and anorexia. Dogs with chronic splenic torsion display a wide variety of clinical signs, including anorexia, weight loss, intermittent vomiting, abdominal distention, PU-PD, hemoglobinuria, and abdominal pain. Physical examination usually reveals marked splenomegaly, and radiographs typically reveal a C-shaped spleen. Ultrasonography of the abdomen in these patients may show greatly distended splenic veins. Hematologic abnormalities usually include regenerative anemia, leukocytosis with a regenerative left shift, and leukoerythroblastosis. Disseminated intravascular coagulation appears to be a common complication in dogs with torsion of the spleen. A high percentage of dogs with splenic torsion have hemoglobinuria, possibly as a consequence of intravascular or intrasplenic hemolysis. Dogs with splenic torsion and hemoglobinuria seen at our clinic occasionally have a positive direct Coombs test result. The treatment of choice for dogs with splenic torsion is splenectomy.

Splenic masses are more common than diffuse splenomegaly in dogs, whereas the opposite is true for cats. Most splenectomies in dogs are done to remove splenic masses. Because splenic masses in cats are extremely uncommon, the following discussion pertains primarily to localized splenomegaly in dogs.

Most oncologists use the rule of two thirds—two thirds of the splenic masses are tumors, two thirds of the tumors are malignant, and two thirds of the malignant tumors are hemangiosarcomas (HSAs). However, the prevalence of different histologic types of splenic masses may vary geographically.

Splenic masses can be classified according to their histopathologic features and biologic behavior as neoplastic or nonneoplastic. Neoplastic splenic masses can be benign or malignant and mainly include hemangiomas (HAs) and HSAs, although the former are less common than the latter. Other neoplastic splenic masses found occasionally are leiomyosarcomas, fibrosarcomas, leiomyomas, myelolipomas, metastatic carcinomas or sarcomas, malignant histiocytic tumors, and occasionally lymphomas. As a general rule, the larger the splenic mass, the less likely it is to be a malignant tumor (Mallinckrodt and Gottfried, 2011). Nonneoplastic splenic masses include primarily hematomas,

lymphoreticular hyperplasia, and abscesses, although splenic infarcts are occasionally described as splenic masses in dogs. As noted, a splenic mass is occasionally diagnosed as a hyperplastic nodule (or nodular hyperplasia) on histopathology after splenectomy. Almost 2 decades ago, Spangler and Kass (1998) proposed using the term *splenic fibrohistiocytic nodule* (FHN) to describe a continuum of focal lesions composed of macrophages, spindle cells, and lymphoid cells. They graded them into well, moderately, and poorly differentiated, and proposed that the grading had prognostic value.

However, recent studies have challenged this concept, and it is now believed that the splenic FHN is a catchall term for a variety of disorders in dogs. In a review of 31 splenic FHNs using histology and immunohistochemistry (Moore et al., 2012), 13 (42%) were reclassified as nodular hyperplasia, 4 (13%) as lymphoma, 8 (26%) as stromal sarcomas, and 6 (19%) as histiocytic sarcomas. Reclassifying these lesions has allowed for a more accurate prognosis.

However, other authors disagree with this approach. Recently, Sabatini et al. conducted a histopathologic, immunophenotyping, and molecular study of splenic nodular lesion in dogs and found that 29% were diagnosed as lymphoid nodular hyperplasia (LNH), 34% as complex nodular hyperplasia (CNH), 31% as marginal zone lymphoma, and 6% as mantle cell lymphoma (Sabatini et al., 2018). LNH and CNH are lesions traditionally classified as FHN. Regardless of the histologic subtype, the median survival time after splenectomy in this study was 1087 days.

HSAs are malignant vascular tumors of the spleen; they are extremely common in dogs, constituting the most common primary neoplasm in surgically collected splenic tissues (i.e., splenectomy). These neoplasms are extremely rare in cats. For a more detailed discussion, see Chapter 81.

Clinical Features

History taking and physical examination in dogs with splenomegaly are similar to those in dogs with lymphadenopathy. The clinical signs in dogs with splenomegaly are vague and nonspecific; they include anorexia, weight loss, weakness, abdominal distention, vomiting, diarrhea, PU-PD, or a combination of these. PU-PD is relatively common in dogs with marked splenomegaly, particularly in those with splenic torsion. Although the pathogenesis of the PU-PD is unclear, psychogenic polydipsia provoked by abdominal pain and distention of the splenic stretch receptors may be a contributory mechanism. Splenectomy in these dogs usually results in prompt resolution of the signs. Other signs associated with splenomegaly result from the hematologic consequences of the splenic enlargement and include spontaneous bleeding caused by thrombocytopenia, pallor caused by anemia, and fever caused by neutropenia or the primary disorder.

During a routine physical examination in pups and cats, the normal spleen is easily palpated as a flat structure oriented dorsoventrally in the left anterior abdominal quadrant. In some deep-chested dogs (e.g., Irish Setters, German Shepherd Dogs), the normal spleen is also easily palpated during routine examination in the ventral midabdomen or left anterior quadrant. This is also the case in Miniature Schnauzers and in some Cocker Spaniels. The fullness of the stomach determines to what extent a normal spleen is palpable in other breeds of dogs. It is easily palpated postprandially because its contour conforms to the greater curvature of the stomach so that it lies parallel to the last rib. However, not all enlarged spleens are palpable, and not every palpable spleen is abnormal. The characteristics of the spleen on palpation vary. In dogs an enlarged spleen can be smooth or irregular ("lumpy-bumpy"). In most cats with marked splenomegaly, the surface of the organ is smooth; a diffusely enlarged, lumpy spleen in a cat suggests systemic mast cell disease. As noted, animals with hematologic abnormalities secondary to splenomegaly may also have pallor, petechiae, or ecchymoses.

APPROACH TO PATIENTS WITH LYMPHADENOPATHY OR SPLENOMEGALY

Clinicopathologic Features

A complete blood count (CBC), serum biochemistry profile, and urinalysis should be obtained, particularly in dogs and cats with generalized or regional lymphadenopathies and those with diffuse splenomegaly. Changes in the CBC may indicate a systemic inflammatory process (e.g., leukocytosis with neutrophilia, left shift, monocytosis) or hemolymphatic neoplasia (e.g., circulating blasts in acute leukemia or lymphoma, marked lymphocytosis suggestive of chronic lymphocytic leukemia or ehrlichiosis). Occasionally the causative agent may be identified during examination of a blood smear (e.g., histoplasmosis, mycoplasmosis, trypanosomiasis, babesiosis). The polymerase chain reaction (PCR) assay for clonality and immunophenotyping with flow cytometry is commonly used in our clinic in patients with lymphadenopathy or splenomegaly and circulating abnormal cells or lymphocytosis. PCR for infectious agents should always be done in patients with splenitis or lymphoreticular hyperplasia.

The spleen exerts a marked influence on the CBC, resulting in two patterns of hematologic changes in dogs and cats with splenomegaly: hypersplenism and hyposplenism, or asplenia. Hypersplenism results from increased MP activity, but it is rare and characterized by cytopenias in the presence of a hypercellular bone marrow; these changes resolve after splenectomy. Hyposplenism is more common and results in hematologic changes similar to those seen in splenectomized animals, such as thrombocytosis, schistocytosis, acanthocytosis, Howell-Jolly bodies, and increased numbers of reticulocytes and nucleated RBCs. We documented the release of reticulocytes stored in the spleen in response to catecholamines in racing Greyhounds.

Anemia in dogs and cats with lymphadenopathy or splenomegaly can occur as a result of the several mechanisms already discussed. In brief, anemia of chronic disease can be

seen in inflammatory, infectious, or neoplastic disorders; hemolytic anemia is usually present in patients with hemoparasitic lymphadenopathies or splenomegaly and in some dogs with malignant histiocytosis or hemophagocytic syndrome. Severe nonregenerative anemia may be seen in dogs with chronic ehrlichiosis, in cats with feline leukemia virus–related disorders or feline immunodeficiency virus–related disorders, and in dogs and cats with primary bone marrow neoplasms (e.g., leukemias, multiple myeloma).

Thrombocytopenia is a common finding in patients with ehrlichiosis, RMSF, anaplasmosis, sepsis, lymphomas, leukemias, multiple myeloma, systemic mastocytosis, and some immune-mediated disorders. Pancytopenia is common in dogs with chronic ehrlichiosis or systemic immune-mediated disorders, in dogs and cats with lymphoma or leukemia, and in cats with disorders associated with retroviral infections.

Two major serum biochemical abnormalities are of diagnostic value in dogs and cats with lymphadenopathy or diffuse splenomegaly: hypercalcemia and hyperglobulinemia. Hypercalcemia is a paraneoplastic syndrome that occurs in approximately 10% to 20% of dogs with lymphoma and multiple myeloma, although it may also occur in dogs with blastomycosis or other chronic inflammatory disorders. It is extremely rare in cats with these diseases. Monoclonal hyperglobulinemia commonly occurs in dogs and cats with multiple myeloma and occasionally in dogs with lymphoma, ehrlichiosis, or leishmaniasis (see Chapter 89). Polyclonal hyperglobulinemia commonly occurs in dogs and cats with systemic mycoses, in cats with feline infectious peritonitis, and in dogs with ehrlichiosis, anaplasmosis, or leishmaniasis (see Chapter 89).

Serologic and microbiologic studies should always be conducted in dogs and cats with suspected infectious lymphadenopathy-splenomegaly. Serologic tests or PCR assay for canine ehrlichiosis, RMSF, brucellosis, and systemic mycoses may help diagnose regional or systemic lymphadenopathies. Lymph node specimens for bacterial and fungal cultures should also be obtained if necessary.

Imaging

Radiographic abnormalities in dogs with lymphadenopathy can be related to the primary disorder or can reflect the location and degree of lymphadenopathy. In general, plain radiographs or computed tomography (CT) scans are helpful in dogs and cats with solitary lymphadenopathy to search for primary bone inflammation or neoplasia, in those with generalized peripheral (superficial) lymphadenopathy to detect intrathoracic or intraabdominal lymph node enlargement (see Fig. 79.7), and in those with deep regional lymphadenopathy involving the thoracic cavity to determine the distribution and size of the affected nodes and changes in the pulmonary parenchyma and pleural space.

The spleen is normally well visualized on plain abdominal radiographs, but its appearance can vary widely. On dorsoventral or ventrodorsal views, the spleen is seen between the gastric fundus and left kidney. The size and location of the spleen are more variable on lateral radiographs than on ventrodorsal or dorsoventral projections. In some breeds, such as Greyhounds, the spleen appears to be large on plain radiographs and ultrasonograms. On plain radiographs, large splenic masses usually appear in the caudal abdomen or the midabdomen. Tranquilization or anesthesia usually results in a diffuse congestive splenomegaly, making radiographic interpretation of splenic size extremely difficult. CT is a useful diagnostic tool for dogs with focal or diffuse splenomegaly.

Ultrasonography is the noninvasive procedure of choice to evaluate intraabdominal lymphadenopathy and splenomegaly because it can accurately depict the size of enlarged lymph nodes and the spleen (Figs. 88.5 and 88.6) so that the patient's response to therapy can be monitored. In addition, ultrasound-guided FNA or biopsies can be performed with minimal complications. Abdominal ultrasonography can reveal diffuse splenomegaly, splenic masses, splenic congestion, hepatic nodules, or other changes; in addition, color flow Doppler allows for the evaluation of splenic blood flow (Huynh and Berry, 2017). A major issue a clinician frequently must deal with is the incidental splenic nodule in an older dog; these lesions are common and usually clinically irrelevant but tend to cloud the clinical picture in a patient with intraabdominal neoplasia. If possible, splenic nodules should be aspirated and evaluated cytologically; occasionally, immunophenotyping or PARR are needed to distinguish between lymphoma and regenerative nodules. Of note, however, is that the presence of hepatic nodules in a dog with a splenic mass does not constitute a valid reason for an owner to decline treatment or request euthanasia because regenerative liver nodules are indistinguishable from metastatic lesions. Moreover, hypoechoic splenic nodules are frequently found in normal dogs. Computerized tomography cannot readily distinguish between benign and malignant masses in dogs (Jones et al., 2016).

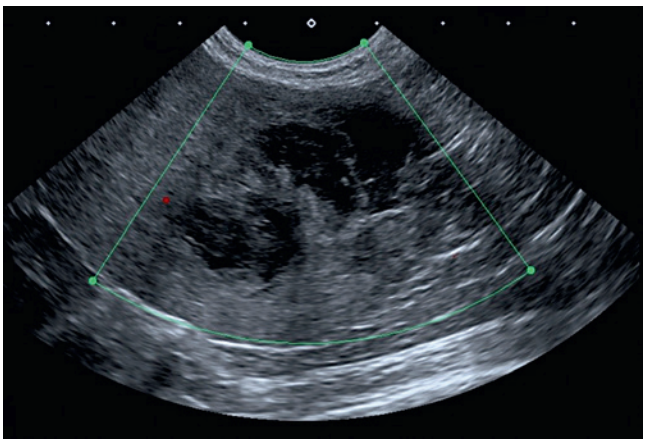


FIG 88.5
Ultrasonographic appearance of a complex rapidly growing splenic mass in a 12-year-old female spayed Greyhound. Note the lack of blood flow on color flow Doppler. Splenectomy revealed a hyperplastic lymphoid nodule with hematoma formation.

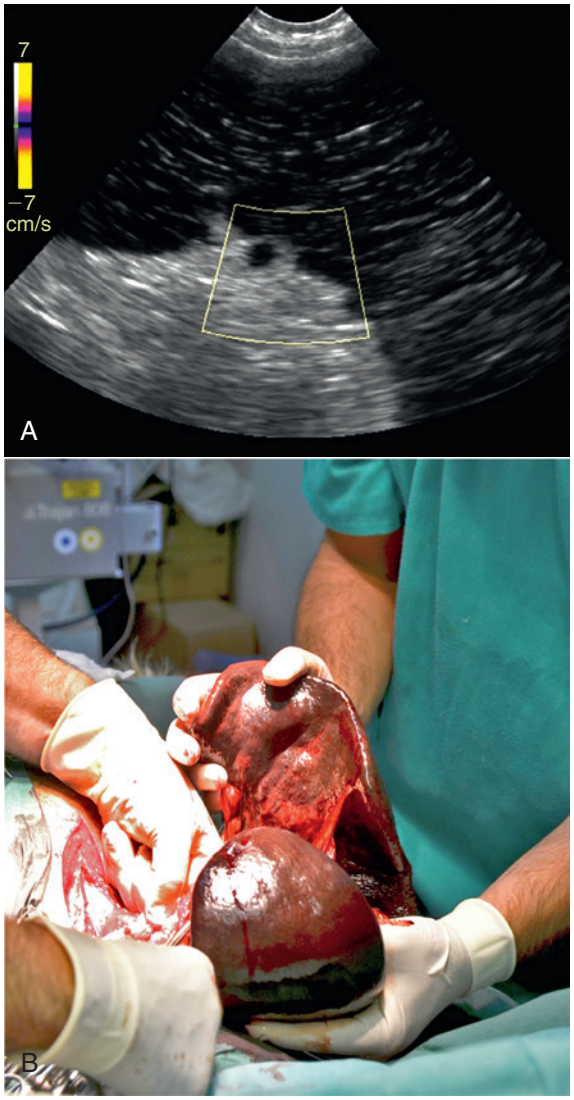


FIG 88.6
(A) Ultrasonographic appearance of a splenic torsion in a Chow Chow. Note the hypoechoic echotexture and lack of blood flow on color Doppler. **(B)** Surgical procedure in the same dog. Notice the markedly enlarged, deep purple torsed spleen. (**A** courtesy Dr. Pablo Gómez Ochoa, Vetoclok, Zaragoza, Spain.)

Radionuclide imaging of the spleen (and, less commonly, of lymph nodes) using technetium-99m–labeled sulfur colloid has become an accepted method of splenic imaging in humans and small animals. However, this technique only evaluates the spleen's ability to clear particulate matter and rarely provides a morphologic diagnosis.

Additional Diagnostic Tests

Evaluation of bone marrow aspirates or core biopsy specimens may be beneficial in dogs and cats with generalized lymphadenopathy or splenomegaly caused by hemolymphatic neoplasia or systemic infectious diseases. For example, acute or chronic leukemia in dogs may be difficult to diagnose on the basis of lymph node cytologic findings alone because the diagnosis is usually that of lymphoma, with the presence of well-differentiated or poorly differentiated lymphoid cells. In those cases, the combination of hematologic and bone marrow findings is usually diagnostic. Bone marrow evaluation should always be done before splenectomy in patients with cytopenias because the spleen may assume the primary hematopoietic function in dogs and cats with primary bone marrow disorders, such as hypoplasia or aplasia. Splenectomy in these animals could remove the sole source of circulating blood cells, leading to death.

Cytologic evaluation of lymph node and splenic aspirates provides the clinician with a wealth of information and often constitutes the definitive diagnostic procedure in animals with lymphadenopathy or diffuse splenomegaly. In my experience, cytologic evaluation of appropriately collected specimens yields diagnostic findings in approximately 80% to 90% of dogs and 70% to 75% of cats with lymphadenopathy and in approximately 80% of dogs and cats with diffuse splenomegaly.

Although superficial lymph nodes can be aspirated with minimal difficulty, the successful aspiration of intrathoracic or intraabdominal lymph nodes or spleen requires some expertise and occasionally must be done under the guidance of imaging techniques (e.g., ultrasonography, CT; see Chapter 74). To perform FNA of a superficial node, the area does not have to be surgically prepared. However, the aspiration of intrathoracic and intraabdominal structures (e.g., spleen) requires surgical preparation of the area and adequate restraint of the animal. Certain intraabdominal lymph nodes (e.g., markedly enlarged mesenteric or iliac nodes) are easily aspirated transabdominally by using manual isolation of the mass. Splenic aspirates are obtained with the animal in right lateral or dorsal recumbency, with manual restraint or mild sedation. Transabdominal splenic FNA in dogs or cats chemically restrained with phenothiazine tranquilizers or barbiturates usually yields blood-diluted specimens as a result of splenic congestion; the same occurs when a syringe is attached to the needle and suction is applied (LeBlanc et al., 2009).

Splenic biopsies for histopathology can also be obtained percutaneously using ultrasonographic guidance and a Tru-Cut–style needle. In a recent study, percutaneous FNA samples were compared with needle core biopsies (NCBs). Forty-one dogs with splenic lesions were studied prospectively (Watson et al., 2010). Safety was assessed in 38 dogs, and no complications were encountered. Clinical and anatomic pathologists reviewed each FNA and NCB sample, respectively, without knowledge of the other's results. Diagnoses were categorized as neoplastic, benign, inflammatory, normal, or nondiagnostic. The level of agreement between sampling methods was categorized as complete, partial, disagreement, or not available. Test correlation was performed in 40 dogs. Nondiagnostic results occurred in 5 of 40 NCB (12.5%) and no FNA samples. Neoplasia was diagnosed in 17 of 40 dogs (42.5%), benign changes in 20 of 40 dogs (50%), inflammatory disorders in 0 of 40 dogs, and normal in 2 of 40 dogs (5%). One of the 40 dogs (2.5%) had a

diagnosis that was equivocal for neoplasia on both tests and therefore was not categorized. Of the 35 dogs that had diagnostic samples, cytopathologic and histopathologic diagnoses agreed completely in 18 of 35 dogs (51.4%) and partially in 3 of 35 dogs (8.6%) and were in disagreement in 14 of 35 dogs (40.0%). Pathologists collaboratively reviewed diagnoses that were in disagreement or partial agreement and altered their individual diagnoses in 6 of 17 dogs (35.3%) to be within partial or complete agreement, respectively. Percutaneous FNA and NCB can be performed safely in dogs with sonographic splenic changes. Results suggest that adding NCB to FNA provides complementary information in dogs with suspected splenic neoplasia. This combined protocol may improve detection of splenic neoplasia and provide neoplastic subclassification.

In a patient with generalized lymphadenopathy, the clinician must decide which lymph node to aspirate. Obviously aspiration of a node in which the tissue changes are representative of the ongoing disease is important. Therefore a specimen should not be obtained from the largest lymph node because the necrosis may preclude a definitive diagnosis. Because clinical and subclinical gingivitis is common in older dogs and cats, mandibular lymph nodes should not be routinely aspirated because they are usually reactive, and findings may obscure the primary diagnosis. The techniques of FNA are described in Chapter 74.

Several reviews of the cytologic evaluation of lymphoid tissues have appeared in the veterinary literature (see later, "Suggested Readings"). In brief, normal lymph nodes are composed primarily of small lymphocytes (80%-90% of all cells); a small number of macrophages, medium or large lymphocytes, plasma cells, and mast cells can also be found. Normal spleens are similar except that RBCs are in high concentration given this organ's vascularity. Reactive lymph nodes (Fig. 88.7) and hyperplastic spleens are characterized by variable numbers of lymphoid cells in different stages of development (small, medium, and large lymphocytes; plasma cells); hematopoietic precursors are common in dogs and cats with splenic hyperplasia. The cytologic features of lymphadenitis-splenitis vary with the causative agent and the type of reaction elicited. Causative agents can frequently be identified in cytologic specimens (see Fig. 74.2). Metastatic neoplasms have different cytologic features, depending on the degree of involvement and cell type. Carcinomas, adenocarcinomas, melanomas, and mast cell tumors are easily diagnosed on the basis of cytologic findings. However, the cytologic diagnosis of sarcomas may be difficult because the neoplastic cells that comprise this tumor do not exfoliate easily. Primary lymphoid neoplasms (lymphomas) are characterized by a monomorphic population of lymphoid cells, which are usually immature and show a fine chromatin pattern, one or more nucleoli, basophilic cytoplasm, and vacuolation (Fig. 88.8). For a more detailed description of cytologic changes, see Chapter 74.

When the cytologic examination of an enlarged lymph node or spleen does not yield a definitive diagnosis, excision of the affected node or incisional or even excisional splenic biopsy to obtain a specimen for histopathologic examination is indicated. Excision of the whole node is preferable; core biopsy specimens are difficult to interpret because the lymph node architecture is often poorly preserved. A percutaneous needle biopsy of the spleen can be done under ultrasonography; alternatively, a wedge of tissue can be obtained during a splenic biopsy or, if the surgeon deems it necessary, a splenectomy can be performed; recently, single-port laparoscopy-assisted splenectomy techniques have been described in dogs (Wright et al., 2016). Care should be taken in handling the tissues during surgical

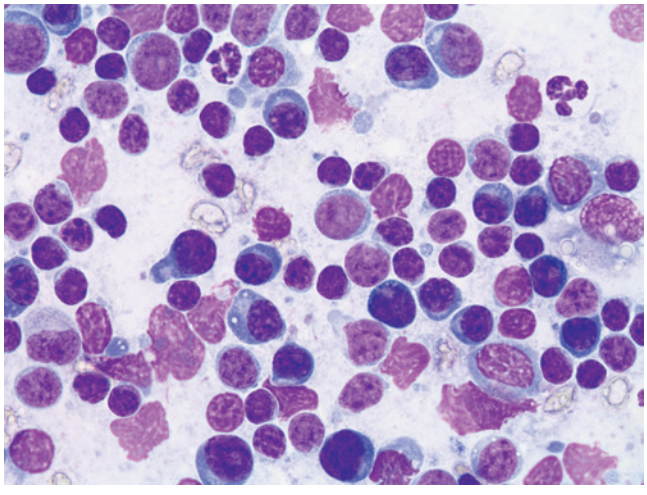


FIG 88.7
Cytologic features of a reactive lymph node in a dog. Note the heterogeneous cell population containing small, intermediate, and large lymphocytes and abundant plasma cells (Diff-Quik stain; ×1000).

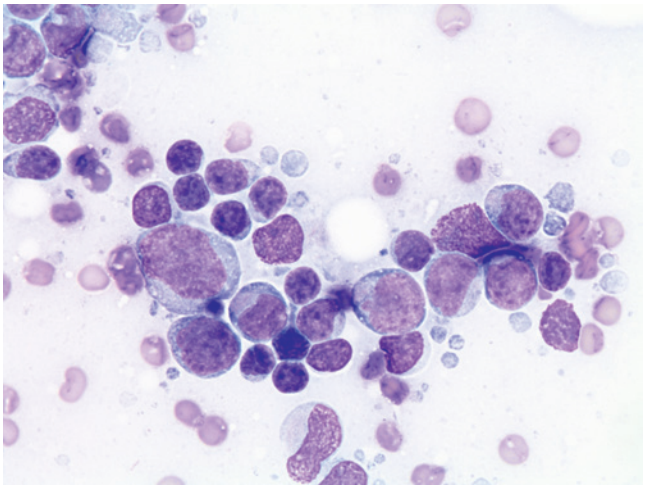


FIG 88.8
Cytologic features of a lymph node aspirate from a dog with massive generalized lymphadenopathy (lymphoma). Note a monomorphic population of large round cells with a lacy chromatin pattern (neoplastic cells) intermixed with small, darker, normal lymphocytes; lymphoglandular bodies are present (Diff-Quik stain; ×1000).

manipulation because trauma may induce considerable artifactual changes, which would preclude interpretation of the specimen. The popliteal lymph nodes are easily accessible and are the ones usually excised in dogs and cats with generalized lymphadenopathy.

Once a node is excised, it should be sectioned in half lengthwise, impression smears made for cytologic analysis, and the node fixed in 10% buffered formalin (one part of tissue to nine parts of fixative). The specimen is then ready to be sent to a laboratory for evaluation. Samples can also be saved for cytochemical or immunohistochemical evaluation, ultrastructural studies, microbiologic studies, and/or molecular evaluation, including a PCR assay for organisms or clonality. The same guidelines apply to the preparation of splenic specimens.

MANAGEMENT OF LYMPHADENOPATHY OR SPLENOMEGALY

As noted, no specific treatment exists for dogs or cats with local, regional, or generalized lymphadenopathy or diffuse splenomegaly. Treatment should be directed at the cause(s) of the lymphadenopathy or splenomegaly rather than at the enlarged lymph nodes or spleen. Exploratory celiotomies or laparoscopy provide considerable information regarding the gross morphologic characteristics of an enlarged spleen and adjacent organs and tissues. However, direct visualization of these structures may be misleading because differentiation of some benign splenic masses (e.g., hematoma, HA) from their malignant counterpart (e.g., HSA) on the basis of gross morphology alone may be impossible. As discussed earlier (see "Imaging"), in rare cases the surgeon may recommend to the owners that the animal be euthanized on the operating table because it has a splenic mass and nodules in the liver, only to find out that the hepatic nodules represent nodular hyperplasia or EMH and the primary mass was actually benign (e.g., HA or hematoma).

Splenectomy is indicated in the event of splenic torsion (see Fig. 88.6, *B*), splenic rupture, symptomatic splenomegaly, or most splenic masses. The value of splenectomy is questionable in dogs with immune-mediated blood disorders, dogs and cats with splenomegaly caused by lymphoma in which chemotherapy has not induced splenic remission, and dogs and cats with leukemias. Splenectomy is contraindicated in patients with bone marrow hypoplasia in which the spleen is the main site of hematopoiesis.

Although rare, a syndrome of postsplenectomy sepsis has been documented in approximately 3% of dogs that undergo this surgical procedure in our clinic. The syndrome is similar to its human counterpart. Most dogs with postsplenectomy sepsis evaluated at our clinic were undergoing immunosuppressive therapy at the time of surgery or had undergone splenectomy for a neoplasm. This sepsis is usually rapid in onset (hours to days), so prophylactic bactericidal antibiotic therapy is recommended postoperatively. All dogs with clinically recognized postsplenectomy sepsis at our clinic died within 12 hours of onset, despite aggressive treatment.

The clinician occasionally encounters a patient in which the enlarged lymph node mechanically compresses or occludes a viscus, airway, or vessel. This may result in marked clinical abnormalities, such as intractable coughing caused by tracheobronchial lymphadenopathy (see Fig. 79.7), colonic obstruction caused by iliac lymphadenopathy, or anterior vena cava syndrome caused by cranial vena cava and thoracic duct obstruction. Several treatment options are available for these situations. If the lymph node is surgically resectable, excision or drainage should be attempted. If the node is not surgically resectable or if surgery or anesthesia poses a high risk for the animal, one or more of the following can be used:

1. Irradiation can shrink a neoplastic lymph node and ameliorate the signs in animals with primary or metastatic neoplastic lesions. Antiinflammatory doses of corticosteroids can be used (0.5 mg/kg orally q24h) in animals with fungal lesions such as *Histoplasma*-induced tracheobronchial lymphadenopathy.
2. Intralesional injections of corticosteroids (prednisolone, 50-60 mg/m^2) can be successful in dogs and cats with solitary lymphomas or metastatic mast cell tumors if irradiation is not feasible.
3. Systemic antibiotic therapy may be beneficial in animals with solitary suppurative lymphadenitis.

Suggested Readings

Ballegeer EA, et al. Correlation of ultrasonographic appearance of lesions and cytologic and histologic diagnoses in splenic aspirates from dogs and cats: 32 cases (2002-2005). *J Am Vet Med Assoc*. 2007;230:690.

Clifford CA, et al. Magnetic resonance imaging of focal splenic and hepatic lesions in the dog. *J Vet Intern Med*. 2004;18:330.

Couto CG, et al. Benign lymphadenopathies. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. ed 6. Ames, Iowa: Wiley-Blackwell; 2010:412.

Couto CG. A diagnostic approach to splenomegaly in cats and dogs. *Vet Med*. 1990;85:220.

DeGroot W, et al. Primary splenic torsion in dogs: 102 cases (1992-2014). *J Am Vet Med Assoc*. 2016;248:661.

Ferri F, et al. Splenitis in 33 dogs. *Vet Pathol*. 2016;54:147.

Fife WD, et al. Comparison between malignant and nonmalignant splenic masses in dogs using contrast-enhanced computed tomography. *Vet Radiol Ultrasound*. 2004;45:289.

Gamblin RM, et al. Nonneoplastic disorders of the spleen. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine: diseases of the dog and cat*. ed 5. St Louis: Saunders; 2000:1857.

Horvath SJ, et al. Effects of racing on reticulocyte concentrations in Greyhounds. *Vet Clin Pathol*. 2014;43:15.

Huynh E, Berry CR. Small animal abdominal ultrasonography: the spleen. Today's Veterinary Practice. March/April:93; 2017.

Jones ID, Lamb CR, Radiology RDV. Associations between dual-phase computed tomography features and histopathologic diagnoses in 52 dogs with hepatic or splenic masses. *Vet Radiol Ultrasound*. 2016;57:144–2016.

LeBlanc CJ, et al. Comparison of aspiration and nonaspiration techniques for obtaining cytologic samples from the canine and feline spleen. *Vet Clin Pathol*. 2009;38:242.

Liotta A, et al. Prevalence, location and concurrent diseases of ultrasonographic cyst-like lesions of abdominal lymph nodes in dogs. *Vet Rec*. 2017;180:326.

MacNeill AL. Cytology of canine and feline cutaneous and subcutaneous lesions and lymph nodes. *Top Companion Anim Med*. 2011;26:62.

Mallinckrodt MJ, Gottfried SD. Mass-to-splenic volume ratio and splenic weight as a percentage of body weight in dogs with malignant and benign splenic masses: 65 cases (2007–2008). *J Am Vet Med Assoc*. 2011;239:1325.

Moore AS, et al. Histologic and immunohistochemical review of splenic fibrohistiocytic nodules in dogs. *J Vet Intern Med*. 2012;26:1164.

Moore FM, et al. Distinctive peripheral lymph node hyperplasia of young cats. *Vet Pathol*. 1986;23:386.

O'Brien RT, et al. Sonographic features of drug-induced splenic congestion. *Vet Radiol Ultrasound*. 2004;45:225.

O'Keefe DA, et al. Fine-needle aspiration of the spleen as an aid in the diagnosis of splenomegaly. *J Vet Intern Med*. 1987;1:102.

Radhakrishnan A, Mayhew PD. Laparoscopic splenic biopsy in dogs and cats: 15 cases (2006-2008). *J Am Anim Hosp Assoc*. 2013;49:41.

Sabattini S, et al. Canine splenic nodular lymphoid lesions: immunophenotyping, proliferative activity, and clonality assessment. *Vet Pathol*. 2018;55:645.

Salavati Schmitz S. Retrospective characterisation and outcome of canine idiopathic mesenteric purulent lymphadenitis and lymph node abscesses at a teaching hospital from 2005 to 2015. *J Small Anim Pract*. 2016;57:690.

Sharpley JL, et al. Color and power Doppler ultrasonography for characterization of splenic masses in dogs. *Vet Radiol Ultrasound*. 2012;53:586.

Smith K, O'Brien R. Radiographic characterization of enlarged sternal lymph nodes in 71 dogs and 13 cats. *J Am Anim Hosp Assoc*. 2012;48:176.

Spangler WL, et al. Prevalence and type of splenic diseases in cats: 455 cases (1985-1991). *J Am Vet Med Assoc*. 1992;201:773.

Spangler WL, et al. Prevalence, type, and importance of splenic diseases in dogs: 1,480 cases (1985-1989). *J Am Vet Med Assoc*. 1992;200:829.

Spangler WL, Kass PH. Pathologic and prognostic characteristics of splenomegaly in dogs due to fibrohistiocytic nodules: 98 cases. *Vet Pathol*. 1998;35:488.

Suami H, et al. Lymphatic territories (lymphosomes) in a canine: an animal model for investigation of postoperative lymphatic alterations. *PLoS One*. 2013;8:e69222.

Watson AT, et al. Safety and correlation of test results of combined ultrasound-guided fine-needle aspiration and needle core biopsy of the canine spleen. *Vet Radiol Ultrasound*. 2010;52:317.

Wright T, et al. Laparoscopic-assisted splenectomy in dogs: 18 cases (2012-2014). *J Am Vet Med Assoc*. 2016;248:916.

CHAPTER 89

Hyperproteinemia



The plasma protein fraction is composed mainly of albumin, globulins, and fibrinogen; fibrinogen is absent in serum as a result of clotting and conversion into fibrin. In some breeds, such as the Greyhound, serum protein concentrations are below the reference ranges for most laboratories (Fayos et al., 2005). The term *hyperproteinemia* is given to an absolute or relative increase in the serum or plasma protein concentration. Before further evaluation of a cat or dog with hyperproteinemia, the clinician should make sure that the condition is not attributable to a preanalytic issue (e.g., interference of other substances in protein determination), which constitutes one of the most common causes of hyperproteinemia. Lipemia and, to a lesser degree, hemolysis typically result in artifactual increases in the plasma or serum protein concentration.

Once true hyperproteinemia has been established, the clinician should determine whether it is relative or absolute. Relative hyperproteinemia is usually accompanied by erythrocytosis and is caused by hemoconcentration (i.e., dehydration). However, in an anemic cat or dog, relative hyperproteinemia may be present in association with a normal packed cell volume (PCV); that is, the PCV is low, but hemoconcentration results in an artifactual increase. The relative proportions (ratio) of albumin and globulin provide considerable information regarding the pathogenesis of hyperproteinemia. This information is usually contained in reports of serum biochemistry profiles from most referral diagnostic laboratories and in-house analyzers. Occasionally only the total serum protein and serum albumin concentrations are reported. In this case, the total globulin concentration is determined simply by subtracting the albumin concentration from the total protein concentration.

In dogs and cats with relative hyperproteinemia (i.e., hemoconcentration), both the albumin and globulin concentrations are increased above the reference values, whereas in those with absolute hyperproteinemia, only the globulin concentration is increased, usually in association with a mild or marked hypoalbuminemia. Hyperalbuminemia does not occur because the liver is already at its maximal synthetic capacity. The finding of hyperalbuminemia and hyperglobulinemia indicates the presence of dehydration or a preanalytic issue. Rehydration results in resolution of relative hyperproteinemia.

When exposed to an electrical field (i.e., protein electrophoresis), the protein molecules migrate according to their shape, charge, and molecular weight. Staining of the electrophoresis gel after migration usually reveals six distinct protein bands—albumin (closer to the anode or negative electrode), α_1-globulin, α_2-globulin, β_1-globulin, β_2-globulin, and γ-globulin (closer to the cathode or positive electrode; Fig. 89.1, *A*). The albumin fraction is responsible for conferring oncotic properties on body fluids. Acute-phase reactants (APRs), also termed *acute-phase proteins,* migrate in the α_2 and α_1 regions, whereas immunoglobulins (Igs) and complement usually migrate in the β and γ regions. APRs in dogs and cats include C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin (Hp), α_1-acid glycoprotein (AGP), and ceruloplasmin (Cp). Most of these APRs can be measured in serum, plasma, or fluids in commercial diagnostic laboratories; in-house diagnostic kits for CRP are commercially available worldwide. Igs migrate in the following order (from anode to cathode and beginning in the α_2 region): IgA, IgM, and IgG. By evaluating a protein electrophoretogram, the clinician can gain insight into the pathogenesis of the hyperglobulinemia.

Increased production of globulins occurs in a variety of clinical situations but mainly in two groups of disorders: inflammatory-infectious and neoplastic. In inflammation and infection, the hepatocytes elaborate a variety of globulins, collectively termed *APRs,* which result in increases in the α_2- and α_1-globulin fractions. Because the hepatocytes are reprogrammed to produce APRs, the albumin production is switched off, resulting in hypoalbuminemia; albumin is considered a negative APR. In conjunction with these changes, the immune system produces a variety of immune proteins (mainly Igs), which results in increases in the α_2, β, or γ regions or a combination of these.

Because the immune system reacts against an organism (e.g., a bacterium) by producing antibodies against each somatic antigen, several clones of lymphocyte–plasma cells

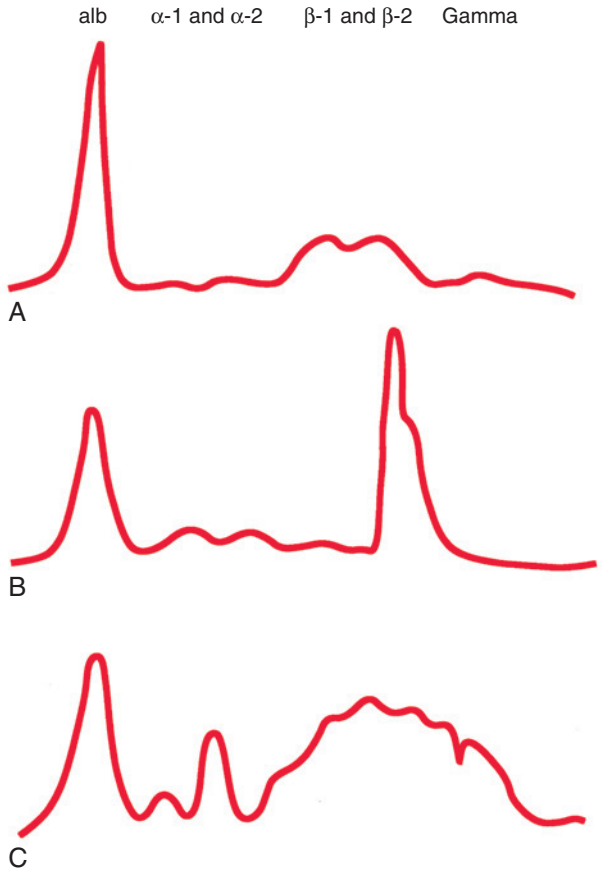


FIG 89.1
(A) Normal canine or feline serum protein electrophoretogram. **(B)** Electrophoretogram from a dog with multiple myeloma and a monoclonal gammopathy in the β_2-γ region. Note the narrow spike approximately the same width as the albumin band. **(C)** Electrophoretogram from a cat with feline infectious peritonitis and a typical polyclonal gammopathy. Note the α-2 spike (APRs) and the broad-based β-γ spikes.

are instructed to produce specific antibody molecules simultaneously; that is, each clone is programmed to produce one specific antibody type against a specific antigen. As a consequence, immune stimulation leads to the appearance of a polyclonal band in the β or γ region, or both. This polyclonal band is broad-based and irregular and contains most of the Igs and complement generated by the immune cells. A typical inflammatory-infectious electrophoretogram therefore consists of a normal to mildly decreased albumin concentration and hyperglobulinemia resulting from increased concentrations of α_2-globulins (i.e., APR) and β-γ globulins (polyclonal gammopathy; see Fig. 89.1, *C*).

Typical inflammatory-infectious electrophoretograms are seen in several common disorders, including chronic pyoderma, pyometra, and other chronic suppurative processes; feline infectious peritonitis (FIP); feline and canine mycoplasmosis and other hemoparasite infections; canine ehrlichiosis, anaplasmosis, and leishmaniasis; chronic immune-mediated disorders (e.g., systemic lupus erythematosus, immune polyarthritis); and some neoplastic diseases, although these are rare (Box 89.1). Polyclonal gammopathies are also common in otherwise healthy old cats.

Monoclonal gammopathies occur when one clone of immune cells produces the same type and subtype of Ig molecule. Because these molecules are identical, they migrate in a narrow band (monoclonal spike, or M component), located typically in the β or γ region (see Fig. 89.1, *B*). Monoclonal gammopathies occur in dogs with multiple myeloma, chronic lymphocytic leukemia, or lymphoma (the latter infrequently). They are also occasionally present in dogs with ehrlichiosis or leishmaniasis; recently, a monoclonal gammopathy associated with *Bartonella henselae* infection was reported in a dog (Tabar et al., 2011) (Box 89.2). In cats

BOX 89.1

Diseases Associated With Polyclonal Gammopathies in Dogs and Cats

Infectious

- **Chronic pyoderma**
- **Pyometra**
- Chronic pneumonia
- **Feline infectious peritonitis**
- Mycoplasmosis
- Bartonellosis
- **Ehrlichiosis**
- Anaplasmosis
- **Leishmaniasis**
- Chagas disease
- Babesiosis
- **Systemic mycoses**

Immune-Mediated Diseases

Neoplasia

- Lymphomas
- Mast cell tumors
- **Necrotic or draining tumors**

Note: Entries in **boldface** are common causes; entries in regular typeface are uncommon causes.

BOX 89.2

Diseases Associated With Monoclonal Gammopathies in Dogs and Cats

Multiple myeloma
Chronic lymphocytic leukemia
Lymphoma
"Idiopathic" monoclonal gammopathy
Ehrlichiosis
Leishmaniasis
Bartonellosis
Feline infectious peritonitis
Chronic inflammation

monoclonal gammopathies are uncommon and occur in association with plasma cell tumors or lymphoma, but they can rarely occur in cats with FIP (Taylor et al., 2010; Qurollo et al., 2014).

Occasionally an M component is detected in an otherwise asymptomatic cat or dog, but additional evaluation fails to reveal a source for the monoclonal gammopathy. Although this likely represents the counterpart of human idiopathic monoclonal gammopathy, the patient should be reevaluated frequently for a clinically emerging malignancy. In cats the source of the M component is usually the spleen, in which a neoplastic population of well-differentiated plasma cells is frequently identified in asymptomatic cats with a monoclonal gammopathy. Therefore these cats likely have atypical myeloma.

The treatment of dogs and cats with monoclonal or polyclonal gammopathies is aimed at the primary disease. Refer to specific sections throughout this text for discussion of these treatments.

Suggested Readings

Breitschwerdt EB, et al. Monoclonal gammopathy associated with naturally occurring canine ehrlichiosis. *J Vet Intern Med*. 1987;1:2.

Burkhard MJ, et al. Monoclonal gammopathy in a dog with chronic pyoderma. *J Vet Intern Med*. 1995;9:357.

Cerón JJ, et al. Electrophoresis and acute phase protein measurement. In: Weiss DJ, Wardrop KJ, eds. *Schalm's veterinary hematology*. 6th ed. Ames, Iowa: Wiley-Blackwell; 2010:1157.

Ceroón JJ, et al. Acute phase proteins in dogs and cats: current knowledge and future perspectives. *Vet Clin Pathol*. 2008;34:85.

Fayos M, et al. Serum protein electrophoresis in retired racing Greyhounds. *Vet Clin Pathol*. 2005;34:397.

Font A, et al. Monoclonal gammopathy in a dog with visceral leishmaniasis. *J Vet Intern Med*. 1994;8:233.

Patel RT, et al. Multiple myeloma in 16 cats: a retrospective study. *Vet Clin Pathol*. 2005;34:341.

Qurollo BA, et al. Co-infection with Anaplasma platys, Bartonella henselae, Bartonella koehlerae and "Candidatus Mycoplasma haemominutum" in a cat diagnosed with splenic plasmacytosis and multiple myeloma. *J Feline Med Surg*. 2014;16(8):713–720.

Tabar MD, et al. Gammopathy in a Spanish dog infected with Bartonella henselae. *J Small Anim Pract*. 2011;52(4):209–212.

Taylor SS, et al. Serum protein electrophoresis in 155 cats. *J Feline Med Surg*. 2010;12(8):643–653.

Weiser MG, et al. Granular lymphocytosis and hyperproteinemia in dogs with chronic ehrlichiosis. *J Am Anim Hosp Assoc*. 1991;27:84.

CHAPTER 90

Fever of Undetermined Origin



FEVER AND FEVER OF UNDETERMINED ORIGIN

The term *fever* refers to a syndrome of malaise or nonspecific systemic clinical signs accompanied by pyrexia or hyperthermia. In this chapter, however, the terms *fever* and *pyrexia* are used interchangeably. Fever constitutes a protective physiologic response to infectious and noninfectious causes of inflammation that enhances the host's ability to eliminate a noxious agent.

A variety of stimuli, including bacteria, endotoxins, viruses, immune complexes, activated complement, and necrotic tissue, trigger the release of endogenous pyrogens by the phagocytic system, mainly the mononuclear cells, or macrophages. These endogenous pyrogens include interleukin-1, tumor necrosis factor, and interleukin-6, among others. They activate the preoptic nucleus of the hypothalamus, raising the set point of the thermostat by generating heat through muscle contraction and shivering, and conserving heat through vasoconstriction.

In humans several patterns of fever have been associated with specific disorders; however, this does not appear to be the case in dogs and cats. In people with continuous fever, the pyrexia is maintained for several days or weeks. This type of fever is associated with bacterial endocarditis, central nervous system lesions, tuberculosis, and some malignancies. In people with intermittent fever, the body temperature decreases to normal but rises again for periods of 1 to 2 days; this is seen in brucellosis and some malignancies. In remittent fever the temperature varies markedly each day but is always above normal (39.2° C [103° F]); this type of fever is associated with bacterial infections. The term *relapsing fever* is used to refer to febrile periods that alternate with variable periods of normal body temperature, as seen in humans with malaria.

The term *fever of undetermined* (or unknown) *origin* (FUO) is used liberally in veterinary medicine to refer to a febrile syndrome for which a diagnosis is not evident. In human medicine, FUO refers to a febrile syndrome of more than 3 weeks' duration that remains undiagnosed after 1 week of thorough in-hospital evaluation. If the term FUO were to be used in the same way in animals as is recommended for humans, few dogs and cats would actually have it. Therefore, in this chapter, the discussion focuses on the approach to a dog or cat with fever that does not respond to antibacterial antibiotic treatment and for which a diagnosis is not obvious after a minimal workup has been performed (e.g., complete blood count [CBC], serum biochemistry profile, urinalysis).

As a general rule, the clinician typically presumes that a dog or cat with fever has an infection until proved otherwise. This appears to be true in reality, as shown by the fact that a large proportion of dogs and cats with fever respond to nonspecific antibacterial treatment. No clinicopathologic evaluation is performed in most of these animals because the fever responds promptly to treatment.

DISORDERS ASSOCIATED WITH FEVER OF UNDETERMINED ORIGIN

In humans, certain infectious, neoplastic, and immune-mediated disorders are commonly associated with FUO. Approximately one third of patients have infectious diseases, one third have cancer (mainly hematologic malignancies, such as lymphoma and leukemia), and the remaining third have immune-mediated, granulomatous, or miscellaneous disorders. In 10% to 15% of patients with FUO, the underlying disorder remains undiagnosed, despite intensive efforts. In a study of 66 dogs with fever, infectious diseases were diagnosed in 26% of the patients, immune-mediated disease in 35%, neoplasia in 8%, and a diagnosis could not be obtained in 23% (Battersby et al., 2006). In a more recent study of 50 dogs with fever evaluated in a teaching hospital in France, 48% of dogs were diagnosed with inflammatory noninfectious diseases, 18% with infectious disease, and 6% with neoplasia; a final diagnosis could not be obtained in 28% of cases (Chervier et al., 2012). In this study, of the initial diagnostic procedures, hematology (23%), biochemistry (25%), and imaging (27%) were the most helpful in obtaining a diagnosis, whereas immunology and bacteriology were the

least useful (≈4% each); cytology and histopathology were the advanced diagnostic methods that provided the most answers (56%).

Thus, in contrast to what was previously thought, infectious diseases do not appear to be the most common cause of FUO in dogs (and likely cats). Instead, inflammatory noninfectious disorders, including immune-mediated diseases, represent most cases with FUO that are eventually diagnosed (Table 90.1). Interestingly, despite aggressive evaluation, the cause of the fever cannot be determined in 10% to 25% of small animals.

DIAGNOSTIC APPROACH TO THE PATIENT WITH FEVER OF UNDETERMINED ORIGIN

A dog or cat with FUO should be evaluated in a systematic fashion. In general, a three-stage approach is used at our

TABLE 90.1

Causes of Fever of Undetermined Origin in Dogs and Cats

CAUSE	SPECIES AFFECTED
Infectious	
Bacterial	
Bacterial endocarditis	D
Brucellosis	D
Tuberculosis	D, C
Mycoplasmosis	D, C
Plague	C
Borreliosis	D
Bartonellosis	D, C
Suppurative infection (e.g., abscess [liver, pancreas], stump pyometra, prostatitis, discospondylitis, pyelonephritis, peritonitis, pyothorax, septic arthritis)	D, C
Rickettsial	
Ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, salmon poisoning	D, C
Mycotic	
Histoplasmosis	D, C
Blastomycosis	D, C
Coccidioidomycosis	D
Viral	
Feline infectious peritonitis	C
Feline leukemia virus infection	C
Feline immunodeficiency virus infection	C
Circovirus	D
Protozoal	
Babesiosis	D
Hepatozoonosis	D
Cytauxzoonosis	C
Chagas disease	D
Leishmaniasis	D, C
Immune-Mediated	
Polyarthritis	D, C
Vasculitis	D
Meningitis	D
Systemic lupus erythematosus	D, C
Immune hemolytic anemia	D, C
Steroid-responsive fever	D, C
Steroid-responsive neutropenia	D, C
Neoplastic	
Acute leukemia	D, C
Chronic leukemia	D, C
Lymphoma	D, C
Malignant histiocytosis	D
Multiple myeloma	D, C
Necrotic solid tumors	D, C
Miscellaneous	
Metabolic bone disorders	D
Drug induced (tetracycline, penicillins, sulfa)	D, C
Tissue necrosis	D, C
Hyperthyroidism	D, C
Idiopathic	D, C

C, Cat; *D*, dog.

BOX 90.1

Diagnostic Evaluation of Dog or Cat With Fever of Undetermined Origin

First Stage

- CBC
- Serum biochemistry profile and thyroxine concentration
- Urinalysis
- Urine bacterial culture and susceptibility
- FNA of enlarged organs, masses, or swellings

Second Stage

- Thoracic radiographs
- Abdominal ultrasonography
- Echocardiography
- Serial bacterial blood cultures
- Immune tests (antinuclear antibody, rheumatoid factor)
- Acute-phase reactant measurements (e.g., CRP)
- Serum protein electrophoresis
- Serologic tests or PCR assay (see Table 90.1)
- Arthrocentesis (cytologic studies and culture)
- Biopsy of any lesion or enlarged organ
- Bone marrow aspiration (for cytologic studies and bacterial and fungal culture)
- Cerebrospinal fluid analysis
- Leukocyte or ciprofloxacin scanning
- Exploratory celiotomy

Third Stage

- Therapeutic trial (antipyretics, antibiotics, corticosteroids)

CBC, Complete blood count; *CRP,* C-reactive protein; *FNA,* fine-needle aspiration; *PCR,* polymerase chain reaction.

clinic (Box 90.1). The first stage consists of a thorough history taking and physical examination, as well as a minimal database (CBC, serum biochemistry, urinalysis). The second stage consists of additional noninvasive and invasive diagnostic tests. The third stage consists of a therapeutic trial, which is instituted if no diagnosis can be determined after completion of the second stage.

History and Physical Examination

When a febrile patient does not respond to antibacterial treatment, a course of action must be formulated. A thorough history should be obtained and a complete physical examination performed. The history rarely provides clues to the cause of the fever. However, a history of ticks may indicate a vector-borne disease, administration of tetracycline (mainly to cats) may indicate a drug-induced fever, and travel to areas in which systemic mycoses are endemic should prompt further investigation, consisting of cytologic or serologic studies or fungal cultures/polymerase chain reaction (PCR).

During a physical examination, the lymphoreticular organs should be evaluated because numerous infectious diseases affecting these organs (e.g., ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, bartonellosis, leishmaniasis, leukemia, systemic mycoses) may cause fever. Enlarged lymph nodes or spleen should be evaluated cytologically by performing fine-needle aspiration (FNA). An FNA sample can also be obtained for bacterial and fungal culture and susceptibility or for PCR assay if the cytologic studies reveal evidence of infection or inflammation. Any palpable mass or swelling should also be evaluated by using specimens obtained by FNA to rule out granulomatous, pyogranulomatous, suppurative inflammation, and neoplasia (see Chapter 74).

The clinician should thoroughly inspect and palpate the oropharynx, searching for signs of pharyngitis, stomatitis, or tooth root abscesses. The bones should also be thoroughly palpated, particularly in young dogs, because metabolic bone disorders such as hypertrophic osteodystrophy and panosteitis can cause fever associated with bone pain. Palpation and passive motion of all joints is also indicated in search of monoarthritis, oligoarthritis, or polyarthritis. A neurologic examination should be conducted to detect signs of meningitis or other central nervous system lesions. In older cats, the ventral cervical region should be palpated to detect thyroid enlargement or nodules.

The thorax should be auscultated carefully in search of a murmur, which could indicate bacterial endocarditis. A thorough ocular examination may reveal changes suggestive of a specific cause (e.g., chorioretinitis in cats with feline infectious peritonitis or in dogs with monocytic ehrlichiosis).

Clinicopathologic Evaluation

A minimum database consisting of a CBC, serum biochemistry profile, urinalysis, urine bacterial culture, and susceptibility testing should always be carried out in dogs and cats with persistent fever. The CBC may provide important clues regarding the cause of the fever (Table 90.2). A serum biochemistry profile may also yield diagnostic information in dogs and cats with FUO and can provide indirect information on parenchymal organ function. Some laboratories include C-reactive protein (CRP) in their profile; the CRP concentration is often elevated in patients with infectious and other inflammatory diseases but is not specific. Hyperglobulinemia and hypoalbuminemia may indicate an infectious, immune-mediated, or neoplastic disorder (see Chapter 89). The finding of pyuria or white blood cell casts in a urinalysis may indicate a urinary tract infection, which may be the cause of the FUO (i.e., pyelonephritis). Proteinuria associated with inactive urine sediment should prompt the clinician to evaluate a urine protein-to-creatinine ratio to rule out glomerulonephritis or amyloidosis as the cause of the fever.

Other diagnostic tests that may be required in patients with FUO are listed in Box 90.1. Echocardiography is indicated only if the patient has a heart murmur because it rarely detects a valvular lesion in dogs without murmurs. Some of the infectious diseases listed in Table 90.1 can be diagnosed on the basis of serologic findings, culture, or PCR testing.

Fluid from several joints should be aspirated for cytologic evaluation and possibly bacterial culture because

TABLE 90.2

Hematologic Changes in Dogs and Cats With Fever of Undetermined Origin

HEMATOLOGIC CHANGE	CAUSE OF THE FEVER
Regenerative anemia	Immune-mediated disease, hemoparasites (e.g., *Mycoplasma, Babesia*), drugs
Nonregenerative anemia	Infection, chronic inflammation, immune-mediated disease, tissue necrosis, malignancy, endocarditis
Neutrophilia with left shift	Infection, immune-mediated disease, tissue necrosis, malignancy, endocarditis
Neutropenia	Leukemia, immune-mediated disease, pyogenic infection, bone marrow infiltrative disease, drugs
Monocytosis	Infection, immune-mediated disease, tissue necrosis, lymphoma, endocarditis, histiocytosis
Lymphocytosis	Ehrlichiosis, anaplasmosis, Chagas disease, leishmaniasis, chronic lymphocytic leukemia
Eosinophilia	Hypereosinophilic syndrome, eosinophilic inflammation, lymphoma
Thrombocytopenia	Rickettsiae, leukemia, lymphoma, drugs, immune-mediated disease
Thrombocytosis	Infections (chronic), immune-mediated disease

polyarthritis may be the only manifestation of a widespread immune-mediated or infectious disorder (e.g., anaplasmosis, granulocytic ehrlichiosis). Thoracic radiography and abdominal ultrasonography should be performed to search for a silent septic focus. In dogs and cats with neurologic signs associated with fever, a cerebrospinal fluid tap should be performed; in dogs, immune-mediated vasculitis or meningitis can cause marked temperature elevations. If a diagnosis has still not been reached, bone marrow aspirates for cytologic studies, and bacterial and fungal culture should also be obtained. A leukocyte or ciprofloxacin scan may reveal a hidden septic focus, but these are rarely done in practice. Finally, if a definitive diagnosis is ultimately not obtained, a therapeutic trial of specific antibacterial or antifungal agents or immunosuppressive doses of corticosteroids can be initiated.

Treatment

If a definitive diagnosis is obtained, a specific treatment should be initiated. The problem arises if the clinician cannot arrive at a definitive diagnosis. In these patients, changes in the CBC are usually the only clinicopathologic abnormality (see Table 90.2), that is, results of bacterial and fungal cultures, serologic tests, PCR assays, imaging studies, and FNAs are negative or normal. If the patient has already been treated with a broad-spectrum bactericidal antibiotic, a therapeutic trial of immunosuppressive doses of corticosteroids is warranted. However, before instituting immunosuppressive treatment, the owners should be informed of the potential consequences of this approach, mainly that a dog or cat with an undiagnosed infectious disease may die as a result of systemic dissemination of the organism after the start of treatment. Dogs and cats undergoing a therapeutic trial of corticosteroids should be kept in the hospital and monitored frequently for worsening of clinical signs, in which case steroid therapy should be discontinued. In patients with immune-mediated (or steroid-responsive) FUO, the pyrexia and clinical signs usually resolve within 24 to 48 hours of the start of treatment.

If no response to corticosteroids is observed, two courses of action remain. In one, the patient can be released and given antipyretic drugs, such as aspirin (10-25 mg/kg orally [PO] q12h in dogs, and 10 mg/kg PO q72h in cats) or other nonsteroidal antiinflammatory drugs (NSAIDs) and then returned to the clinic for a complete reevaluation in 1 to 2 weeks. Antipyretics should be used with caution, however, because fever is a protective mechanism, and lowering the body temperature may be detrimental in an animal with an infectious disease. Also of note is that some NSAIDs have ulcerogenic effects, can cause cytopenias, and may result in tubular nephropathy if the patient becomes dehydrated or receives other nephrotoxic drugs. The second course of action is to continue the trial of antibiotics by using a combination of bactericidal drugs (e.g., ampicillin and enrofloxacin) for a minimum of 5 to 7 days.

Suggested Readings

Battersby IA, et al. Retrospective study of fever in dogs: laboratory testing, diagnoses and influence of prior treatment. *J Small Anim Pract*. 2006;47:370.

Chervier C, et al. Causes, diagnostic signs, and the utility of investigations of fever in dogs: 50 cases. *Can Vet J*. 2012;53:525.

Dunn KJ, Dunn JK. Diagnostic investigations in 101 dogs with pyrexia of unknown origin. *J Small Anim Pract*. 1998;39:574.

Feldman BF. Fever of undetermined origin. *Compend Contin Educ*. 1980;2:970.

Flood J. The diagnostic approach to fever of unknown origin in dogs. *Compend Contin Educ Vet*. 2009;31:14.

Flood J. The diagnostic approach to fever of unknown origin in cats. *Compend Contin Educ Vet*. 2009;31:26.

Harkin KR. Uncovering the Cause of Fever in Dogs. *Today's Vet Pract*. 2016;July/August:30–35.

Harkin KR. Uncovering the Cause of Fever in Cats. *Today's Vet Pract*. 2017;March/April:75–84.

Scott-Moncrieff JC, et al. Systemic necrotizing vasculitis in nine young beagles. *J Am Vet Med Assoc*. 1992;201:1553.

PART FOURTEEN ▪ Infectious Diseases

Michael R. Lappin

CHAPTER 91

Laboratory Diagnosis of Infectious Diseases



Clinical syndromes induced by infectious agents are common in small animal practice. A combination of signalment, history, and physical examination findings is used to develop a list of differential diagnoses ranking the most likely infectious agents involved. For example, young, unvaccinated cats with conjunctivitis are generally infected by herpesvirus type 1, *Chlamydia felis,* or *Mycoplasma felis;* if a dendritic ulcer is present, herpesvirus type 1 is most likely. Results of a complete blood count (CBC), serum biochemical panel, urinalysis, radiographs, or ultrasonography can also suggest infectious diseases. For example, a dog with polyuria, polydipsia, neutrophilic leukocytosis, azotemia, pyuria, and an irregularly marginated kidney on radiographic examination likely has pyelonephritis. After making a tentative diagnosis, the clinician then must determine whether to "test or treat." Empiric treatment is sometimes adequate in simple, first-time infections of dogs or cats without life-threatening disease (see Chapter 92). However, having a definitive diagnosis is usually preferred so that treatment, prevention, prognosis, and zoonotic issues can be addressed optimally.

Documenting that the infectious agent is still present, using cytology, culture, antigen assays, and molecular diagnostic assays is the best way to make a definitive diagnosis. Antibody detection is commonly used to aid in the diagnosis of specific infectious diseases but can be inferior to organism demonstration for three reasons: (1) Antibodies can persist long after an infectious disease has resolved, (2) positive antibody test results do not confirm clinical disease induced by the infectious agent, and (3) in peracute infections, results of serum antibody tests can be negative if the humoral immune responses have not had time to develop. This chapter discusses the common organism demonstration and antibody detection techniques used in small animal practice.

DEMONSTRATION OF THE ORGANISM

FECAL EXAMINATION

Examination of feces can be used to help diagnose parasitic diseases of the gastrointestinal (see Chapter 27) and respiratory tracts (see Chapter 20). The techniques used most frequently include direct and saline smear, stained smear, fecal flotation, and Baermann technique; each procedure can easily be performed in a small animal practice.

Direct Smear

Fresh, liquid feces or feces that contain large quantities of mucus should be microscopically examined immediately for the presence of protozoal trophozoites, including those of *Giardia* spp. in cases with small-bowel diarrhea and *Trichomonas foetus* (*T. blagburni* proposed) in cases with large-bowel diarrhea. A direct saline smear can be made to potentiate observation of these motile organisms. A 2 mm × 2 mm × 2 mm quantity of fresh feces is mixed thoroughly with 1 drop of 0.9% NaCl or water. The surface of the feces or mucus coating the feces should be used because the trophozoites are most common in these areas. After application of a coverslip, the smear is evaluated for motile organisms by examining it under ×100 magnification (i.e., using the 10× objective in most microscopes).

Stained Smear

A thin smear of feces from all dogs and cats with diarrhea can be made. Material should be collected by rectal swab, if possible, to increase the chances of finding white blood cells and some organisms like *Histoplasma capsulatum*. A cotton swab is gently introduced 3 to 4 cm through the anus into the terminal rectum, directed to the wall of the rectum, and gently rotated several times. Placing 1 drop of 0.9% NaCl on the cotton swab will facilitate passage through the anus and

not adversely affect cell morphology. The cotton swab is rolled on a microscope slide gently multiple times to give areas with varying smear thickness (Fig. 91.1). After air-drying, the slide can be stained. White blood cells and bacteria morphologically consistent with *Campylobacter* spp. (spirochetes) or *Clostridium perfringens* (spore-forming rods; Fig. 91.2) can be observed after staining with Diff-Quik or Wright or Giemsa stains (see Cytology section). However, these findings do not confirm the diagnosis as there are many spirochetes in feces and cytologic detection of suspected *C. perfringens* spores that do not always correlate to the presence of enterotoxins. *Histoplasma capsulatum* or *Prototheca* may be observed in the cytoplasm of mononuclear cells. Methylene blue in acetate buffer (pH 3.6) stains trophozoites of the enteric protozoans. Iodine and acid methyl green stains are also used for the demonstration of protozoans. Modified acid-fast staining of a thin fecal smear can be performed in dogs and cats with diarrhea to aid in the diagnosis of cryptosporidiosis. *Cryptosporidium* spp. are the only enteric organisms of approximately 4 to 6 µm in diameter that will stain pink to red with acid-fast stain (Fig. 91.3).

Fecal Flotation

Cysts, oocysts, and eggs in feces can be concentrated to increase the sensitivity of detection. A variety of techniques are available for use in veterinary clinics. Centrifugation techniques are more sensitive than passive flotation techniques. Most eggs, oocysts, and cysts are easily identified after centrifugation in zinc sulfate solution (Box 91.1) or Sheather sugar solution. These procedures are superior to passive flotation techniques for the demonstration of protozoan cysts (particularly *Giardia* spp.; Fig. 91.4). Many clinicians are now using big service laboratories for this service, but in one study, a smaller university laboratory had a greater sensitivity than a commercial laboratory for detection of *Giardia* cysts (Hascall et al., 2016). Fecal sedimentation recovers most cysts and ova but also contains debris.

Baermann Technique

This technique is used to concentrate motile larvae from feces. The feces are diluted in water, placed in a funnel clamped at the ventral end, and the larva concentrate by gravity. Some respiratory parasites are passed as larvated eggs but release larvae shortly after being passed in feces. Eggs or larvae from respiratory parasites can also be detected by cytologic evaluation of airway washings (Fig. 91.5).

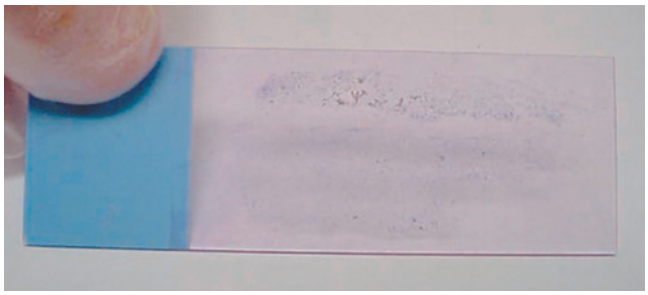


FIG 91.1
Diff-Quik–stained fecal smear showing appropriate smear thickness.

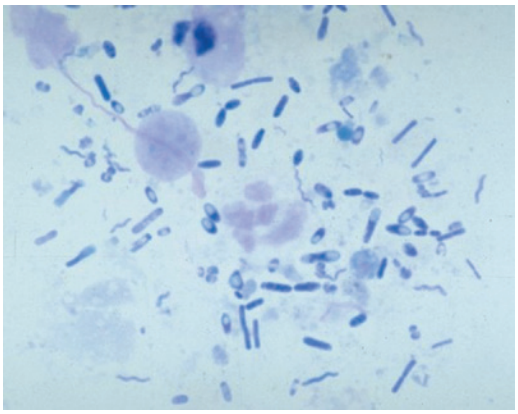


FIG 91.2
Wright-stained, thin fecal smear. A neutrophil and spore-forming rods are present in the center of the field.

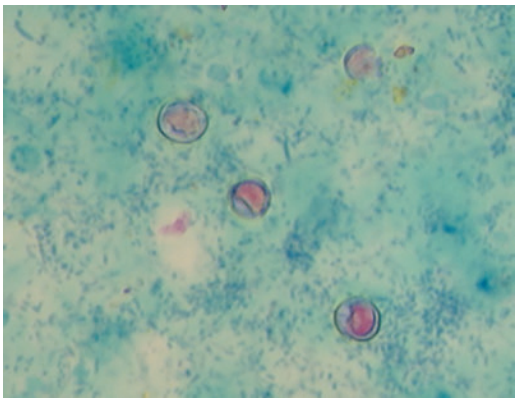


FIG 91.3
Cryptosporidium parvum oocysts stained with a modified acid-fast stain. The oocysts are approximately 4 × 6 µm.

BOX 91.1

Zinc Sulfate Centrifugation Procedure

1. Place 1 g fecal material in a 15-mL conical centrifuge tube.
2. Add 8 drops of Lugol iodine and mix well.
3. Add 7 to 8 mL of zinc sulfate (1.18 specific gravity)* and mix well.
4. Add zinc sulfate until there is a slight positive meniscus.
5. Cover the top of the tube with a coverslip.
6. Centrifuge at 1500 to 2000 rpm for 5 minutes.
7. Remove the coverslip and place on a clean microscope slide for microscopic examination.
8. Examine the entire area under the coverslip for the presence of ova, oocysts, or larvae at ×100.

*Add 330 g zinc sulfate to 670 mL distilled water.

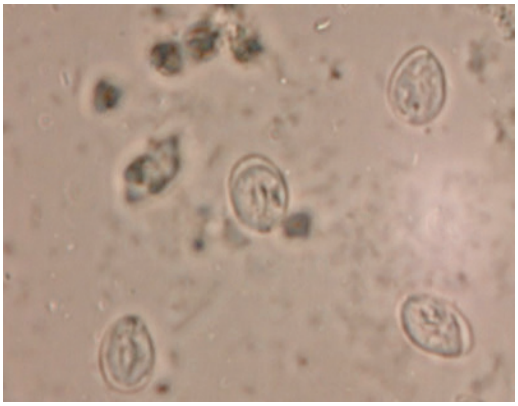


FIG 91.4
Giardia cysts after zinc sulfate flotation. The cysts are approximately 10 × 8 µm.

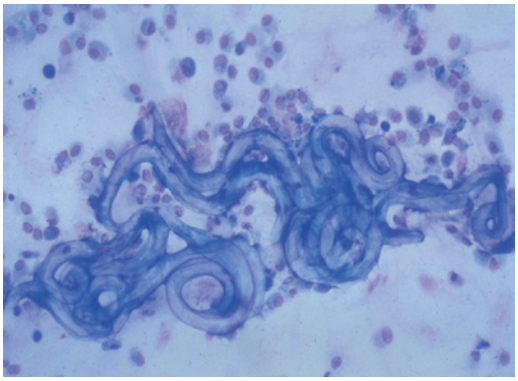


FIG 91.5
Aelurostrongylus abstrusus larvae in an airway washing collected by bronchoalveolar lavage. (Courtesy Dr. Timothy Hackett, Colorado State University, Fort Collins.)

Preservation of Feces

Feces should be refrigerated, not frozen, until assayed. If present, refrigerated *Toxoplasma gondii* oocysts will not likely sporulate and become infectious. In addition, refrigerated feces have less overgrowth of yeast, leading to fewer false-positive results. If a fecal sample is to be sent to a diagnostic laboratory for further analysis and will not be evaluated within 48 hours, it should be preserved. Polyvinyl alcohol, merthiolate-iodine-formalin, and 10% formalin preservation can be used. Ten percent formalin is commonly used because of its routine availability; the clinician should add 1 part feces to 9 parts formalin and mix well.

CYTOLOGY

Cytologic evaluation of exudates, bone marrow aspiration, blood smears, synovial fluid, gastric brushings, duodenal secretions, urine, prostatic washings, airway washings, fecal smears, tissue imprints, and aspiration biopsies is an inexpensive and extremely valuable tool for the documentation of infectious agents; see individual chapters for cytologic findings for select infectious agents. Cytologic demonstration of some infectious agents constitutes a definitive diagnosis. It is no longer recommended to use morphologic appearance and Gram stain of bacteria to aid in the selection of empiric antibiotics while waiting for results of culture and antimicrobial susceptibility testing as the results are not accurate (Lappin et al., 2017).

For demonstration of most infectious agents, thin smears are preferred. Blood can be prepared as follows: 1 drop of blood approximately the size of a match head is placed at one end of a clean microscope slide. The short edge of another slide (i.e., spreader slide) is placed against the slide at a 30-degree angle and pulled back until the blood and the spreader slide make contact. After the blood spreads across the width of spreader slide, the slide is smoothly and quickly pushed away from the blood across the length of the slide ("push" smears). For materials other than blood, the spreader slide is laid gently on top of the material; the slides are then smoothly and rapidly pulled apart on parallel planes ("pull" smears). Cells in airway washings, prostatic washings, urine, aqueous humor, and cerebrospinal fluid (CSF) should be pelleted by centrifugation at 2000 g for 5 minutes before staining. Multiple slides should always be made, if possible. After being placed on the microscope slide, the material is air-dried at room temperature, fixed if indicated by the procedure used, and stained. Slides that are not stained immediately should be fixed by dipping in 100% methanol and air-dried.

Cytologic specimens can be stained with routine stains; immunocytochemical techniques for certain pathogens are available (see Immunologic Techniques, p. 1432). Stains routinely used for the diagnosis of infectious diseases in small animal practice include Wright-Giemsa stain, Diff-Quik, Gram stain, and acid-fast stain. Immunocytochemical techniques (e.g., fluorescent antibody staining of bone marrow cells for feline leukemia virus) are only performed in reference or research laboratories (see Immunologic Techniques, p. 1432). The laboratory should be contacted for specific specimen handling information.

Bacterial Diseases

If bacterial disease is suspected, materials are collected aseptically and handled initially for culture (see Culture Techniques, p. 1431). After slides are prepared for cytologic evaluation, one is generally stained initially with Wright-Giemsa or Diff-Quik stain. If bacteria are noted, Gram stain of another slide is performed to differentiate gram-positive and gram-negative agents. If filamentous, gram-positive rods are noted, acid-fast staining can help differentiate *Actinomyces* (not acid fast) from *Nocardia* (generally acid fast). If macrophages or neutrophils are detected, acid-fast staining is indicated to assess for *Mycobacterium* spp. within the cytoplasm; *Mycobacterium* spp. can often be seen on Diff-Quik or Wright-Giemsa stained slides (see Fig. 74.2). Bacteria can be present in small numbers or can be intracellular (*Bartonella* spp.), so failure to document organisms cytologically does not totally exclude the diagnosis. Bacterial culture of all samples with increased numbers of neutrophils

or macrophages should always be considered. Some organisms such as *Mycoplasma* are rarely documented cytologically, whereas other organisms require special stains for optimal visualization. For some, bacteria culture has never been successful. For example, the hemoplasmas of dogs and cats (previously called *Haemobartonella felis* and *Haemobartonella canis*) can be detected on the surface of red blood cells (RBCs) but have never been successfully cultured. Until the advent of molecular diagnostic techniques (see p. 1432), documentation of infection was based on cytology alone; Wright-Giemsa stain is the best stain to use in practice for these organisms. However, falsely negative results based on cytology are common, and therefore molecular techniques should be considered in cytology-negative cases if the index of suspicion is high.

Rickettsial Diseases

Anaplasma spp. (Fig. 91.6) and *Ehrlichia* spp. are occasionally found within the cytoplasm of cells in the peripheral blood, lymph node aspirates, bone marrow aspirates, or synovial fluid (see Chapter 95). Morulae of these genera can be found in different cell types. Wright-Giemsa stain is superior to Wright or Diff-Quik stain for the demonstration of morulae. *Rickettsia rickettsii* in endothelial cells lining vessels can be documented by immunofluorescent antibody staining (see Immunologic Techniques, p. 1432).

Fungal Diseases

Arthrospores and conidia of dermatophytes can be identified cytologically. Hairs plucked from the periphery of a lesion are covered with 10% to 20% potassium hydroxide on a microscope slide to clear debris. The slide is then heated, but not boiled, and examined for dermatophytes. All cats with chronic, draining skin lesions should have imprints of the lesions made and stained with Wright-Giemsa stain followed by microscopic examination for the characteristic round, oval, or cigar-shaped yeast phase of *Sporothrix schenckii* within the cytoplasm of mononuclear cells (see Fig. 99.3). Periodic acid–Schiff stain is superior to Wright-Giemsa stain for the demonstration of fungi.



FIG 91.6
Anaplasma phagocytophilum morula *(arrow)* in the cytoplasm of an experimentally infected cat.

Cutaneous Parasitic Diseases

Cheyletiella spp., *Demodex* spp., *Sarcoptes scabiei, Notoedres cati,* and *Otodectes cynotis* are the most common small animal cutaneous parasites. Definitive diagnosis is based on cytologic demonstration of the organisms. *Cheyletiella* is demonstrated by pressing a piece of transparent tape against areas with crusts, placing the tape on a microscope slide, and examining it microscopically. *Demodex* spp. are most commonly detected in deep skin scrapings and follicular exudates; *Cheyletiella* spp., *S. scabiei,* and *N. cati* are detected in wide, more superficial scrapings. *O. cynotis* or its eggs are detected in ceruminous exudates from the ear canals.

Systemic Protozoal Diseases

The most common systemic protozoal diseases and the cytologic appearance and location of these agents are described in Chapter 98. Cytologic demonstration of these agents leads to a presumptive or definitive diagnosis of the disease. Wright-Giemsa or Giemsa staining of thin blood films should be used to demonstrate *Leishmania* spp., *Trypanosoma cruzi, Babesia* spp., *Hepatozoon americanum,* and *Cytauxzoon felis.* Collection of blood from an ear margin vessel may increase the chances of demonstrating the protozoans found in blood, particularly *Babesia* spp. and *C. felis. T. gondii* and *Neospora caninum* cause similar syndromes in dogs, but their tachyzoites are difficult to distinguish morphologically; immunocytochemical staining or PCR is required to differentiate these agents. These protozoans can also be distinguished by evaluating for seroconversion because antibodies are specific to each agent. With the exception of *T. gondii* and *N. caninum,* systemic protozoans are rare or regionally defined in the United States. See Chapter 98 for further discussion of these agents.

Viral Diseases

Rarely, viral inclusion bodies are detected cytologically after staining with Wright-Giemsa. Distemper virus infection causes inclusions in circulating lymphocytes, neutrophils, and erythrocytes of some dogs. Rarely, feline infectious peritonitis virus results in intracytoplasmic inclusions in circulating neutrophils. Feline herpesvirus 1 (FHV-1) transiently results in intranuclear inclusion bodies in epithelial cells.

TISSUE TECHNIQUES

Tissues collected from animals with suspected infectious diseases can be evaluated by several different techniques. Tissue samples should be aseptically placed in appropriate transport

media for culture procedures or inoculated into laboratory animals, if indicated, before further handling.

Gently blotting the cut edge of the tissue on a paper towel to remove excess blood and then lightly touching the tissue multiple times to a microscope slide make tissue impressions for cytologic examination. Tissue specimens can then be frozen, placed into 10% buffered formalin solution, or placed into glutaraldehyde-containing solutions. Frozen specimens are generally superior for immunohistochemical staining and molecular diagnostic procedures. Routine histopathologic evaluation is performed on formalin-fixed tissues. Special stains can be used to maximize the identification of some infectious agents. The clinician should alert the histopathology laboratory to the infectious agents most suspected to allow for appropriate stain selection. Glutaraldehyde-containing fixatives are superior to other fixatives for electron microscopic examination of tissues; this technique can be more sensitive than other procedures for demonstration of viral particles. Molecular diagnostic assays like fluorescence in situ hybridization (FISH) are now being used to identify nucleic acids of infectious agents within tissues (see Molecular Diagnostics, p. 1432).

CULTURE TECHNIQUES

Bacteria, fungi, viruses, and some protozoans can be cultured. In general, a positive culture can be used to establish a definitive diagnosis. Aerobic bacterial culture can be combined with antimicrobial susceptibility testing to determine optimal drug therapy. Successful culture depends on collecting the optimal materials without contamination, transporting the materials to the laboratory as quickly as possible in the most appropriate medium to minimize organism death or overgrowth of nonpathogens, and using the most appropriate culture materials.

Culture results of body systems with normal bacterial and fungal flora, including the skin, ears, mouth, nasal cavity, trachea, feces, and vagina, are the most difficult to interpret. Finding positive culture results and inflammatory cells cytologically suggests the organism is inducing disease. Culture of a single agent, particularly if the organism is relatively resistant to antimicrobials, is more consistent with a disease-inducing infection than if multiple, antibiotic-susceptible bacteria are cultured. Materials for routine aerobic bacterial culture can be placed on sterile swabs if the swabs remain moist and are placed on appropriate culture media within 3 hours of collection. If a delay of greater than 3 hours is expected, swabs containing transport medium should be used. These swabs should be refrigerated or frozen to inhibit bacterial growth if cultures are not to be started within 4 hours; some bacteria will grow more rapidly than others, potentially masking fastidious organisms. Most aerobes will survive at 4° C (routine refrigeration temperature) in tissue or on media-containing swabs for 48 hours. Solid-phase transport media that will support the growth of most aerobes, anaerobes, *Mycoplasma* spp., and fungi for several days if refrigerated are also routinely available. Routine aerobic culture is generally successful on fluid samples (e.g., urine, airway washings) stored at 20° C for 1 to 2 hours, 4° C for 24 hours, or 4° C for 72 hours if placed in transport medium.

Anaerobes can be successfully cultured from fluid collected aseptically into a syringe and the needle covered with a rubber stopper if the material is to be placed on culture media within 10 minutes of collection. Because of time limitations, transport media is generally required for samples from animals with suspected anaerobic infections. These media will support the growth of most anaerobes for 48 hours if stored at 4° C.

Samples for blood culture should be collected aseptically from a large vein after surgical preparation of the skin. In general, three 5-mL samples are collected over a 24-hour period in stable patients or at 1- to 3-hour intervals in septic patients. Unclotted whole blood is placed directly into transport media that will support the growth of aerobic and anaerobic bacteria, and it is incubated at 20° C for 24 hours. Culture for *Bartonella* spp. from blood of dogs or cats is generally performed on whole blood samples collected aseptically and placed in an EDTA-containing tube. In dogs, the combination of culture and PCR performed on 3 mL of blood in EDTA collected up to 3 days weekly may be required to detect *Bartonella* spp. infections (see Chapter 94).

Culture of feces for *Salmonella* spp. or *Campylobacter* spp. and performance of antimicrobial sensitivity testing is occasionally indicated in small animal practice, particularly if the animal has signs of sepsis or an outbreak is suspected. Approximately 2 to 3 g of fresh feces should be submitted to the laboratory immediately for optimal results; however, *Salmonella* and *Campylobacter* are usually viable in refrigerated fecal specimens for 3 to 7 days. To increase the likelihood of achieving positive culture results, a transport medium should be used if a delay is expected. The laboratory should be notified of the suspected pathogen so that appropriate culture media can be used.

Mycoplasma and *Ureaplasma* cultures are most commonly performed on airway washings, synovial fluid, exudates from chronic draining tracts in cats, urine from animals with chronic urinary tract disease, and the vagina of females with genital tract disease. Samples should be transported to the laboratory in Amies medium or modified Stuart bacterial transport medium. *Mycoplasma* spp. culture should be specifically requested.

Mycobacterium spp. grow slowly, and culture is often limited by overgrowth of other bacteria. Special medium is required; therefore the laboratory should be specifically instructed to culture for *Mycobacterium* spp. Tissue samples or exudates from animals with suspected *Mycobacterium* spp. infection should be refrigerated immediately after collection and transported to the laboratory as soon as possible. Exudates should be placed in transport media.

Cutaneous fungal agents can be cultured in the small animal office by using routinely available culture media. Materials from dogs or cats with suspected systemic fungal infection can be transported to the laboratory as described for bacteria, and the laboratory can be told specifically that fungal culture is necessary. The yeast phase of the systemic

fungi occurs in vivo and is not zoonotic; the mycelial phase of *Blastomyces, Coccidioides,* and *Histoplasma* grows in culture and will infect human beings. Thus in-house culture for these agents is not recommended.

Viral agents can be isolated from tissues or secretions at some laboratories. Contact the laboratory before submitting samples. Samples should be collected aseptically as for bacteria, placed in transport media, and immediately refrigerated to inhibit bacterial growth. The samples should be transported to the laboratory on cold packs but not frozen.

IMMUNOLOGIC TECHNIQUES

Infectious agents or their antigens can be detected in body fluids, feces, cells, or tissues by using immunologic techniques. In general, polyclonal or monoclonal antibodies against the agent in question are used in a variety of different test methods, including direct fluorescent antibody assay with cells or tissue, agglutination assays, and enzyme-linked immunosorbent assay (ELISA). Sensitivities and specificities vary by test but are generally high for most assays. Positive results with these tests generally prove infection; this is in contrast to antibody detection procedures, which only document exposure to an infectious agent. Contact the laboratory for details concerning specimen transport before collection.

Commercially available assays for the detection of antigens of *Dirofilaria immitis, Cryptococcus neoformans, Blastomyces dermatitidis,* and feline leukemia virus (FeLV) are used most frequently with blood from small animal patients. The *Cryptococcus neoformans* latex agglutination procedure can also be performed on aqueous humor, vitreous humor, and CSF (see Chapter 97).

Parvovirus *Giardia* spp. antigen detection procedures are available for use with feces of dogs and cats. Parvovirus assays detect both canine and feline parvovirus antigen and may be affected transiently by administration of modified-live vaccines (Abd-Eldaim, 2009; Freisl et al., 2017). Both CPV2c and CPV2b are detected by currently available assays (Markovich et al., 2012). Most *Giardia* antigen tests marketed for use with human or pet feces detect the *Giardia* assemblages that infect dogs or cats (Rishniw et al., 2010). Samples are occasionally antigen positive but cyst negative on fecal flotation. In this situation either the antigen test is falsely positive or the fecal flotation is falsely negative, and both tests should be repeated on a new fecal sample. Alternately, the feces can be evaluated further for *Giardia* cysts by fluorescent antibody assay (next paragraph) or polymerase chain reaction. None of the currently available ELISA-based *Cryptosporidium parvum* antigen tests marketed for use with human feces consistently detects *Cryptosporidium felis* or *Cryptosporidium canis* and should therefore not be used with feces from dogs and cats.

Immunocytochemistry and immunohistochemistry techniques are widely available for the documentation of a variety of infectious diseases. These procedures are particularly valuable for the detection of viral diseases, detection of agents present in small numbers, and for differentiation among agents with similar morphologic features. In general, these techniques are more sensitive and specific than histopathologic techniques and are comparable with culture. For example, focal feline infectious peritonitis granulomatous disease can be documented by immunohistochemical staining (see Chapter 96). A fluorescent antibody-based assay (Merifluor *Cryptosporium/Giardia*, Meridian Bioscience Inc., Saco, ME) for the detection of *Giardia* spp. cysts and *Cryptosporidium* spp. oocysts in feces is commonly used to aid in the diagnosis of these infections in dogs and cats (Mekaru et al., 2007).

MOLECULAR DIAGNOSTICS

A number of different techniques can be used to amplify the DNA or RNA of infectious agents (Veir and Lappin, 2010). Polymerase chain reaction is used frequently for DNA amplification (Fig. 91.7). With a reverse transcriptase step, RNA is converted to DNA; therefore the technique

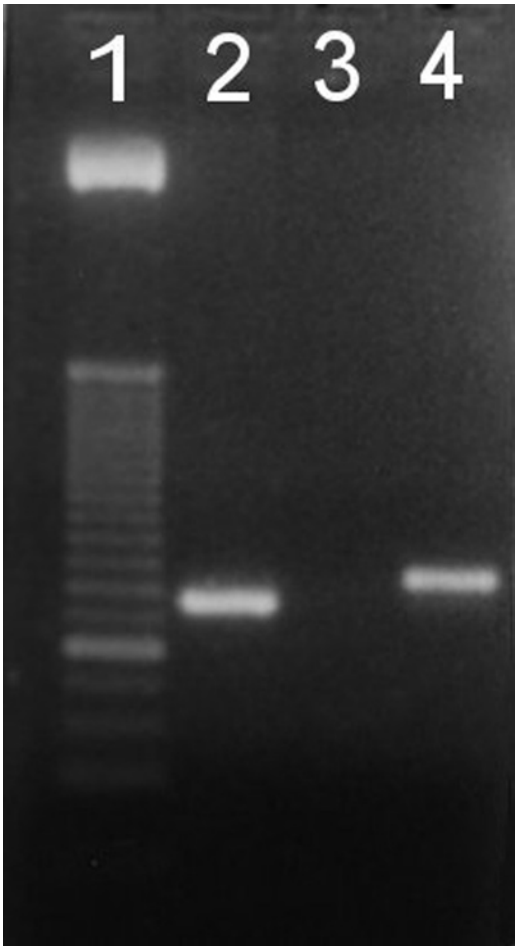


FIG 91.7
Photograph of a polymerase chain reaction assay for hemoplasmas showing the two different band sizes that help differentiate species: *Mycoplasma haemofelis (Lane 2)* and *Candidatus M. haemominutum (Lane 4). Lane 1* is a base pair ladder, and *Lane 3* is a negative sample. In this assay, *Candidatus M. turicensis* is included in the *M. haemofelis* amplicon.

can also be used to amplify RNA (RT-PCR). In general, molecular diagnostic assays are usually more sensitive than other organism demonstration techniques. These assays can be of great benefit for documentation of infectious agents that are difficult to culture (e.g., *Ehrlichia* spp.) or cannot be cultured (e.g., hemoplasmas). Specificity can be quite high depending on the primers used in the reaction. For example, primers can be designed to detect one genus but not others. Primers can also be designed to identify only one species. For example, a PCR assay can be developed to detect all *Ehrlichia* spp. and *Anaplasma* spp. or just one species such as *Ehrlichia canis*. Assays that contain multiple sets of primers to detect nucleic acids of many different infectious agents can also be used.

Another use of molecular diagnostics is FISH. In this molecular technique, nucleic acids of infectious agents can be identified within tissues. One recent infectious disease example using FISH showed that *Borrelia burgdorferi* was not in the renal tissues of dogs with presumed Lyme nephropathy, supporting the hypothesis that this clinical syndrome is likely to have an immune-mediated component (Hutton et al., 2008). In addition, FISH was used to help prove that Boxer colitis was a syndrome associated with *Escherichia coli* (Simpson et al., 2006).

Because of the inherent sensitivity of the reaction, molecular diagnostic assays can give false-positive results if sample contamination occurs during collection or at the laboratory performing the procedure. False-negative results can occur if the sample is handled inappropriately or if the patient is receiving antibiotics that are effective against that specific organism; this is of particular importance for detection of RNA viruses by reverse transcriptase polymerase chain reaction (RT-PCR). Results may also be affected by treatment. Another potential problem is that minimal standardization exists among commercial laboratories offering molecular diagnostic assays.

Although molecular diagnostic assays can be one of the most sensitive for documentation of infections, positive test results do not always prove that the infection is causing clinical illness. For example, because the technique detects DNA of both live and dead organisms, positive test results may be achieved even if the infection has been controlled. When the organism being tested for commonly infects the background population of healthy pets, interpretation of results for a single animal can be difficult. For example, FHV-1 commonly infects cats and is commonly carried by healthy cats. Thus although PCR is the most sensitive way to document infection by FHV-1, the positive predictive value for disease of a FHV-1 PCR result is actually quite low. In one study, more positive FHV-1 PCR results were detected in the healthy control group than in the group with conjunctivitis (Burgesser et al., 1999). In addition, the currently available PCR assays for FHV-1 also amplify modified-live vaccine strains, so a positive result does not even indicate presence of a pathogenic strain. Real-time PCR can be used to determine the amount of microbial DNA or RNA in a sample. The nucleic acid load may correlate to the presence of disease or therapeutic responses for some agents (Low et al., 2007; Veir and Lappin, 2010). However, minimal data exist for use of quantitative PCR for these purposes and the reader is directed to specific agent chapters for further information. Because of these findings, small animal practitioners must carefully assess the predictive values of currently available PCR assays and the expertise and reliability of the laboratory that will be performing the assays.

ANIMAL INOCULATION

Animal inoculation can be used to identify some infectious diseases. For example, oocysts of *T. gondii* cannot be distinguished morphologically from those of *Hammondia hammondi* or *Besnoitia darlingi;* only *T. gondii* is infectious for human beings. *T. gondii* can be differentiated from the other coccidians by inoculation of sporulated oocysts into mice and monitoring for *T. gondii*–specific antibody production. However, because live animals are required, animal inoculation is rarely used in small animal practice.

ELECTRON MICROSCOPY

Electron microscopy is a highly sensitive procedure for organism identification in body fluids and tissues. Glutaraldehyde-containing fixatives are used most commonly. One of the most clinically relevant uses of electron microscopy is for the detection of viral particles in feces of animals with gastrointestinal signs of diseases.

ANTIBODY DETECTION

SERUM

A variety of different methods exists for detecting serum antibodies against infectious agents; complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, indirect fluorescent antibody assay (IFA), ELISA, and Western blot immunoassay are commonly used methods. Complement fixation, hemagglutination inhibition, serum neutralization, and agglutination assays generally detect all antibody classes in a serum sample. Western blot immunoassay, IFA, and ELISA can be adapted to detect specific immunoglobulin (Ig) M, IgG, or IgA responses. Western blot immunoassay can be used to identify the immunodominant antigens recognized by the humoral immune responses (Fig. 91.8).

Comparison of IgM, IgA, and IgG antibody responses against an infectious agent can be used to attempt to prove recent or active infection. In general, IgM is the first antibody produced after antigenic exposure. Antibody class shift to IgG occurs in days to weeks. Serum and mucosal IgA immune responses have also been studied for some infectious agents, including *T. gondii,* feline coronaviruses, and *Helicobacter felis.*

Timing of antibody testing is important. In general, serum antibody tests in puppies and kittens cannot be interpreted as specific responses until at least 8 to 12 weeks of age because of the presence of antibodies from the dam passed

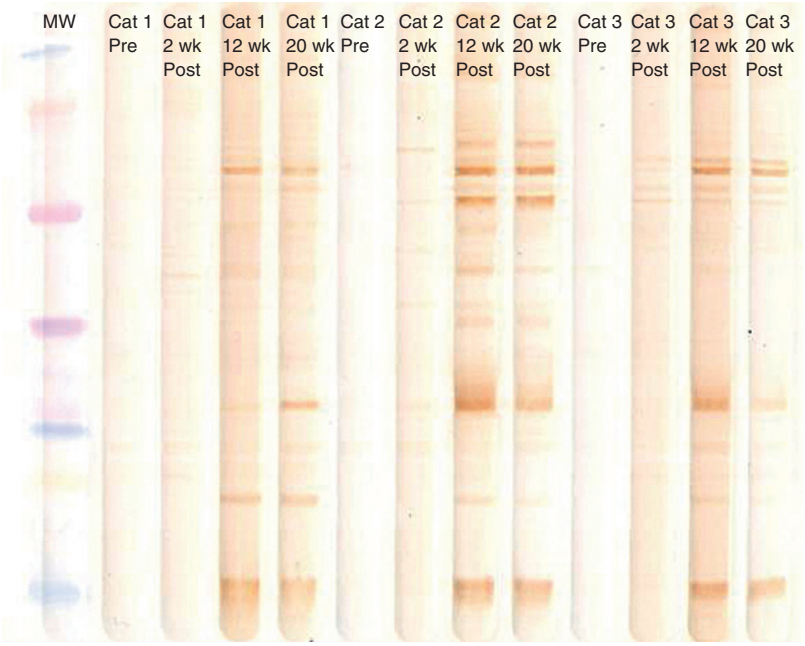


FIG 91.8
Bartonella spp. antigen recognition pattern by feline serum antibodies determined by Western blot immunoassay. *MW,* Molecular mass standards; *Post,* weeks after infection.

to the puppy or kitten in the colostrum. Most infectious agents can induce disease within 3 to 10 days of initial exposure; with many assays serum IgG antibodies are usually not detected until 1 to 2 weeks after initial exposure. On the basis of these facts, falsely negative serum antibody tests during acute disease can be common in small animal practice. If specific serum antibody testing is initially negative in an animal with acute disease, repeat antibody testing should be performed in 2 to 3 weeks to assess for seroconversion. Documentation of increasing antibody titers is consistent with recent or active infection. Assessment of both the acute and convalescent sera in the same assay on the same day is preferable to avoid interassay variation.

Sensitivity is the ability of an assay to detect a positive sample; specificity is the ability of an assay to detect a negative sample. Sensitivity and specificity vary with each assay. Positive predictive value is the ability of a test result to predict presence of disease; negative predictive value is the ability of a test result to predict absence of disease. Many of the infectious agents encountered in small animal practice infect a large percentage of the population, resulting in serum antibody production. However, they only induce disease in a small number of animals in the infected group. Examples include coronaviruses, canine distemper virus, *T. gondii, Bartonella* spp., and *Borrelia burgdorferi.* For these examples, even though assays with good sensitivity and specificity for the detection of serum antibodies are available, the predictive value of a positive test for presence of disease is extremely low. This is because antibodies are commonly detected in healthy carriers. Diagnostic utility of some serologic tests is also limited because of the presence of antibodies induced by vaccination. Examples include feline coronaviruses, some *B. burgdorferi* assays, some *Leptospira* spp. assays as well as those for FHV-1, parvoviruses, FIV calicivirus, and canine distemper virus.

The clinician should interpret positive results in serum antibody tests only as evidence of present or prior infection by the agent in question. Recent or active infection is suggested by the presence of IgM, an increasing antibody titer over 2 to 3 weeks, or seroconversion (negative antibody result on the first test and positive antibody result on convalescent testing). However, detection of recent infection based on antibody testing does not always prove disease. Conversely, failure to document recent or active infection based on serologic testing does not exclude a diagnosis of clinical disease. For example, many cats with toxoplasmosis develop clinical signs of disease after serum antibody titers have reached their plateau. The magnitude of antibody titer does not always correlate with active or clinical disease. For example, many cats with clinical toxoplasmosis have IgM and IgG titers that are at the low end of the titer scale; conversely, many healthy cats have IgG titers greater than 1:16,384 years after infection with *T. gondii.* Similarly, *Bartonella* spp. antibody magnitude does not correlate to clinical illness in cats.

BODY FLUIDS

Some infectious agents induce disease of the eyes or central nervous system (CNS). Documentation of agent-specific antibodies in aqueous humor, vitreous humor, or CSF can be used to support the diagnosis of infection of these tissues. Quantification of ocular and CSF antibodies is difficult to

interpret if serum antibodies and inflammatory disease are present, because serum antibodies leak into ocular fluids and CSF in the face of inflammation. Detection of local production of antibodies within the eye or CNS has been used to aid in the diagnosis of canine distemper virus infection, feline toxoplasmosis, and feline bartonellosis (see Chapters 94, 96, and 98). The following is a method to prove local antibody production by the eye or CNS:

$$\frac{\text{Aqueous humor or CSF-specific antibody}}{\text{Serum-specific antibody}} \times \frac{\text{Serum total antibody}}{\text{Aqueous humor or CSF total antibody}}$$

A ratio greater than 1 suggests that the antibody in the aqueous humor or CSF was produced locally. This formula has been used extensively in the evaluation of cats with uveitis. Approximately 60% of cats with uveitis in the United States have *T. gondii*–specific IgM, IgA, or IgG values greater than 1 (see Chapter 98). The technique was also used to help prove that FHV-1 and *Bartonella henselae* are causes of uveitis in cats (Powell et al., 2010).

ANTEMORTEM DIAGNOSIS OF INFECTIOUS DISEASES

As discussed, results of organism demonstration assays can be used to prove an infectious agent is still present in the body, and results of antibody assays can be used to prove exposure to infectious agents. However, many of the infectious agents of dogs and cats also colonize the host without inducing illness. Thus the majority of assays discussed are really "infectious *agent* tests" not "infectious *disease* tests." The feline hemoplasmas are great examples of this; although these agents can cause hemolytic anemia in cats and sensitive and specific PCR assays are available to amplify hemoplasma DNA, approximately 20% of healthy cats are PCR-positive. Thus a positive PCR assay result does not document clinical hemoplasmosis but merely documents current infection. The clinical diagnosis of an infectious disease usually includes the combination of the following:

- Clinical signs referable to the agent
- Serologic evidence of exposure to the agent or evidence of infection by organism demonstration techniques
- Exclusion of other causes of the clinical syndrome
- Response to treatment

However, some clinical illnesses resolve spontaneously and some antibodies can have antiinflammatory properties; this combination of findings should only be considered a tentative diagnosis rather than definitive diagnosis for an infectious disease.

Suggested Readings

Abd-Eldaim M, Beall M, Kennedy M. Detection of feline panleukopenia virus using a commercial ELISA for canine parvovirus. *Vet Ther*. 2009;10:E1.

Burgesser KM, et al. Comparison of PCR, virus isolation, and indirect fluorescent antibody staining in the detection of naturally occurring feline herpesvirus infections. *J Vet Diagn Invest*. 1999;11:122.

Dryden MW, et al. Accurate diagnosis of *Giardia* spp and proper fecal examination procedures. *Vet Ther*. 2006;7:4.

Duncan AW, Maggi RG, Breitschwerdt EB. A combined approach for the enhanced detection and isolation of *Bartonella* species in dog blood samples: pre-enrichment liquid culture followed by PCR and subculture onto agar plates. *J Microbiol Methods*. 2007;69:273.

Freisl M, et al. Faecal shedding of canine parvovirus after modified-live vaccination in healthy adult dogs. *Vet J*. 2017;219:15.

Hascall KL, et al. Prevalence of enteropathogens in dogs attending 3 regional dog parks in Northern California. *J Vet Intern Med*. 2016;30:1838.

Hutton TA, et al. Search for *Borrelia burgdorferi* in kidneys of dogs with suspected "Lyme nephritis,". *J Vet Intern Med*. 2008;22:860.

Lappin MR, et al. Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats. *J Am Vet Med Assoc*. 2002;220:38.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Lappin MR. Update on the diagnosis and management of *Toxoplasma gondii* infection in cats. *Top Companion Anim Med*. 2010;25:136.

Low HC, et al. Prevalence of feline herpesvirus 1, *Chlamydophila felis*, and *Mycoplasma* spp DNA in conjunctival cells collected from cats with and without conjunctivitis. *Am J Vet Res*. 2007;68:643.

Markovich JE, et al. Effects of canine parvovirus strain variations on diagnostic test results and clinical management of enteritis in dogs. *J Am Vet Med Assoc*. 2012;241:66.

Mekaru SR, et al. Comparison of direct immunofluorescence, immunoassays, and fecal flotation for detection of *Cryptosporidium* spp. and *Giardia* spp. in naturally exposed cats in 4 Northern California animal shelters. *J Vet Intern Med*. 2007;21:959.

Powell CC, et al. *Bartonella* species, feline herpesvirus-1, and *Toxoplasma gondii* PCR assay results from blood and aqueous humor samples from 104 cats with naturally occurring endogenous uveitis. *J Feline Med Surg*. 2010;12:923.

Rishniw M, et al. Comparison of four *Giardia* diagnostic tests in diagnosis of naturally acquired canine chronic subclinical giardiasis. *J Vet Intern Med*. 2010;24:293.

Simpson KW, et al. Adherent and invasive *Escherichia coli* is associated with granulomatous colitis in boxer dogs. *Infect Immun*. 2006;74:4778.

Veir JK, Lappin MR. Molecular diagnostic assays for infectious diseases in cats. *Vet Clin North Am Small Anim Pract*. 2010;40:1189.

CHAPTER 92

Practical Antimicrobial Chemotherapy



Antimicrobial drugs should only be administered if the index of suspicion for an infection exists. The prescribing veterinarian should also always be cognizant of the potential for selecting for antimicrobial resistant strains of bacteria, particularly when prescribing drugs also used in human beings. Veterinarians should be familiar with judicious use of antimicrobial guidelines for the species in question; the following websites can be of benefit:

1. www.avma.org/KB/Policies/Pages/The-Role-of-the-Veterinarian-in-Animal-Antimicrobial-Use.aspx
2. https://www.avma.org/KB/Policies/Pages/AAFP-AAHA-Basic-Guidelines-of-Judicious-Therapeutic-Use-of-Antimicrobials.aspx

In small animal practice, decisions to institute antimicrobial chemotherapy are made initially without the benefit of results of culture and antimicrobial susceptibility testing. In simple, first-time bacterial infections (sporadic bacterial cystitis), culture and antimicrobial susceptibility testing is often not performed, so logical empirical choices should be made. Groups like the International Society for Companion Animal Infectious Diseases (ISCAID; www.iscaid.org) and the Swedish Veterinary Medical Association (http://www.sva.se/en/antibiotics/use-for-animals-in-sweden) write and publish specific guidelines that can help veterinarians decide when to choose to use antibiotics and which to use. In life-threatening bacterial infections, materials for culture should be collected, but decisions on the choice of antimicrobials must be made before obtaining the culture results; patient survival may depend on the selection of optimal treatment regimens. For many infectious agents such as *Borrelia burgdorferi*, *Ehrlichia* spp., hemoplasmas, *Rickettsia rickettsii*, and the gastrointestinal (GI; e.g., *Giardia*) or systemic (e.g., *Toxoplasma gondii*) protozoans, the organisms are not readily grown in culture, so empirical therapy is always used.

Recognition of the most common infectious agents associated with infection of different organ systems or associated with different clinical syndromes is imperative in the empirical selection of antimicrobials (Table 92.1). The antimicrobial selected must have an appropriate mechanism of action against the suspected pathogen and must achieve an adequate concentration in infected tissues. Bacteriostatic agents may be less effective for treatment of infections in immunosuppressed animals because normal immune responses are required for the drugs to have maximal effect. The owner must be willing to administer the drug in the appropriate interval, and the drug must be affordable. Whether the antimicrobial has potential for toxicity is also an important consideration (Table 92.2). In animals with life-threatening infections, appropriate materials should be submitted for culture and antimicrobial sensitivity testing, if possible, and antibiotics administered parenterally initially. Parenteral antibiotic administration is also indicated in animals with vomiting or regurgitation. Oral administration of antibiotics can be initiated when vomiting, regurgitation, or the life-threatening condition has resolved but only if long-term treatment is needed. In life-threatening infections, administration of antimicrobial agents to treat gram-positive, gram-negative, aerobic, and anaerobic bacteria (four-quadrant approach) is indicated initially, and then therapy can be de-escalated based on clinical response and antimicrobial susceptibility testing.

Most simple, first-time bacterial infections in immunocompetent animals respond adequately to 5 to 7 days of antibiotic therapy. Therapy is generally continued for no more than 1 to 2 days past resolution of clinical signs. Chronic infections, bone infections, infections in immunosuppressed animals, infections resulting in granulomatous reactions, and those caused by intracellular pathogens are generally treated for a minimum of 1 week beyond resolution of clinical signs of disease. Please see specific sections for a more in-depth discussion of duration of therapy.

If therapeutic response to an antibiotic in 72 hours is poor and an antibiotic-responsive infectious disease is still likely, an alternative treatment should be considered. Veterinarians should always know at least two first-line drugs for each common infectious agent or infectious disease syndrome (Tables 92.3 to 92.8) and should have access to a current formulary and the websites previously cited in this chapter.

TABLE 92.1

Antibiotics Used for the Treatment of Bacterial Infections in Dogs and Cats and General Dosing Guidelines*

DRUG	MECHANISM	SPECIES	DOSAGE	ROUTE OF ADMINISTRATION
Acetamides	Protein synthesis inhibition			
Chloramphenicol		D C	25-50 mg/kg, q8h 50 mg/cat q12h	PO PO
Florfenicol		D	20 mg/kg, q6h	PO, IM
Aminoglycosides†	Protein synthesis inhibition			
Amikacin		D C	15-30 mg/kg, q24h 10-14 mg/kg, q24h	IV, IM, SC IV, IM, SC
Gentamicin		D C	9-14 mg/kg, q24h 5-8 mg/kg, q24h	IV, IM, SC IV, IM, SC
Neomycin		B	10-20 mg/kg, q6-12h	PO
Carbapenems	Cell wall synthesis inhibition			
Imipenem-cilastatin		B	5 mg/kg, q6-8h	IV, IM
Meropenem			8.5 mg/kg, q12h (SC) or q8h (IV)	IV, SC
Cephalosporins	Cell wall synthesis inhibition			
Cefadroxil (first generation)		D C	22-30 mg/kg, q12h 22 mg/kg, q24h	PO PO
Cefpodoxime (third generation)		B	5-10 mg/kg, q24h	PO
Cephalexin (first generation)		B	10-30 mg/kg, q8-12h	PO
Cefazolin (first generation)		B	20-35 mg/kg, q6-12h	SC, IM, IV
Cefoxitin (second generation)		B	15-30 mg/kg, q6-8h	SC, IM, IV
Cefotaxime (third generation)		B	20-80 mg/kg, q8-12h	SC, IM, IV
Cefovecin		B	8 mg/kg, once, can repeat in 7-14 days	SC
Ceftiofur	Naxcel	B	2.2-4.4 mg/kg, q24h	SC
Macrolides/lincosamides	Protein synthesis inhibition			
Azithromycin		D	5-10 mg/kg, on day 1 then q3d	PO
Clindamycin		D C	10 mg/kg, q12h 5-15 mg/kg, q12h	PO, SC PO, SC
Erythromycin		B	10-20 mg/kg, q8-12h	PO
Lincomycin		B	15-25 mg/kg, q12h	PO
Tylosin		B	5-15 mg/kg, q12-24h	PO
Nitroimidazole	Protein synthesis inhibition			
Metronidazole§		B B	10-25 mg/kg, q12-24h 10 mg/kg, q8h	PO IV
Ronidazole		B	30 mg/kg, q24h	PO
Penicillins	Cell wall synthesis inhibition			
Amoxicillin		B	22 mg/kg, q12h	PO
Amoxicillin and clavulanate		D C	11 mg/kg, q8-12h 62.5 mg, q8-12h	PO PO

Continued

TABLE 92.1

Antibiotics Used for the Treatment of Bacterial Infections in Dogs and Cats and General Dosing Guidelines*—cont'd

DRUG	MECHANISM	SPECIES	DOSAGE	ROUTE OF ADMINISTRATION
Ampicillin sulbactam		B	20 mg/kg, q8-12h	IV, IM
Ampicillin sodium		B	20-30 mg/kg, q8-12h	SC, IM, IV
Oxacillin		B	22-40 mg/kg, q8h	PO
Penicillin G		B	25,000- 40,000 U/kg, q12h	IV
Ticarcillin and clavulanate		D	20-50 mg/kg, q6-8h	IM, IV
Quinolones	Nucleic acid inhibition			
Enrofloxacin		D C	5-20 mg/kg, q12-24h 5.0 mg/kg, q24h	PO, IM, SC, IV PO, IM, IV
Marbofloxacin		B	2.75-5.5 mg/kg, q24h	PO
Orbifloxacin		D C	2.5-7.5 mg/kg, q24h 7.5 mg/kg, q24h	PO PO
Pradofloxacin		D C	5.0 mg/kg, q24h 7.5 mg/kg, q24hr	PO PO
Potentiated sulfas	Intermediary metabolism inhibition			
Ormetoprim-sulfadimethoxine		D	27.5 mg/kg, q24h	PO
Trimethoprim-sulfadiazine		B	15 mg/kg, q12h	PO
Tetracyclines	Protein synthesis inhibition			
Doxycycline		B	5 mg/kg, q12h OR 10 mg/kg, q24h	PO, IV
Minocycline		D C	5-10 mg/kg, q12h 50 mg/cat, q24h	PO PO
Tetracycline		B	22 mg/kg, q8-12h	PO

B, Dog and cat; *C,* cat; *D,* dog; *IM,* Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.
*The dose ranges and intervals in this table are general. Please see appropriate sections to determine the optimal dose for specific syndromes or infections.
†For parenterally administered aminoglycosides, giving the total daily dose at one time may lessen the potential for renal toxicity.
§The maximal total daily dose should be 50 mg/kg.

The following is a brief discussion of the empirical antimicrobial choices for treatment of infections of various body systems or types of infections. The reader is referred to individual chapters for further information concerning adjunct treatments.

ANAEROBIC INFECTIONS

The anaerobic bacteria with the most clinical relevance in dog and cats are *Actinomyces* spp., *Bacteroides* spp., *Clostridium* spp., *Eubacterium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., and *Porphyromonas* spp. *Actinomyces* is a facultative anaerobe; the other organisms are obligate anaerobes, which cannot use oxygen metabolically and die in its presence. Anaerobic bacteria are part of the normal flora in areas with low oxygen tension and low oxygen-reduction potential, such as the mucous membranes of the oral cavity and vagina. The origin of most anaerobic infections is the animal's own flora. Anaerobic infections are potentiated by poor blood supply, tissue necrosis, prior infection, or immunosuppression. Anaerobic bacteria produce a number of enzymes and factors that induce tissue injury and promote colonization. Most infections involving anaerobes usually have coexisting aerobic bacterial infection, which should be considered when selecting antimicrobial agents.

Anaerobic infections are commonly associated with infections of the oropharynx, central nervous system (CNS), subcutaneous space, musculoskeletal system, GI tract, liver, and female genital tract, and can be associated with clinical disease in animals with aspiration pneumonia or consolidated lung lobes. Dogs and cats with gingivitis or stomatitis, rhinitis, retrobulbar abscesses, retropharyngeal abscesses, pyothorax, otitis media or interna, CNS infection, bite

TABLE 92.2

Potential Antibiotic Toxicities

TOXICITY	ANTIBIOTIC EXAMPLES
Aminoglycosides	Renal tubular disease Neuromuscular blockade Ototoxicity
Beta lactams (penicillins and cephalosporins)	Immune-mediated diseases Vomiting or diarrhea
Chloramphenicol	Bone marrow/aplastic anemia (predominantly cats and humans) Inhibition of drug metabolism
Doxycycline	Esophagitis or strictures in cats given tablets or capsules
Macrolides/ lincosamides	Vomiting or diarrhea Cholestasis Esophagitis or strictures in cats given clindamycin capsules
Nitroimidazoles	Neutropenia (metronidazole) CNS toxicity (metronidazole and ronidazole)
Quinolones	Failure of cartilage development in young, growing animals Retinal dysfunction in some cats with some formulations (enrofloxacin in particular) Potentiation of seizures
Sulfonamides	Hepatic-cholestasis or acute hepatic necrosis (rare) Macrocytic anemia (long-term administration in cats) Thrombocytopenia Suppurative, nonseptic polyarthritis (predominantly Doberman) Keratoconjunctivitis sicca Renal crystalluria (rare)
Tetracyclines	Renal tubular disease Cholestasis Fever, particularly in cats Inhibition of drug metabolism Teeth browning in puppies and kittens (not doxycycline or minocycline)

CNS, Central nervous system.

TABLE 92.3

Empirical Antibiotic Choices for Dogs and Cats With Cutaneous and Soft Tissue Infections

INFECTIOUS AGENT	FIRST CHOICE ANTIBIOTICS
Abscesses (anaerobes)[1,2]	Amoxicillin OR Clindamycin OR Metronidazole OR First- or second-generation cephalosporins
Actinomyces	Penicillins OR Clindamycin OR Chloramphenical OR Minocycline
Gram-negative or resistant pyoderma	Quinolones
Nocardia	Penicillins (high dose) OR Minocycline OR Trimethoprim-sulfonamide OR Amikacin OR Imipenem cilastatin
Staphylococcal pyoderma	Clindamycin or lincomycin OR First-generation cephalosporins OR Amoxicillin-clavulanate OR Trimethoprim-sulfonamide

[1]Cefovecin can be considered if the cat is impossible to medicate orally.
[2]Amoxicillin-clavulanate is not generally required for simple cat bite abscesses and should be considered as a second choice drug if the need is approved by culture.



FIG 92.1
Caudal stomatitis in a cat with suspected secondary anaerobic bacterial infection.

wounds, open wounds, open fractures, osteomyelitis, peritonitis, bacterial hepatitis, pyometra, vaginitis, bacteremia, and valvular endocarditis should be suspected to be infected with anaerobes (Fig. 92.1). Anaerobic infections also should be considered in animals with a history of fighting, a foreign body, recent surgery, recent dental procedures, a history of immunosuppressive drugs or diseases, infections resistant to aminoglycosides or fluoroquinolones, lesions with a putrid odor or black discharge, a painful lesion with a serosanguineous discharge, neutrophilic inflammation with cytologically evident bacteria but negative aerobic culture, and the presence of "sulfur granules" on cytology. Flaccid paralysis *(Clostridium botulinum),* rigid paralysis and trismus *(Clostridium tetani),* and subcutaneous gas production occur in association with some anaerobic infections.

TABLE 92.4

Empirical Antibiotic Choices for Dogs and Cats With CNS or Muscle Infections

SYNDROME OR ORGANISM	FIRST CHOICE ANTIBIOTICS
Bacterial encephalitis	Chloramphenicol OR Quinolone OR Trimethoprim-sulfonamide OR Metronidazole
Bacterial otitis media/interna	Amoxicillin-clavulanate OR Clindamycin OR First-generation cephalosporin OR Quinolone OR Chloramphenicol
Hepatozoon americanum	Acute: clindamycin, AND Trimethoprim – sulfonamide Chronic: decoquinate
Neospora caninum	Clindamycin AND Trimethoprim-sulfonamide
Toxoplasma gondii	Clindamycin OR Azithromycin OR Trimethoprim-sulfonamide

TABLE 92.5

Empirical Antibiotic Choices for Dogs and Cats With Hepatic and Gastrointestinal Infections[#]

INFECTIOUS AGENT	FIRST CHOICE ANTIBIOTICS
Bacterial cholangiohepatitis	Amoxicillin or amoxicillin clavulanate OR First-generation cephalosporin OR Metronidazole AND Quinolones (if septic)
Campylobacter spp.*	Azithromycin OR Erythromycin OR Quinolone
*Clostridium perfringens**	Penicillin derivative OR Tylosin OR Metronidazole
Helicobacter spp.	Metronidazole plus amoxicillin
Hepatic encephalopathy	Neomycin OR Ampicillin OR Metronidazole
Salmonella spp.*	Ampicillin or amoxicillin AND Quinolones*
Small intestinal bacterial overgrowth*	Penicillin derivative OR Metronidazole OR Tylosin

[#]See the text for a discussion of treatment of protozoal infections.
*Usually only administered parenterally for the treatment of bacteremia/sepsis. Cases with diarrhea only generally respond to dietary changes and probiotic administration.

TABLE 92.6

Empirical Antibiotic Choices for Dogs and Cats With Bone or Joint Infections

ORGAN SYSTEM OR INFECTIOUS AGENT	FIRST CHOICE ANTIBIOTICS
Bone	
Discospondylitis	Amoxicillin-clavulanate OR Clindamycin OR First-generation cephalosporin OR Chloramphenicol OR Quinolone OR
Osteomyelitis	Amoxicillin-clavulanate OR Clindamycin OR First-generation cephalosporin OR Chloramphenicol OR Quinolone
Polyarthritis	
Anaplasma (*platys* or *phagocytophilum*)	Doxycycline OR Chloramphenicol
Bartonella spp.	Doxycycline AND Quinolone OR Azithromycin
Borrelia burgdorferi	Doxycycline OR Amoxicillin
Ehrlichia canis	Doxycycline OR Chloramphenicol OR Imidocarb
Ehrlichia ewingii	Doxycycline
L-form bacteria or *Mycoplasma*	Doxycycline OR Quinolone OR Chloramphenicol
Rickettsia rickettsii	Doxycycline OR Quinolone OR Chloramphenicol

Improving the blood supply and oxygenation of the infected area is the primary goal for treatment of anaerobic infections. Antibiotic therapy should be used concurrently with drainage or debridement. Parenteral antibiotics should be administered for several days in dogs or cats with pyothorax, pneumonia, peritonitis, or clinical signs consistent with bacteremia. Beta lactam antibiotics, chloramphenicol, clindamycin, metronidazole, and penicillin G are commonly used for the treatment of anaerobic infections (see Tables 92.1 and 92.3).

BACTEREMIA AND BACTERIAL ENDOCARDITIS

Bacteremia can be transient, intermittent, or continuous. Routine dentistry is a common cause of transient bacteremia. Immunosuppressed or critically ill animals commonly

TABLE 92.7

Empirical Antibiotic Choices for Dogs and Cats With Respiratory Infections

ORGAN SYSTEM OR INFECTIOUS AGENT	FIRST CHOICE ANTIBIOTICS
Feline acute bacterial upper respiratory infection (URI)	Doxycycline OR Amoxicillin
Feline chronic bacterial URI	Doxycycline OR Based on culture and susceptibility testing
Canine infectious respiratory disease complex (bacterial component)	Doxycycline OR Amoxicillin-clavulanate
Bacterial bronchitis (dogs or cats)	Doxycycline OR Based on culture and susceptibility testing
Uncomplicated "community acquired" pneumonia	Doxycycline OR Fluoroquinolone
Pneumonia with clinical evidence of sepsis*	Enrofloxacin# and ampicillin or clindamycin AND Adjust based on culture and susceptibility testing
Pyothorax (dogs or cats)*	Enrofloxacin# and penicillin or clindamycin+ AND Adjust based on culture and susceptibility testing

*For animals with clinical findings of life-threatening disease, the consensus of the ISCAID Working Group was to administer dual agent therapy with the potential for de-escalation of therapy based on culture and antimicrobial susceptibility testing (Lappin et al., 2017).
#Enrofloxacin is often chosen as there is a veterinary product for parenteral administration to dogs and the drug has a wide spectrum against gram-negative organisms and *Mycoplasma* spp. There are other drugs with a wide spectrum against gram-negative bacteria that can be substituted based on antimicrobial susceptibility testing.

TABLE 92.8

Empirical Antibiotic Choices for Dogs and Cats With Urogenital Infections

SYNDROME OR INFECTIOUS AGENT	FIRST CHOICE ANTIBIOTICS
Aerobic infection (uncomplicated)	Amoxicillin OR Trimethoprim-sulfonamide
Aerobic infection (complicated)	Amoxicillin OR Trimethoprim-sulfonamide AND Adjust based on culture and sensitivity results
Brucella canis	Quinolone alone OR Minocycline or doxycycline cycled with a quinolone every 2 weeks
Leptospira spp.	Penicillin G or ampicillin IV during acute phase THEN Doxycycline to eliminate carriers
Mastitis	First-generation cephalosporin OR Amoxicillin or amoxicillin-clavulanate
Mycoplasma/Ureaplasma	Doxycycline OR Quinolone
Prostatitis (gram negative agents)	Trimethoprim-sulfonamide OR Quinolone AND Adjust based on culture and susceptibility testing
Prostatitis (gram positive agents)	Clindamycin AND Adjust by culture and sensitivity results
Pyelonephritis	Fluoroquinolone AND Adjust by culture and sensitivity results
Pyometra	Trimethoprim-sulfonamide OR Quinolone and ampicillin if evidence of sepsis AND Adjust by culture and sensitivity results

IV, Intravenous; *PO,* oral.

develop intermittent bacteremia; the source of infection is commonly the genitourinary or GI systems. Continuous bacteremia occurs most frequently in association with bacterial endocarditis. Bacteremic animals can have intermittent fever, depression, and clinical signs associated with the primary organ system infected. Sepsis is the systemic response to infection and is manifested by peripheral circulatory failure (septic shock).

Staphylococcus spp., *Streptococcus* spp., *Enterococcus* spp., *Corynebacterium* spp., *Escherichia coli*, *Salmonella* spp., *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Proteus* spp., *Pasteurella* spp., *Clostridium* spp., *Fusobacterium* spp., *Bacteroides* spp., and *Bartonella* spp. organisms are commonly isolated from the blood of bacteremic animals (Sykes et al., 2006). Bacterial endocarditis is often caused by Staphylococcus aureus, E. coli, or β-hemolytic *Streptococcus* spp.; *Bartonella* spp. are now recognized as important causes of bacterial endocarditis and myocarditis (see Chapters 6, 7 and 94) in both dogs and cats (Fenimore et al., 2011).

If the source of bacteremia or bacterial endocarditis is likely from an area with mixed flora, such as the GI tract, or if the animal has life-threatening clinical signs of disease, an antibiotic or combination of antibiotics effective against gram-positive, gram-negative, aerobic, and

anaerobic organisms should be used. An aminoglycoside or quinolone for gram-negative organisms combined with ampicillin, a first-generation cephalosporin, metronidazole, or clindamycin for gram-positive and anaerobic organisms is a commonly prescribed combination treatment with the final choice made based on the likely site of bacterial entry. Second- and third-generation cephalosporins, ticarcillin combined with clavulanate, and imipenem are some of the other antimicrobial agents with a four-quadrant spectrum.

For bacteremia, without endocarditis, antimicrobial agents should be administered intravenously for at least 1 to 3 days, and clinical and clinicopathologic evidence of response documented before conversion to oral therapy. The oral treatment is selected on the basis of culture and antimicrobial susceptibility results, and duration of therapy will vary based on the source of the bacteremia. For example, if antibiotics are used parenterally in a bacteremic parvovirus puppy, continued oral therapy is not required after resolution of clinical signs of disease.

For patients with valvular endocarditis, administration of intravenous (IV) antibiotics for at least 7 to 14 days followed by subcutaneous (SC) administration for 7 to 14 days before conversion to oral therapy is recommended by some authors (Calvert and Thomason, 2012); oral antibiotic therapy may be indicated for months. Optimal treatment for valvular endocarditis from bartonellosis in dogs has not been determined, but the combination of at least two drugs is generally required. Although optimal protocols are not known, fluoroquinolones combined with doxycycline, azithromycin, or rifampin may be required in some cases (see Chapters 6 and 94). Administration of amikacin for the first 5 to 7 days of therapy is indicated for dogs or cats with endocarditis associated with bartonellosis. For aerobic or anaerobic bacteria, the blood culture can be rechecked 1 and 4 weeks after discontinuation of therapy to confirm control of the infection. Whether there is clinical utility to performing *Bartonella* spp. serology or culture after successful treatment is unclear (see Chapter 94). The prognosis in dogs and cats with bacterial endocarditis is guarded to poor because of damage to the infected heart valves (see Chapter 6).

CENTRAL NERVOUS SYSTEM INFECTIONS

Azithromycin, chloramphenicol, trimethoprim-sulfonamide, metronidazole, and the quinolones penetrate the CNS and are often considered for empirical treatment of suspected bacterial infections of this system (see Table 92.4). Anaerobic bacterial infection and rickettsial infections (*Ehrlichia* spp. and *R. rickettsii*) of the CNS occur in some cases, making chloramphenicol a logical first choice. Multiple other drugs, including penicillin derivatives, tetracyclines (doxycycline), and clindamycin, may cross into the cerebrospinal fluid (CSF) when inflammation exists. Clindamycin achieves adequate brain tissue concentrations in normal cats and can be used for the treatment of toxoplasmosis (see Chapter 98). Azithromycin, potentiated sulfas, and potentially ponazuril are alternative anti-*Toxoplasma* drugs. Optimal treatment for dogs with *Neospora caninum* infection of the CNS is unknown, but the combination of clindamycin or azithromycin with potentiated sulfas should be considered in acutely affected dogs because of the potentially poor prognosis.

GASTROINTESTINAL TRACT AND HEPATIC INFECTIONS

Oral administration of antimicrobial agents is rarely indicated for bacterial GI infections in dogs or cats because of negative effects on the GI microbiome and availability of alternate therapies like diets and probiotics (Torres-Henderson et al., 2017). However, antibiotics are sometimes needed for the treatment of small intestinal bacterial overgrowth, hepatic encephalopathy, cholangiohepatitis, hepatic abscessation, Boxer colitis, and infection by *Helicobacter* spp., *Campylobacter* spp., *Clostridium perfringens, Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., *Tritrichomonas foetus,* and *Toxoplasma gondii* (see Table 92.5). Administration of parenteral antibiotics may be indicated in dogs and cats with bacteremia from translocation of enteric flora or with *Salmonella* infection. The American College of Veterinary Internal Medicine has recently published a consensus statement on the treatment of enteropathogenic bacterial infections in dogs and cats (Marks et al., 2011). For most GI infections, dietary manipulation and probiotics could also be beneficial or resolve the diarrhea so antimicrobial agents are not required.

Giardia spp. infections often respond clinically to the administration of metronidazole, but infection is usually not eliminated. Administration of a probiotic and institution of a diet change should be considered concurrently when treating dogs or cats with suspected giardiasis (Fenimore et al., 2017). Administration of metronidazole benzoate at 25 mg/kg q12h orally (PO) for 7 days was effective in suppressing cyst shedding to below detectable limits in 26 cats (Scorza and Lappin, 2004). This is the maximal dose of metronidazole that should be used; CNS toxicity can be induced by overdosing or as a cumulative neurotoxin. Fenbendazole is the most commonly used alternate drug in dogs and cats. Febantel is also potentially effective in both species and is labelled for this use in some countries (Bowman et al., 2009). Metronidazole has the advantage of helping treat secondary small intestinal bacterial overgrowth and may have antiinflammatory effects. Nitaxoxanide also can be used to treat *Giardia* spp. infected dogs and should be considered for use when *Cryptosporidium* spp. co-infection and diarrhea are detected concurrently (Moron-Soto et al., 2017). Although ronidazole can be effective for the treatment of *Giardia* spp. infection, it is generally reserved for the treatment of *T. foetus* infections (Fiechter et al., 2012).

For *T. foetus* infections of kittens (and rarely, puppies), ronidazole at 30 mg/kg PO q24h for 14 days often eliminates

clinical signs of disease and trophozoites. However, ronidazole resistance and treatment failures have been detected (Xenoulis et al., 2013). CNS toxicity is also common with ronidazole if overdosed. Fluoroquinolones may be effective in *T. foetus* infected cats that fail to respond clinically to ronidazole.

Most dogs or cats diagnosed with cryptosporidiosis are infected by *C. canis* or *C. felis*, respectively. Although infection with these host-adapted species is common, it is unclear how many infected dogs and cats actually have diarrhea directed related to the infection. Infection studies of healthy dogs or cats rarely induce diarrhea. Thus, if other potential causes of diarrhea, like *Giardia* spp., are detected in a dog or cat positive for *Cryptosporidium*, the other cause of diarrhea should be treated first to see if the diarrhea resolves. Antibiotic treatment does not eliminate *Cryptosporidium* spp. infection; it just potentially lessens clinical signs. Tylosin (10-15 mg/kg q12h PO) has apparently been successful in lessening diarrhea and oocyst shedding in cats and dogs with diarrhea that were positive for *Cryptosporidium*. Azithromycin at 10 mg/kg PO daily for 7 days may lessen diarrhea in some dogs or cats with cryptosporidiosis. If responding after 7 days, continue treatment for at least 1 week past clinical resolution. Nitazoxanide can be considered at 75 mg/kg, PO, twice, 14 days apart in dogs with *Giardia* and *Cryptosporidium* co-infections (Moron-Soto et al., 2017).

The *Toxoplasma gondii* oocyst-shedding period can be shortened by administration of clindamycin, sulfadimethoxine, or ponazuril. However, most cats have completed the oocyst-shedding period in 7 to 14 days, so treatment is not often needed. *Cystoisospora* spp. generally respond to the administration of ponazuril at 50 mg/kg, PO, daily for 3 days (Litster et al., 2014). Use of sulfadimethoxine, other sulfa-containing drugs, or clindamycin is generally not needed.

Diarrhea associated with enteric bacterial infections generally will respond to dietary changes and administration of probiotics. If antibiotics are deemed necessary, *C. perfringens* and bacterial overgrowth generally respond to treatment with tylosin, amoxicillin, or ampicillin. Dogs or cats with suspected campylobacteriosis or salmonellosis should have fecal culture performed to determine antimicrobial sensitivity if other pets or people in the family become ill. GI signs of campylobacteriosis or salmonellosis are generally self-limited with supportive care alone, so these infections are often only treated parenterally and if systemic signs of disease (e.g., fever) exist because of rapid resistance that occurs after oral administration of antibiotics. Appropriate antibiotics for the empirical treatment of salmonellosis while awaiting susceptibility testing results include ampicillin and trimethoprim-sulfonamide; quinolones are also effective. Visible *Helicobacter* spp. infections were eliminated after administration of oral metronidazole (11-15 mg/kg PO q12h), amoxicillin (22 mg/kg PO q12h), and bismuth subsalicylate suspension (0.22 mL/kg PO q6-8h) for 3 weeks (Jergens et al., 2009). Boxer colitis is likely associated with *Escherichia coli* and is generally treated with enrofloxacin administered at 10 mg/kg PO q24h for 8 weeks (Marks et al., 2011).

Dogs or cats with apparent bacteremia or sepsis from enteric bacteria should be treated with parenteral antibiotics with a spectrum against anaerobic and gram-negative organisms. The combination of enrofloxacin with a penicillin or metronidazole is generally effective. Second-generation cephalosporins or imipenem are also appropriate choices.

The most common bacteria in one study of hepatic infections were *E. coli*, *Enterococcus*, *Streptococcus*, *Clostridium*, and *Bacteroides* (Wagner et al., 2007). Dogs or cats with hepatic infections and signs of bacteremia should be treated with antibiotics that kill gram-positive, gram-negative, and anaerobic bacteria, as previously discussed. Bacteremic hepatic infections generally respond to amoxicillin-clavulanate, first-generation cephalosporins, or metronidazole; a fluoroquinolone should be added if signs of sepsis are present. Decreasing numbers of enteric flora by oral administration of penicillins, metronidazole, or neomycin can lessen the clinical signs of hepatic encephalopathy.

MUSCULOSKELETAL INFECTIONS

Osteomyelitis and discospondylitis are commonly associated with infections by *Staphylococcus, Streptococcus, Proteus, Pseudomonas* spp., *E. coli,* and anaerobes (Siqueira et al., 2014). Recently, *Bartonella* spp. infections have also been identified in cats, dogs, and humans (Varanat et al., 2009). First-generation cephalosporins, amoxicillin-clavulanate, and clindamycin are logical antibiotics for empirical therapy of these conditions because of their spectrum of activity against the gram-positive organisms and anaerobic bacteria, and their ability to achieve high concentrations in bone (see Table 92.6). Quinolones should be used if gram-negative organisms (including *Brucella canis*) or *Bartonella* spp. infections are suspected. Antibiotic treatment should be continued for a minimum of 2 weeks beyond resolution of radiographic changes. Repeated treatment may be required, as bone infections can be difficult to eliminate.

Dogs and cats with septic polyarthritis should be treated in the same way as those with osteomyelitis, and the source of infection should be removed, if possible. *Anaplasma phagocytophilum*, *E. ewingii*, *Bartonella* spp., *Borrelia burgdorferi, Ehrlichia* spp., L-form bacteria, *Mycoplasma* spp., *Rickettsia rickettsii,* and other chronic infections can induce nonseptic, suppurative polyarthritis from local infection in the joints or immune complexes. Occasionally, morulae of *A. phagocytophilum* or *E. ewingii* are identified cytologically in the joint fluid or in circulating neutrophils. In general, the cytologic findings in joint fluid induced by these agents are similar to those of immune-mediated polyarthritis. For this reason, doxycycline is a logical empirical antibiotic choice for dogs with nonseptic, suppurative polyarthritis pending the results of further diagnostic tests. Amoxicillin and cefovecin are alternative drugs for the treatment of *B. burgdorferi* infection (Wagner et al., 2015) but are not effective for the treatment of most other infections associated with polyarthritis and so should be second choices to doxycycline.

Fluoroquinolones can also be used for *R. rickettsii, Mycoplasma,* and L-form bacterial infections. *Bartonella* spp. infections generally are treated with two antimicrobial agents as discussed in the bacteremia section.

Muscle disease from *T. gondii* infection often resolves during treatment with clindamycin hydrochloride, azithromycin, or trimethoprim-sulfonamide (see Table 92.4). Ponazuril at 20 mg/kg, PO, once daily may also be effective for the treatment of toxoplasmosis. Optimal duration of therapy is unknown, and no drug consistently eliminated *T. gondii* from the tissues. Although many dogs with neosporosis die, some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine; sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine; or clindamycin alone. For dogs with acute *Hepatozoon americanum* infection, the combination of trimethoprim-sulfadiazine, pyrimethamine, and clindamycin for 14 days is highly successful; the use of decoquinate at 10 to 20 mg/kg q12h with food lessens the likelihood of recurrence of clinical disease and prolongs survival time.

RESPIRATORY TRACT INFECTIONS

Antimicrobial use guidelines (Lappin et al., 2017) for treatment of infectious respiratory diseases in dogs and cats were recently published by the Antimicrobial Guidelines Working Group of the ISCAID. The Working Group made first-choice antimicrobial recommendations for acute bacterial upper respiratory infections (URIs) in cats, chronic bacterial URIs in cats, bacterial causes of the canine infectious respiratory disease syndrome (CIRDS), bronchitis in dogs and cats, pneumonia in dogs and cats, and pyothorax in dogs and cats (see Table 92.7).

Allergies and irritants most commonly induce serous nasal discharge, and antibiotics are not indicated in the management of these syndromes. Many causes of epistaxis are local to the nasal cavity or sinuses and include trauma, foreign bodies, masses, and fungal disease that do not respond to antibiotic therapy. However, diseases associated with vasculitis also are associated with epistaxis; *B. vinsonii, E. canis,* and *R. rickettsii* are implicated most frequently in this syndrome. Administration of doxycycline may result in resolution of disease if these organisms are involved. See Chapters 94 and 95 for a complete discussion of the diagnosis and treatment of these infectious agents.

If mucopurulent nasal discharge is present in dogs or cats with other clinical manifestations of upper respiratory disease like congestion and sneezing, there is usually a bacterial component. Primary bacterial pathogens include *Bordetella bronchiseptica, Chlamydia felis* (cats), and some *Mycoplasma* spp., *Pasteurella* spp., and *Streptococcus equi*, var. *zooepidemicus* (dogs). Many dogs or cats with suspected bacterial URIs have bacterial infections secondary to other primary diseases, including foreign bodies, viral infections, tooth root abscesses, neoplasms, trauma, and fungal infections. In these examples, the normal respiratory flora that usually only colonizes the tissues can be associated with infection. *Pasteurella* spp. *Staphylococcus* spp., *Streptococcus* spp., *Mycoplasma* spp., and a variety of gram-negative organisms and anaerobic bacterial can be involved. Because the upper respiratory passageways have a normal flora, it is difficult to assess the results of culture and antimicrobial susceptibility testing or polymerase chain reaction results from samples collected from these tissues. The source of the primary insult should always be removed if possible; see Chapter 14 for a review of respiratory diagnostic techniques.

The ISCAID Working Group recommends doxycycline at 5 mg/kg, PO, q24h or 10 mg/kg, PO, q24h for the initial treatment of cats with acute bacterial URI and dogs with suspected bacterial causes of the CIRDS (see Table 92.7). Amoxicillin in cats and amoxicillin-clavulanate in dogs were considered the alternate empirical choices. If clinical signs have not resolved within 10 days, the ISCAID Working Group guidelines suggests performing a complete workup, potentially including deep cultures, before using other antibiotics like azithromycin, amoxicillin-clavulanate, cefovecin, or fluoroquinolones (Lappin et al., 2017).

The ISCAID Working Group recommended that dogs or cats with suspected bacterial bronchitis be administered doxycycline while waiting for bacterial culture and antimicrobial susceptibility results. Dogs or cats with uncomplicated community acquired pneumonia should be administered doxycycline. Common bacteria associated with pneumonia in dogs include *E. coli, Klebsiella* spp., *Pasteurella* spp., *Pseudomonas* spp., *B. bronchiseptica, Streptococcus* spp., *Staphylococcus* spp., and *Mycoplasma* spp. In cats, *Bordetella, Pasteurella,* and *Mycoplasma* organisms are commonly isolated. Aspiration of GI contents is a common cause of bacterial pneumonia with a mixed population of bacteria. Multiple species of bacteria are typically cultured from dogs and cats with bronchopneumonia. *Bordetella bronchiseptica* and *S. equi* var. *zooepidemicus* are the most important primary pathogen in dogs and cats; most other bacteria colonize after airways have been previously damaged. If consolidated lung lobes are detected radiographically, an anaerobic infection should be assumed. Dogs or cats with pneumonia and signs of sepsis should be administered a fluoroquinolone combined with a penicillin or clindamycin parenterally while finishing the diagnostic workup and then de-escalate therapy as indicated (Lappin et al., 2017). Optimal duration of treatment for bacterial pneumonia is unknown, but the consensus at this time is to reevaluate dogs and cats with pneumonia no later than 10 to 14 days after starting treatment. Additional studies are needed to determine whether the current recommendations for a minimum of 4 weeks of therapy are needed.

Whether species of *Mycoplasma* infecting dogs and cats are capable of being primary respiratory pathogens is unknown. *Chlamydia felis* in cats is not a common cause of lower respiratory tract infection. *Yersinia pestis* causes pneumonia in cats in Western states (see Chapter 99);

aminoglycosides, tetracycline derivatives, and quinolones can be used successfully in those cats.

Toxoplasma gondii occasionally causes pneumonia in neonatally infected, transplacentally infected, and immunosuppressed cats and dogs (see Chapter 98). Clindamycin or potentiated sulfas should be used if toxoplasmosis is suspected. Azithromycin may also be effective for the treatment of toxoplasmosis. *Neospora caninum* has occasionally been associated with pneumonia in dogs and should be treated with a combination of clindamycin and potentiated sulfas.

If pyothorax is attributable to penetration of foreign material from an airway or esophagus into the pleural space, thoracotomy is usually required for removal of devitalized tissue and the foreign body (see Chapter 24). Pyothorax occasionally results from hematogenous spread of bacteria to the pleural space; this may be common in cats. Pleural lavage through chest tubes is the most effective treatment for patients with pyothorax and no obvious foreign material. Most dogs and cats with pyothorax have mixed aerobic and anaerobic bacterial infections. Animals with pyothorax and clinical signs of bacteremia should initially be administered a combination of fluoroquinolones and a penicillin or clindamycin, and then the antibiotic therapy should be adjusted based on the culture, susceptibility results, and clinical response (Lappin et al., 2017). Treatment duration is determined by clinical responses and repeated thoracic radiographs, and is usually at least 4 weeks duration.

SKIN AND SOFT TISSUE INFECTIONS

Staphylococcus pseudointermedius is the most common cause of pyoderma in dogs and cats. Any organism, including gram-negative types, can induce deep pyoderma. Most soft tissue infections, including open wounds and abscesses, are infected with a mixed population of bacteria; the aerobic and anaerobic flora from the mouth are often involved. Recommended empirical antibiotic choices for routine cases of pyoderma and soft tissue infections are listed in Table 92.3. Guidelines for the diagnosis and treatment of superficial bacterial folliculitis have been published that discuss optimal topical and systemic treatments (Hillier et al., 2014). When systemic treatment is deemed appropriate, the first-tier drugs recommended included clindamycin, lincomycin, first-generation cephalosporins, amoxicillin-clavulanate, or potentiated sulfas. Other drugs to be used as second and third tiers (third-generation cephalosporins, doxycycline, minocycline, chloramphenicol, fluoroquinolones) should also be based on antimicrobial susceptibility results (Hillier et al., 2014). Fluoroquinolones are often the antibiotic class of choice for the treatment of gram-negative infections.

The World Association for Veterinary Dermatology published recommendations for the approach to methicillin-resistant staphylococcal infections (Morris et al., 2017). Many key points were presented, including use of topical therapy with known antistaphylococcal efficacy as the primary treatment modality for any surface or superficial pyoderma involving methicillin-resistant staphylococcal infections, and empirical drug selection for systemic therapy is always contraindicated when a methicillin-resistant staphylococcal infection is suspected due to the high prevalence of multidrug resistance within these strains. The case management of suspect cases should always be guided by antimicrobial sensitivity results.

Other explanations for cutaneous and soft tissue infections that fail to respond to routine treatments include infections with gram-negative bacteria, L-form bacteria, *Mycoplasma* spp., *Mycobacterium* spp., systemic fungi, or *Sporothrix* spp. (see Fig. 99.3), These cases should undergo further diagnostic testing and appropriate treatments administered. If not previously done, microscopic examination of tissue or pustule aspirates should be performed for the presence of *Sporothrix* organisms and bacteria morphologically similar to *Mycobacterium* spp. After surgical preparation of the skin, deep tissues should be obtained for aerobic, anaerobic, *Mycoplasma,* fungal, and atypical *Mycobacterium* spp. culture (see Chapter 91).

UROGENITAL TRACT INFECTIONS

Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats were recently published by the Antimicrobial Guidelines Working Group of the ISCAID (Weese et al., 2011; Weese et al., 2017). The Working Group recommended that amoxicillin or trimethoprim-sulfonamide be prescribed to dogs or cats with uncomplicated infections (sporadic bacterial cystitis). Dogs or cats with complicated infections should be administered amoxicillin or trimethoprim-sulfonamide and then have the antimicrobial therapy guided by results of culture and antimicrobial susceptibility results. Classically, antibiotics were administered for 7 to 14 days to animals with simple urinary tract infections. However, recent evidence suggests short-term protocols could be effective. For example, in a recent study of dogs with simple urinary tract infections, administration of enrofloxacin at 18 to 20 mg/kg PO q24h for 3 days or amoxicillin-clavulanic acid at 13.75 to 25 mg/kg PO q12h for 14 days had similar microbiologic cure rates (Westropp et al., 2012). There is no indication for repeat urinalysis or culture for simple infections if clinical signs resolve and the drugs are administered as prescribed (Weese et al., 2011; Weese et al., 2017). For cases with complicated infections, antimicrobial therapy should be administered for at least 4 weeks with monitoring of clinical response, and urine culture and susceptibility testing (usually 5 days after stopping treatment). It is possible that shorter duration of therapy for complicated cases could be considered.

All dogs and cats with urinary tract infection and azotemia should be assumed to have pyelonephritis and be treated accordingly, even if further diagnostic procedures are not performed. The ISCAID Working Group recommends administration of a fluoroquinolone initially with adjustments based on susceptibility results. If *Leptospira* spp.

infection is suspected and oral doxycycline cannot be administered, intravenous administration of ampicillin at 20 mg/kg IV q6h is indicated followed by doxycycline to eliminate the renal carrier phase (Sykes et al., 2011). Treatment for pyelonephritis and other chronic, complicated urinary tract infections should be continued for at least 4 to 6 weeks. Urinalysis, culture, and antimicrobial susceptibility testing should be performed 7 days after starting treatment and 1 week after cessation of treatment. It is possible that shorter duration of therapy for complicated cases could be considered. Some infections cannot be eliminated and require administration of pulse or continuous antibiotic therapy, but an optimal protocol will need to be developed on a case-by-case basis.

Mycoplasma and *Ureaplasma* infections have been documented in dogs with clinical signs of urinary tract infections (Ulgen et al., 2006). If poor response to penicillin derivatives, cephalosporins, or trimethoprim-sulfonamide is observed, culture for *Mycoplasma* spp. should be performed. Chloramphenicol, doxycycline, or quinolone treatment should be effective for *Mycoplasma* and *Ureaplasma* infections.

Most bacterial prostatic infections involve gram-negative bacteria. During acute prostatitis, almost all antibiotics penetrate the prostate well because of inflammation; trimethoprim-sulfonamide or veterinary fluoroquinolones are usually effective. After reestablishment of the blood-prostate barrier in dogs with chronic prostatitis, the acidic prostatic fluid allows only the basic antibiotics (pK_a less than 7) to penetrate well (see Table 92.8). Chloramphenicol, because of its high lipid solubility, also penetrates prostatic tissue well. In acute prostatitis, administration of acidic antibiotics, including penicillins and first-generation cephalosporins, may initially penetrate well, lessening clinical signs of disease but not eliminating the infection. This predisposes to chronic bacterial prostatitis and prostatic abscessation. For this reason, the use of penicillins and first-generation cephalosporins is contraindicated for the treatment of urinary tract infections in male dogs. In dogs with chronic prostatitis, antimicrobial therapy should be continued for at least 6 weeks and should be based on culture and sensitivity results of urine or prostatic aspirates. Most agents isolated are susceptible to trimethoprim-sulfonamide or veterinary fluoroquinolones. Urine and prostatic fluid should be cultured 7 days and 28 days after therapy. Whether shorter durations of treatment could be considered is unknown.

Brucella canis causes a number of clinical syndromes in dogs, including epididymitis, orchitis, endometritis, stillbirths, abortion, discospondylitis, and uveitis. Ovariohysterectomy or neutering lessens contamination of the human environment. (See Chapter 99 for a discussion of the zoonotic potential.) Long-term antibiotic administration usually does not lead to a complete cure (Wanke et al., 2006). Some dogs become antibody-negative, but the organism can still be cultured from tissues. Several antibiotic protocols have been suggested for dogs with brucellosis (see Table 92.8). However, owners should be carefully counselled concerning zoonotic risks before initiating treatment.

Vaginitis generally results from overgrowth of normal flora secondary to primary diseases, including herpesvirus infection, urinary tract infection, foreign bodies, vulvar or vaginal anomalies, vaginal or vulvar masses, or urinary incontinence. In dogs and cats with bacterial vaginitis from overgrowth of flora and resolution of the primary insult, broad-spectrum antibiotics, including amoxicillin, trimethoprim-sulfonamide, first-generation cephalosporins, tetracycline derivatives, and chloramphenicol, are typically successful. Because *Mycoplasma* and *Ureaplasma* organisms are part of the normal vaginal flora, providing a clinical disease association is virtually impossible; positive cultures do not confirm disease because of the organism (see Chapter 94). Hence a positive vaginal culture from an asymptomatic dog (excluding *B. canis*) is meaningless.

In all dogs and cats with pyometra, ovariohysterectomy or medically induced drainage of the uterus is imperative. Antibiotic treatment is for the bacteremia that commonly occurs concurrently (i.e., *E. coli* and anaerobes). Animals with clinical signs of bacteremia or sepsis should be treated with a four-quadrant antibiotic choice (see Table 92.5). Broad-spectrum antibiotics with efficacy against *E. coli,* such as potentiated sulfas or amoxicillin-clavulanate, are appropriate empirical choices pending the results of culture and antimicrobial susceptibility testing. Potentiated sulfas and the quinolones commonly are effective for *E. coli* but are not as effective as other drugs for the treatment of anaerobic infections in vivo.

Ampicillin, amoxicillin, and first-generation cephalosporins achieve good concentrations in milk and are relatively safe for the neonate; therefore they can be used in the empirical treatment of mastitis. Chloramphenicol, quinolones, and tetracycline derivatives should be avoided because of potential adverse effects on the neonate.

Suggested Readings

Bowman DD, et al. Treatment of naturally occurring, asymptomatic *Giardia* sp. in dogs with Drontal Plus flavour tablets. *Parasitol Res*. 2009;105(suppl 1):S125–S134.

Calvert CA, Thomason JD. Cardiovascular infections. In: Greene CE, eds. *Infectious Diseases of the Dog and Cat*. 4th ed. Elsevier; 2012:912–923.

Fenimore A, et al. *Bartonella* spp. DNA in cardiac tissues from dogs in Colorado and Wyoming. *J Vet Intern Med*. 2011;25:613–616.

Fenimore A, et al. Evaluation of metronidazole with and without *Enterococcus faecium* SF68 in shelter dogs with diarrhea. *Top Companion Anim Med*. 2017;32:100.

Fiechter R, et al. Control of *Giardia* infections with ronidazole and intensive hygiene management in a dog kennel. *Vet Parasitol*. 2012;187:93.

Hillier A, et al. Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). *Vet Dermatol*. 2014;25:163.

Jang SS, et al. Organisms isolated from dogs and cats with anaerobic infections and susceptibility to selected antimicrobial agents. *J Am Vet Med Assoc*. 1610;210:1997.

Jergens AE, et al. Fluorescence in situ hybridization confirms clearance of visible *Helicobacter* spp. associated with gastritis in dogs and cats. *J Vet Intern Med*. 2009;23:16–23.

Jessen LR, et al. Effect of antibiotic treatment in canine and feline urinary tract infections: a systematic review. *Vet J*. 2015;203:270.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Litster AL, et al. Use of ponazuril paste to treat coccidiosis in shelter-housed cats and dogs. *Vet Parasitol*. 2014;202:319.

Marks SL, et al. Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. *J Vet Intern Med*. 2011;25:1195.

Moron-Soto M, et al. Efficacy of nitazoxanide to treat natural *Giardia* infections in dogs. *Parasit Vectors*. 2017;10:52.

Morris DO, et al. Recommendations for approaches to meticillin-resistant staphylococcal infections of small animals: diagnosis, therapeutic considerations and preventative measures: clinical Consensus Guidelines of the World Association for Veterinary Dermatology. *Vet Dermatol*. 2017;28(3):304–e69.

Scorza V, Lappin MR. Metronidazole for treatment of giardiasis in cats. *J Fel Med Sung*. 2004;6:157.

Siqueira EG, et al. Exogenous bacterial osteomyelitis in 52 dogs: a retrospective study of etiology and in vitro antimicrobial susceptibility profile (2000-2013). *Vet Q*. 2014;4:201.

Stull JW, Weese JS. Hospital-associated infections in small animal practice. *Vet Clin North Am Small Anim Pract*. 2015;45:217.

Sykes JE, et al. Evaluation of the relationship between causative organisms and clinical characteristics of infective endocarditis in dogs: 71 cases (1992.2005). *J Am Vet Med Assoc*. 2006;228:1723.

Sykes JE, et al. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25:1.

Torres-Henderson C, et al. Effect of *Enterococcus faecium* strain SF68 on gastrointestinal signs and fecal microbiome in cats administered amoxicillin-clavulanate. *Top Companion Anim Med*. 2017;32:104.

Torres-Henderson C, et al. Pilot study to evaluate the role of *Mycoplasma* species in cat bite abscesses. *J Feline Med Surg*. 2014;16:997.

Ulgen M, et al. Urinary tract infections due to *Mycoplasma canis* in dogs. *J Vet Med A Physiol Pathol Clin Med*. 2006;53:379.

Varanat M, et al. Recurrent osteomyelitis in a cat due to infection with *Bartonella vinsonii* subsp. *berkhoffii* genotype II. *J Vet Intern Med*. 2009;23:1273.

Wagner KA, et al. Bacterial culture results from liver, gallbladder, or bile in 248 dogs and cats evaluated for hepatobiliary disease: 1998-2003. *J Vet Intern Med*. 2007;21:417.

Wagner B, et al. Comparison of effectiveness of cefovecin, doxycycline, and amoxicillin for the treatment of experimentally induced early Lyme borreliosis in dogs. *BMC Vet Res*. 2015;11:163.

Wanke MM, et al. Use of enrofloxacin in the treatment of canine brucellosis in a dog kennel (clinical trial). *Theriogenology*. 2006;66:1573.

Weese JS, et al. Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats: Working Group of the International Society for Companion Animal Infectious Diseases. *Vet Med Int*. 2011;2011:263768. doi:10.4061/2011/263768.

Weese JS, et al. International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats. *Vet J*. 2017;247:8–25.

Westropp JL, et al. Evaluation of the efficacy and safety of high dose short duration enrofloxacin treatment regimen for uncomplicated urinary tract infections in dogs. *J Vet Intern Med*. 2012;26:506–512.

Walther B, et al. Multidrug-resistant opportunistic pathogens challenging veterinary infection control. *Vet Microbiol*. 2017;200:71.

Xenoulis PG, et al. Intestinal *Tritrichomonas foetus* infection in cats: a retrospective study of 104 cases. *J Feline Med Surg*. 2013;15:1098.

CHAPTER 93

Prevention of Infectious Diseases



Preventing infections is always preferred over treating infections. Avoiding exposure is the most effective way to prevent infections. Most infectious agents of dogs and cats are transmitted in fecal material, respiratory secretions, reproductive tract secretions, or urine; by bites or scratches; or by contact with vectors or reservoirs. Some infectious agents such as feline herpesvirus 1 (FHV-1), *Bordetella bronchiseptica,* and influenza viruses can be transmitted by direct contact with clinically normal, infected animals. Many infectious agents are environmentally resistant and can be transmitted by contact with a contaminated environment (fomites). The avoidance of zoonotic transfer of infectious agents is extremely important because some zoonotic diseases, such as plague and rabies, are life-threatening (see Chapter 99). Recognition of risk factors associated with infectious agents is the initial step in the prevention of infectious diseases. Veterinarians should strive to understand the biology of each infectious agent so that they can counsel clients and staff on the best strategies for prevention.

There are many parasitic diseases that are of importance to pets as well as their owners due to risk of zoonotic transfer, like ascarids and hookworms. There are also multiple vector-borne diseases of importance in dogs and cats, with those associated with fleas or ticks being most common in most countries. Thus one of the most important parts of any infectious disease prevention program is to provide parasite control. As discussed in Chapter 99, routine deworming and vector control are indicated for both indoor and outdoor pets. Use of the Companion Animal Parasite Council guidelines is an easy and effective way to help avoid internal and external parasitic diseases (www.capcvet.org).

Vaccines available for some infectious agents can either prevent infection (canine distemper, canine parvovirus, feline panleukopenia) or lessen clinical illness (respiratory agents) when infection occurs. Use of vaccine guidelines from the American Association of Feline Practitioners (AAFP; www.catvets.com), the American Animal Hospital Association (www.aahanet.org), and the World Small Animal Veterinary Association (www.wsava.org) can help practicing veterinarians made logical vaccination protocols for individual pets. However, in most countries a significant proportion of dogs and cats are not vaccinated. For example, in a recent study in Great Britain, only 77.9% of dogs, cats, and rabbits seen at veterinary clinics were vaccinated (Sanchez-Vizcaino, 2018). The veterinary industry needs to continue to strive to increase vaccine compliance, particularly for rabies. In addition, vaccines are not uniformly effective, are not available for all pathogens, and sometimes induce serious adverse effects. Therefore the development of sound biosecurity procedures is also paramount to avoid exposure to infectious agents when developing a preventive medicine program.

BIOSECURITY PROCEDURES FOR SMALL ANIMAL HOSPITALS

Most hospital-borne infections (nosocomial) can be prevented by following simple biosecurity guidelines (Box 93.1). The following general guidelines to consider were adapted from those used at the Veterinary Medical Center at Colorado State University (http://csuvets.colostate.edu/biosecurity). A number of excellent reviews are also available (Stull et al., 2015; Stull and Weese, 2015).

GENERAL BIOSECURITY GUIDELINES

Contaminated hands are the most common source of infectious agent transmission in the hospital environment. Fingernails of personnel having patient contact should be cut short. Hands should be washed before and after attending to each individual animal as follows. Collect clean paper towels and use to turn on water faucets; wash hands for 30 seconds with antiseptic soap, being sure to clean under fingernails; rinse hands thoroughly; use the paper towel to dry hands; and use the paper towel to turn off the water faucets. Use of antiseptic lotion should be encouraged. Personnel should not touch patients, clients, food, doorknobs, drawer or cabinet handles or contents, equipment, or medical records with soiled hands or gloves.

All employees should wear an outer garment such as a smock or scrub suit when attending to patients. Footwear should be protective, clean, and cleanable. A minimum of two sets of outer garments should always be available, and

BOX 93.1

General Hospital Biosecurity Guidelines

- Wash hands before and after each patient contact.
- Wear gloves when handling patients when zoonotic diseases are on the list of differential diagnoses.
- Minimize contact with hospital materials (instruments, records, door handles, etc.) while hands or gloves are contaminated.
- Always wear an outer garment, such as a smock or scrub shirt, when handling patients.
- Change outer garments when soiled by feces, secretions, or exudates.
- Clean and disinfect equipment (stethoscopes, thermometers, bandage scissors, etc.) after each use with animals likely to have an infectious disease.
- Examination tables, cages, and runs should be cleaned and disinfected after each use.
- Litter boxes and dishes should be cleaned and disinfected after each use.
- Place animals with suspected infectious diseases into an examination room or an isolation area immediately on admission into the hospital.
- Treat animals with suspected infectious diseases as outpatients if possible.
- Procedures that use general hospital facilities, such as surgery and radiology, should be postponed until the end of the day if possible.
- Do not consume fluids or drink in areas where patient care is provided.

they should be changed immediately after contamination with feces, secretions, or exudates. Equipment such as stethoscopes, pen lights, thermometers, bandage scissors, lead ropes, percussion hammers, and clipper blades are suspected to serve as fomites and should be cleaned and disinfected after each use with animals likely to have a transmissible infectious disease (Haun et al., 2016). Disposable thermometer covers or thermometers should be used.

To avoid zoonotic transfer of infectious diseases, food or drink should not be consumed in areas where animal care is provided. All areas where animals are examined or treated should be cleaned and disinfected immediately after use, irrespective of infectious disease status of the individual animal.

PATIENT EVALUATION

Prevention of infectious diseases starts with the front desk personnel. Staff should be trained to recognize the presenting complaints for the infectious agents in the geographic area of the hospital. Animals with gastrointestinal signs, respiratory signs, or ectoparasites are the most likely to be contagious. Infectious gastrointestinal disease should be suspected in all dogs and cats with small- or large-bowel diarrhea whether the syndrome is acute or chronic. Infectious respiratory disease should be suspected in all dogs and cats with sneezing or coughing (Lappin et al., 2017). The index of suspicion for infectious diseases is increased for dogs or cats with acute disease and fever, particularly if the animal is from a crowded environment such as a breeding facility, boarding facility, or shelter.

Front desk personnel should indicate clearly on the hospital record that gastrointestinal signs, respiratory signs, or ectoparasites are present. If the presenting complaint is known before admission into the hospital, an optimal method would be to meet the client in the parking area to determine the infectious disease risk before the pet enters the hospital. If an infectious gastrointestinal or respiratory disease is suspected, the animal should be transported (i.e., not allowed to walk on the premises) to an examination room or the isolation facility. If a patient with acute gastrointestinal or respiratory disease or ectoparasites is presented directly to the reception desk, the receptionist should contact the receiving clinician, technician, or student immediately and coordinate placement of the animal in an examination room to minimize hospital contamination. Animals with suspected infectious diseases should be treated as outpatients if possible. If hospitalization is required, the animal should be transported to the appropriate housing area by the shortest route possible, preferably with a gurney to lessen hospital contamination. The gurney and any hospital materials in contact with potentially contaminated employees (including examination tables and doorknobs) should be immediately cleaned and disinfected as previously mentioned.

HOSPITALIZED PATIENTS

If possible, all animals with suspected infectious diseases, such as *Salmonella* spp., *Campylobacter* spp., parvovirus infection, canine infectious respiratory disease complex (CIRDC), acute feline upper respiratory disease syndrome, rabies, or plague, should be housed in an isolated area of the hospital. The number of staff members entering the isolation area should be kept to a minimum. On entry into the isolation area, outerwear should be left outside, and surgical booties or other disposable shoe covers should be placed over the shoes. Alternatively, a foot bath filled with disinfectant should be placed by the exit and used when leaving the area. The room should be entered, and a disposable gown (or smock designated for the patient) and latex gloves should be put on. A surgical mask should be worn when attending dogs or cats with suspected plague or tularemia, and extreme care should be taken to avoid being bitten. Separate equipment and disinfectant supplies should be used in the isolation area.

All biologic materials submitted to clinical pathology laboratories or diagnostic laboratories from animals with suspected or proven infectious diseases should be clearly marked as such. Fecal material should be placed in a plastic, screw-capped cup with a tongue depressor or while the clinician is wearing gloves. Place the cup in a clean area and place the lid on with a clean, gloved hand. Remove the used gloves and place the cup in a second bag clearly marked

with the name of the infectious disease suspected. The outer surface of the bag should be disinfected before leaving the isolation area.

Disposable materials should be placed in plastic bags in the isolation area. The external surfaces of the bags should be sprayed with a disinfectant before being removed from the isolation area. After attending to the patient, contaminated equipment and surfaces should be cleaned and disinfected, and contaminated outer garments and shoe covers should be removed. Hands should be washed after discarding the contaminated outerwear. Dishes and litter pans should be cleansed thoroughly with detergent before returning them to the central supply area of the hospital. Optimally, materials such as outerwear and equipment to be returned to the central supply area should be placed in plastic bags and sprayed with a disinfectant before transport. Procedures requiring general hospital facilities such as surgery and radiology should be postponed to the end of the day, if possible, and the contaminated areas disinfected before use with other animals. Animals should be discharged by the shortest path to the parking lot possible.

Some animals with infectious diseases can be maintained in the general hospital boarding or treatment areas with special management techniques. For example, cats positive for the feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) should not be placed in the isolation area, if possible, to avoid exposing them to other infectious agents. Because neither of these two viruses is transmitted by aerosolization, cats with these infectious diseases can be housed in close proximity to other cats. The cages should be labeled appropriately, and the infected cats should not be caged next to or above seronegative cats. In addition, no direct contact or sharing of litter boxes or food bowls should occur between infected and naïve cats.

BASIC DISINFECTION PROTOCOLS

To lessen the spread of potential infectious agents, hospitalized animals should never be moved from cage to cage. The key to effective disinfection is cleanliness. Cage papers and litter boxes soiled by feces, urine, blood, exudates, or respiratory secretions should be removed and placed in trash receptacles. Bulk fecal material should also be placed in trash receptacles.

Many infectious agents are resistant to disinfectants or require prolonged contact time to be inactivated (Greene, 2012). Contaminated surfaces, including the cage or run floors, walls, ceiling, door, and door latch, should be wetted thoroughly with a disinfectant that is then blotted with clean paper towels or mops. Surfaces should be in contact with the disinfectant for 10 to 15 minutes if possible, particularly if known infectious agents are present. Soiled paper towels should be placed in trash receptacles. If infectious disease is suspected, the trash bags should be sealed, the surface of the bag sprayed with a disinfectant, and the trash bags discarded.

Contaminated surfaces in examination rooms should be cleaned to remove hair, blood, feces, and exudates. Examination tables, countertops, floors, canister lids, and water taps should be saturated with disinfectant for 10 minutes. Surfaces should be blotted with paper towels until dry, and the soiled towels should be placed in a trash receptacle. Urine or feces on the floor should be contained with paper towels, blotted, and placed in trash receptacles. The soiled area of the floor should be mopped with disinfectant.

Disinfectants are relatively effective for viral and bacterial agents but require high concentrations and long contact times to kill parasite eggs, cysts, and oocysts. Cleanliness is the key to lessening hospital-borne infection with these agents; detergent or steam cleaning inactivates most of these agents. Litter pans and dishes should be thoroughly cleaned with detergent and scalding water.

BIOSECURITY PROCEDURES FOR CLIENTS

Housing animals indoors in a human environment to prevent exposure to other animals, fomites, or vectors is the optimal way to prevent infectious diseases. However, some infectious agents can be carried into the home environment with the owners, by other pets that are allowed outdoors, by vectors, or by paratenic or transfer hosts. Although most infections occur in both immunocompromised and immunocompetent animals, clinical disease is often more severe in immunocompromised animals. Puppies, kittens, old or debilitated animals, animals with immunosuppressive diseases (e.g., hyperadrenocorticism, diabetes mellitus, cancer), animals with concurrent infections, and animals treated with glucocorticoids or cytotoxic agents are examples of immunocompromised patients. Avoiding exposure to infectious agents in this group is particularly important because of the potential for increased susceptibility to disease. These animals may also be less likely to have appropriate responses to immunization. Kennels, veterinary hospitals, dog parks, dog and cat shows, and shelters have an increased likelihood for infectious agent contact because of the concentration of potentially infected animals and should be avoided when possible. Areas such as parks are common sources of infectious agents that survive for long periods in the environment; parvoviruses and enteric parasites like *Giardia* spp. are classic examples (Hascall et al., 2016). Owners should avoid bringing new animals with unknown histories into a home environment with other pets until the new animal is evaluated by a veterinarian for infectious disease risk. If people are in contact with animals outside the home environment, they should wash their hands before contact with their own pet. The owner should consult the veterinarian concerning vaccination protocols and other preventive medical procedures most indicated for each individual patient. Of most importance are flea control (*Bartonella* spp., *Rickettsia felis*); tick control (*Borrelia burgdorferi,* rickettsial agents); *Dirofilaria imitis* prevention; and strategic deworming for roundworms and hookworms.

VACCINATION PROTOCOLS

VACCINE TYPES

Vaccines are available for some infectious agents of dogs and cats and can be administered to prevent infection or limit disease depending on the agent. Vaccination can stimulate humoral, mucosal, or cell-mediated immune responses. Humoral immune responses are characterized by the production of immunoglobulin M (IgM), IgG, IgA, and IgE class antibodies, which are produced by B lymphocytes and plasma cells after being presented an antigen by macrophages. Binding of antibodies to an infectious agent or its toxins helps prevent infection or disease by facilitating agglutination (viruses), improving phagocytosis (opsonization), neutralizing toxins, blocking attachment to cell surfaces, initiating the complement cascade, and inducing antibody-dependent cell-mediated cytotoxicity. Antibody responses are most effective in controlling infectious agents during extracellular replication or toxin production. Cell-mediated immune responses are mediated principally by T lymphocytes. Antigen-specific T lymphocytes either destroy the infectious agent or mediate destruction of the agent by producing cytokines that stimulate other white blood cells, including macrophages, neutrophils, and natural killer cells. Cell-mediated immunity is required for the control of most cell-associated infections.

Currently available vaccines are either infectious (attenuated [modified-live] organisms or live virus–vectored recombinant vaccines) or noninfectious (killed virus, killed bacteria [bacterins], and subunit vaccines).

Attenuated vaccines replicate in the host to effectively stimulate an immune response and therefore generally have low antigen mass and do not require adjuvants. Different products are administered locally (e.g., modified-live *B. bronchiseptica* intranasal or oral vaccines) or parenterally (e.g., modified-live canine distemper vaccine). In live virus–vectored recombinant vaccines, the specific DNA that codes for the immunogenic components of the infectious agent is inserted into the genome of a nonpathogenic organism (vector) that will replicate in the species being vaccinated. As the vector replicates in the host, it expresses the immunogenic components of the infectious agent, resulting in the induction of specific immune responses. Because the virus-vectored vaccine is live and replicates in the host, adjuvants and high-antigen mass are not required. Because only DNA from the infectious agent is incorporated into the vaccine, no risk of reverting to the virulent parent strain exists, as occasionally occurs with attenuated vaccines. Only vectors that do not induce disease in the animal being vaccinated are used. Another advantage to vaccines of this type is the potential ability to overcome inactivation by maternal antibodies.

Killed virus, killed bacteria (bacterins), and subunit vaccines are noninfectious and therefore usually require higher antigen mass than infectious vaccines to stimulate immune responses because they do not replicate in the host. Some noninfectious vaccines may stimulate immune responses of lesser magnitude and shorter duration than infectious vaccines unless adjuvants are added. Adjuvants improve immune responses in part by stimulating uptake of antigens by macrophages that present the antigens to lymphocytes. Although adjuvants have historically been associated with vaccine adverse effects, most newer-generation adjuvants induce less inflammation than older adjuvants like those containing aluminum. Subunit vaccines can be superior to killed vaccines that use the entire organism because only the immunogenic parts of the organism are used, which may decrease the potential for vaccine reactions. However, for some infections, use of only one antigen does not induce adequate protection (e.g., feline calicivirus vaccines). Native DNA vaccines and gene-deleted vaccines are currently being evaluated for several infectious diseases.

VACCINE SELECTION

Selection of optimal vaccines for use in dogs and cats can be complicated as multiple products for most infectious agents are available, but efficacy studies that directly compare different products are often lacking. The veterinarian may need to choose from infectious and noninfectious options for the same vaccine antigen. Some vaccine antigens are for intranasal or oral administration, and others are for parenteral administration. Not all vaccines for a given infectious disease are comparable in every situation. Long-term duration of immunity studies and studies evaluating a vaccine's ability to block infection by multiple field strains are not available for all individual products. When making decisions about which products to use or when evaluating a new vaccine, the practitioner should request information concerning efficacy, challenge studies, duration of immunity studies, adverse reactions, and cross-protection capability. Vaccine issues are commonly debated in veterinary journals and continuing education meetings; these are excellent sources of current information. Use of vaccine guidelines from the AAFP (www.catvets.com; Scherk et al., 2013), the American Animal Hospital Association (www.aahanet.org), and the World Small Animal Veterinary Association (www.wsava.org) can help practicing veterinarians made logical vaccination protocols for individual pets.

Not all dogs and cats need all available vaccines. Vaccines are not innocuous and should only be given if indicated. The type of vaccine and route of administration for the disease in question should also be considered. A benefit, risk, and cost assessment should be discussed with the owner of each individual animal before determining the optimal vaccination protocol. For example, FeLV only lives outside the host for minutes; it is highly unlikely that an owner would bring the virus into the household. Therefore cats housed indoors are not likely to come in contact with the virus.

Before administering vaccines, the animal should be evaluated for factors that may influence the ability to respond to the vaccine or that may affect whether vaccination could be detrimental. For example, hypothermic animals may have poor T lymphocyte and macrophage function and may not

respond appropriately to vaccination. Immunosuppressed animals, including those with FeLV infection, FIV infection, canine parvovirus infection, *Ehrlichia canis* infection, and debilitating diseases, may not respond appropriately to vaccination, and modified-live vaccines could potentially induce the disease in these animals.

If high levels of specific antibodies are present, efficacy of some vaccines is diminished. This is a particularly important consideration when vaccinating puppies or kittens from well-vaccinated dams. Disease may also develop in vaccinated puppies and kittens because infection had already occurred and was incubating when the animal was vaccinated. Vaccines can be rendered ineffective from mishandling. As most vaccine manufacturers will support their products if administered by a veterinary health care professional, it could be advantageous for owners to not purchase and administer vaccines on their own. Vaccines should not be administered while the animal is under anesthesia because if a vaccine reaction occurs, clinical signs may not be recognized.

Adverse reactions can potentially occur with any vaccine. However, they are relatively uncommon in dogs and cats and recently have been reviewed (Gershwin, 2018). In a study of more than 1.2 million dogs, the overall rate of adverse reactions was 38.2/10,000 dogs that had received vaccines within the previous 3 days (Moore et al., 2005). In a study of 496,189 cats, the overall rate of adverse reactions was 51.6/10,000 cats that had received vaccines within the previous 30 days (Moore et al., 2007). In another study, vaccine associated hypersensitivity reactions were estimated at 6.5 per 10,000 vaccinated dogs (Yao et al., 2015). Vaccination has been associated with injection site sarcomas in some cats and can be life threatening. These tumors can occur after administration of infectious or noninfectious vaccines (Dyer et al., 2009), but to date studies attempting to link different vaccine types or individual products to tumor formation have had variable results (Kass et al., 2003; Srivastav et al., 2012). Injection site sarcomas have developed after administration of other substances including parasiticides, long-lasting glucocorticoids, meloxicam, cisplatin, antibiotics, and microchips. It is apparent that tumor development may relate to a genetic predisposition, but *P53* gene testing has not provided definitive results in all cases (Banerji et al., 2007; Mucha et al., 2012). Based in the information available to date, it is impossible to determine the risk for individual cats to develop injection site sarcomas, and the validity of current recommendations to avoid all adjuvants have been questioned (Kass, 2018). Currently, the optimal way to avoid injection site sarcomas is to administer only products absolutely indicated by this route, including using the longest vaccination interval acceptable for the vaccine used. In addition, if a cat has previously developed an injection site sarcoma, it is likely of risk of developing a second tumor, and parenteral injections should be avoided if possible.

Feline vaccines for which the viruses were grown on cell cultures induce antibodies that cross-react with feline renal tissues (Lappin et al., 2005), and some hypersensitized cats have developed lymphocytic-plasmacytic interstitial nephritis (Lappin et al., 2006b). The immunodominant cell line antigen recognized by parenterally vaccinated cats is alpha enolase, which is present in all mammalian cells (Whittemore et al., 2010). In people, anti-enolase antibodies are markers for immune-mediated disease, including nephritis. Whether postvaccination or naturally occurring anti-enolase antibodies are associated with nephritis in cats is still being studied. Intranasal products can result in transient sneezing and coughing, but in cats are not associated with the development of anti-enolase antibodies (Whittemore et al., 2010).

Suspected adverse reactions to vaccination should be reported to the vaccine manufacturer. Administration of any vaccine to animals with proven vaccine-associated sarcoma or immune-mediated diseases, such as immune-mediated polyarthritis, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, glomerulonephritis, or polyradiculoneuritis, is questionable because immune stimulation may exacerbate these conditions. However, the potential legal ramifications of waiving vaccination in these patients should be discussed with the owners and with appropriate state and county representatives when rabies vaccination is in question.

For some infectious agents, including canine distemper virus (CDV), canine parvovirus, feline panleukopenia virus (FPV), feline calicivirus (FCV), and FHV-1, serologic test results have been shown to correlate to resistance to disease after challenge in some studies. The advantages and disadvantages of the use of serologic testing have been reviewed (Moore et al., 2004). If validated laboratories or kits are used, results can be used accurately to make vaccination decisions for some dogs and cats (Lappin et al., 2002). For example, previously vaccinated animals that were presumed to have had a vaccine reaction and are still at risk of exposure to infectious agents could be assessed by serologic testing in lieu of arbitrary vaccination. In general, the positive predictive value of these tests is good (i.e., a positive test result usually predicts resistance on challenge) for CDV, canine parvovirus, and FPV. Commercially available kits for point of care testing are available in some countries.

VACCINATION PROTOCOLS FOR CATS

A physical examination, fecal parasite screen, and assessment of vaccine needs should be performed at least yearly for all cats. The AAFP formed a Feline Vaccine Advisory Panel to produce vaccine recommendations for cats (http://www.catvets.com) in 2013 (Scherk et al., 2013). These guidelines are an excellent source of information for veterinarians when individualizing vaccination protocols. Vaccine antigens were divided into those that were considered core (FPV, FCV, FHV-1) and noncore (rabies, FeLV, FIV, *B. bronchiseptica*, *Chlamydia felis*, and feline infectious peritonitis [FIP]). In contrast to previous AAFP Panel Reports, rabies vaccines are no longer considered core because the

guidelines are meant to be suitable for cats living worldwide and rabies is not endemic in all countries. Other sources for feline vaccine administration recommendations include the ABCD guidelines in Europe (Hosie et al., 2015) and the WSAVA guidelines (http://www.wsava.org/Guidelines/Vaccination-Guidelines).

Core Vaccines

Feline panleukopenia virus, feline calicivirus, feline herpesvirus-1

All healthy kittens and adult cats without a known vaccination history should be routinely vaccinated with an intranasal or parenteral vaccine that contains FPV, FCV, and FHV-1 (FVRCP). Multiple modified-live products and killed products are available, but they vary by country. In general, modified-live FVRCP vaccines are recommended for kittens housed in environments at high risk for exposure to FPV because this type of vaccine is least likely to be inactivated by antibodies transferred to the kitten as part of maternally derived immunity. Killed FVRCP vaccines have the advantage of not replicating in the host, so they are safe for administration to pregnant queens and do not colonize the host. Modified-live FVRCP vaccines for intranasal administration can induce protection against FHV-1 as soon as 4 days after administration, so this route may be preferred for kittens housed in environments at high risk for exposure to FHV-1 (Lappin et al., 2006a). However, it was shown that significant protection against FHV-1 is induced as soon as 1 week after administration of one subcutaneous dose of a killed or modified live FHV-1 containing vaccine (Summers et al., 2017). Modified-live products should not be administered to clinically ill, debilitated, or pregnant animals. Owners should be informed that the administration of intranasal FVRCP vaccines can induce transient, mild sneezing or coughing.

For kittens believed to have no more than routine risk of exposure to FPV, FCV, or FHV-1, administration of FVRCP vaccines is recommended starting no sooner than 6 weeks of age, with boosters every 3 to 4 weeks until 16 to 20 weeks of age. Older kittens and adult cats with unknown vaccination history should be administered two killed or two modified-live FVRCP doses 3 to 4 weeks apart. A booster FVRCP vaccine should be administered 1 year later and then every 3 years, lifelong (Scherk et al., 2013). As previously discussed, serologic test results for antibodies against FPV, FCV, and FHV-1 can be used to help determine vaccine needs (Lappin et al., 2002).

Some variants of FCV induce systemic vasculitis in cats (virulent systemic calicivirus; VS-FCV), and clinical signs can be severe in some cats even if previously vaccinated with FVRCP vaccines (Hurley et al., 2004). An inactivated product containing two FCV strains, including a VS-FCV strain, is now available in the United States (CaliciVax, Elanco, Indianapolis, IN). Serum from cats vaccinated with this product has been shown to cross-neutralize more FCV field strains than serum from cats vaccinated with products containing only one FCV strain (Huang et al., 2010). Similar results have been seen in other studies in Europe and Japan.

Use of FVRCP vaccines in other situations like boarding, in shelters, and in catteries are presented in the AAFP document (Scherk et al., 2013; www.catvets.com).

Noncore Vaccines

Bordetella bronchiseptica

The currently available *B. bronchiseptica* vaccine for intranasal administration can be administered as early as 4 weeks of age, has an onset of immunity as early as 72 hours, and is believed to have a minimal duration of immunity of 1 year. Many cats have antibodies against *B. bronchiseptica,* the organism is commonly cultured from cats in crowded environments, and sporadic reports have been made of severe lower respiratory disease caused by bordetellosis in kittens and cats in crowded environments or other stressful situations. However, the significance of infection in otherwise healthy pet cats appears to be minimal. *Bordetella* vaccination should be considered primarily for use in cats at high risk for exposure and disease, such as those with a history of respiratory problems and living in shelters with culture-proven outbreaks.

Chlamydia felis

Killed and modified-live *Chlamydia felis*–containing vaccines are available. Infection of cats by *C. felis* generally results in only mild conjunctivitis, is easily treated with antibiotics, and has variable prevalence rates, and the organism is of minimal zoonotic risk to people. In addition, use of FVRCP vaccines that also contained *C. felis* was associated with more vaccine reactions in cats when compared with other products (Moore et al., 2007). Thus whether *C. felis* vaccination is ever necessary in the United States is questioned. The use of this vaccine should be reserved for cats with a high risk of exposure to other cats and in catteries with endemic disease.

Feline leukemia virus

Multiple FeLV-containing vaccines are currently available in some countries. Some contain killed FeLV with and without adjuvants, and one contains recombinant antigens of FeLV without adjuvant. Because of difficulties in assessing efficacy studies performed with different experiment designs, which FeLV vaccine is optimal is unclear. In one recent challenge study, one killed product and the recombinant product performed similarly (Grosenbaugh et al., 2017). At the 2-year challenge in one study, 83% of the vaccinated cats remained FeLV-negative (Jirjis et al., 2010). The AAFP panel recommended vaccinating kittens for FeLV because they are more susceptible than adult cats, and their housing status may not have been determined at that time. Although administration of FeLV vaccines does not block proviral integration, FeLV-associated disease was lessened (Hofmann-Lehmann et al., 2007). FeLV vaccines are most indicated in cats allowed to go outdoors or those that are exposed to cats of unknown FeLV status. Vaccinated cats should be administered two vaccinations initially and a booster 1 year later if indicated by risk assessment. The AAFP Panel recommended 1-year

boosters thereafter in high-risk cats and every 2 years in low-risk cats (Scherk et al., 2013). However, it is difficult to determine whether a cat allowed outdoors is high or low risk as the prevalence rates for FeLV may not be known in all regions. FeLV vaccines are not effective in cats with progressive viremia and are therefore not indicated. However, administration of the vaccine to viremic or latently infected cats does not pose an increased risk of vaccine reaction. FeLV testing should be performed before vaccination because the retrovirus serologic status of all cats should be known to maintain appropriate husbandry.

Feline immunodeficiency virus

A killed vaccine containing two FIV subtypes (clades A and D) is currently available in some countries. Little is known about the efficacy of this vaccine in the field. The primary problem with FIV vaccination at this time is that the vaccine induces antibodies detectable by some of the currently available antibody tests. However, one of the test kits (Witness FeLV/FIV, Zoetis Animal Health) rarely detects FIV antibodies induced by vaccination (Westman et al., 2015). Reverse-transcription polymerase chain reaction for detection of FIV provirus is available in some laboratories but, as discussed in Chapter 96, some FIV-infected cats will be falsely negative in this assay because of low-level viremia.

Feline infectious peritonitis

A relatively safe coronavirus vaccine that may protect some cats from developing FIP is currently available for administration after 16 weeks of age. The vaccine may result in mild, transient sneezing because it is administered intranasally. Antibody-dependent enhancement of infectivity has not been detected in field studies. Results of the vaccine in field studies have been variable. If cats have previously been exposed to coronaviruses, the vaccine is unlikely to be effective. Because the incidence of disease is low, cats are commonly exposed to coronaviruses before vaccination and the efficacy is questionable. The AAFP panel considered this vaccine as noncore and generally not recommended, even in breeding catteries (Scherk et al., 2013). The vaccine may be indicated for seronegative cats entering a known FIP-infected household or cattery.

Rabies

All cats in endemic countries, including the United States, should be vaccinated against rabies. Recommendations concerning rabies can vary by the state and county, and one website can be used to find most requirements (http://www.rabiesaware.org/). Rabies vaccine should be administered as early as 12 weeks of age in accordance with state and local statutes. Cats should be vaccinated 1 year later and then either annually or triennially according to state and local statutes and the vaccine product used for the initial immunization. A live virus–vectored rabies vaccine with a 1-year or 3-year label is available in some countries. This product induces less inflammation than inactivated rabies vaccines that contain adjuvants, but whether this vaccine is less likely to be associated with injection site sarcomas is currently unknown.

VACCINATION PROTOCOLS FOR DOGS

A physical examination, fecal parasite screen, and vaccine needs assessment should be performed at least yearly for all dogs. The American Animal Hospital Association recently published on line the revised version of vaccination guidelines for dogs that also included recommendations for use of canine vaccines in shelters. These guidelines are an excellent source of information for veterinarians to use when individualizing a vaccination protocol for dogs (https://www.aaha.org/guidelines/canine_vaccination_guidelines.aspx). Different forms of vaccine antigens were divided into those that were considered core or noncore. The online AAHA recommendations also have a section on recommendations for dogs that are overdue for various vaccines (www.aaha.org/CanineVaccinesOverdue). The WSAVA guidelines are another excellent source of information concerning vaccination of dogs in different parts of the world (http://www.wsava.org/Guidelines/Vaccination-Guidelines).

Core Vaccines

Canine parvovirus, canine adenovirus, and canine distemper virus

Because canine parvovirus (CPV-2), canine adenovirus 1 (CAV-1; infectious canine hepatitis), and CDV can be life-threatening diseases, all dogs should be vaccinated. For CPV-2, only modified-live products should be used because of increased risk of maternal antibody interference with killed products. Both modified-live CDV and recombinant CDV (rCDV)-containing vaccines are considered adequate by the AAHA Task Force. Because of adverse effects associated with CAV-1 vaccines and poor immune responses associated with killed CAV-2 or modified-live topical CAV-2 vaccines, only modified-live CAV-2 vaccines for parenteral administration should be used. These vaccines cross-protect against canine infectious hepatitis induced by CAV-1 and the kennel cough syndrome induced by CAV-2. All puppies should be administered at least three CPV-2, CAV-2, and CDV-containing vaccines, every 3 to 4 weeks, between 6 and 16 weeks of age, with the last booster being administered at 16 weeks of age or older. Administration of a final dose at 18 to 20 weeks of age should be considered for dogs residing in high-risk environments. Adult dogs with an unknown vaccination history can be given one dose of MLV CPV-2, CAV-2, and CDV-containing vaccines. Vaccinated dogs should receive a booster vaccine 1 year later and then boosters at intervals of 3 years. Several CDV-containing products, including the rCDV vaccine, were recently shown to protect for at least 3 years (Abdelmagid et al., 2004; Larson et al., 2007). Vaccination of dogs with CPV-2b induces neutralizing antibodies against CPV-2a and CPV-2c (Wilson et al., 2014).

Dogs should be evaluated at least yearly for risk of infection by CPV, CDV, and CAV during the physical examination, checked for enteric parasites, and evaluated for *D. immitis* infection in appropriate regions. Positive serologic tests for CDV and CPV are predictive of resistance after challenge and can be used in lieu of arbitrary vaccine

intervals if performed with validated assays. Dogs should complete the puppy series and be boosted at 1 year of age before using titers to help predict vaccine need. If the vaccination status of an adult dog is unknown, the dog should be vaccinated appropriately and then serologic assessment considered in subsequent years.

Rabies

All dogs should be administered a 1-year or 3-year rabies vaccine following the manufacturer's recommendations as early as 12 weeks of age and based on state, provincial, and/or local requirements. Both puppies and adult dogs with unknown vaccination history should receive one dose and return for a booster vaccination 1 year later. Intervals and product after that booster should be based on state and local statutes (http://www.rabiesaware.org/).

Noncore Vaccines

Bordetella bronchiseptica

In general, *B. bronchiseptica* rarely causes life-threatening disease in otherwise healthy animals and is not the only cause of the CIRDC (Lappin et al., 2017). It is therefore considered a noncore vaccine. Although parenteral products administered twice induce strong serum antibody responses, in one study intranasal administration was associated with superior protection on challenge (Davis et al., 2007). It has been shown that immunity against *B. bronchiseptica* can be induced after 1 dose of intranasal or oral vaccines. The intranasal products have a 12 to 14 month duration of immunity. The duration of immunity of parenteral or oral *B. bronchiseptica* vaccines is currently unknown. The intranasal *B. bronchiseptica* vaccines can be administered as early as 3 to 4 weeks of age in outbreaks. *Bordetella bronchiseptica* vaccines for intranasal administration are also available combined with modified live parainfluenza or parainfluenza and adenovirus 2.

Borrelia burgdorferi

The pros and cons of administering *B. burgdorferi* vaccines were discussed in depth in an American College of Veterinary Internal Medicine Consensus Statement (Littman et al., 2018). A total of three of six panelists recommended use of *B. burgdorferi* vaccines in endemic areas, independent of current infection status, if the dog is healthy. However, *B. burgdorferi* vaccination should be considered adjunct to use of tick control products as vaccine failures can be common. Depending on the product used, vaccination can start at 8 or 9 weeks of age, and a second dose is recommended 2 to 4 weeks later, with annual boosters.

Canine influenza

In the United States, there are monovalent vaccines for H3N8 and H3N2 as well as bivalent vaccines containing both. Canine influenza vaccines are killed virus vaccines and should be administered no earlier than 6 weeks of age, with a second dose 2 to 4 weeks later. While not all areas of the United States are considered endemic for these viruses, outbreaks can occur and spread quickly, and some dogs have prolonged shedding of viral nucleic acids (Newbury et al., 2016). Thus influenza vaccination should be discussed with all owners regardless of whether an outbreak is currently in your region. Live attenuated vaccines for these two viruses have been shown to be safe and effective after 1 dose in a mouse model (Rodriguez et al., 2017).

Leptospira spp.

Vaccines containing multiple *Leptospira interrogans* serovars *Canicola*, *Icterohaemorrhagiae*, and *Pomona*) and *Leptospira kirschneri* serovar *Grippotyphosa*, are generally recommended for dogs with high risk in known endemic areas (Sykes et al., 2010). However, some serovars in the environment are not in any vaccine, and minimal cross-protection exists between serovars. Thus clients should realize that, even though their dog has been given a *Leptospira* vaccine, 100% protection cannot be guaranteed. Newer-generation vaccines have fewer adverse effects than previous vaccines. In a recent study (Yao et al., 2015), dogs that were administered a vaccination protocol that included *Leptospira* spp. antigens had an incidence rate of reported adverse events of 53/10,000 dogs (0.53%). If the vaccines are to be used, puppies should receive the first dose as early as 8 to 9 weeks of age with a booster 2 to 4 weeks later. Annual revaccination is recommended. In one recent study of one of the *Leptospira* 4 serovar products, significant protection was present 15 months after completing the immunization protocol (Grosenbaugh and Pardo, 2018).

Parainfluenza virus

Multiple products that contain CPV-2, CDV, and CAV-2 also contain modified-live parainfluenza, so they are commonly administered at the same schedule of those core vaccine antigens. Considered alone, parainfluenza is noncore because it is not life-threatening, is not zoonotic, and is a self-limited cause of CIRDC. However, outbreaks of clinical disease attributed to parainfluenza are still reported (Weese et al., 2013). Modified-live strains for intranasal administration, with some products combined with a live avirulent strain of *B. bronchiseptica*, without or without adenovirus 2 are available. If used, the intranasal vaccine can be administered as early as 3 weeks of age; transient sneezing and coughing can occur. Annual boosters are recommended in previously vaccinated dogs.

Rattlesnake vaccine

The *Crotalus atrox* toxoid vaccine was designed to protect dogs against the venom of the Western Diamondback Rattlesnake. Some cross-protection may exist against the Eastern Diamondback Rattlesnake but not the Mojave Rattlesnake. Local reactions to this toxoid are common. If used in high-risk dogs in high-risk areas, practitioners should follow the manufacturer's label.

Suggested Readings

Abdelmagid OY, et al. Evaluation of the efficacy and duration of immunity of a canine combination vaccine against virulent parvovirus, infectious canine hepatitis virus, and distemper virus experimental challenges. *Vet Ther*. 2004;5:173.

Banerji N, Kapur V, Kanjilal S. Association of germ-line polymorphisms in the feline p53 gene with genetic predisposition to vaccine-associated feline sarcoma. *J Hered*. 2007;98(421).

Brown CM, et al. National Association of State Public Health Veterinarians; compendium of animal rabies prevention and control. *J Am Vet Med Assoc*. 2016;248(505):2016.

Davis R, et al. Comparison of the mucosal immune response in dogs vaccinated with either an intranasal avirulent live culture or a subcutaneous antigen extract vaccine of *Bordetella bronchiseptica*. *Vet Ther*. 2007;8:1.

Dyer F, et al. Suspected adverse reactions, 2008. *Vet Rec*. 2009; 165:162.

Gershwin LJ. Adverse reactions to vaccination: from anaphylaxis to autoimmunity. *Vet Clin North Am Small Anim Pract*. 2018;48:279.

Greene CE. Environmental factors in infectious disease. In: Greene CE, eds. *Infectious diseases of the dog and cat*. 4th ed. St Louis: Elsevier; 2012:1078.

Grosenbaugh DA, et al. Efficacy of a nonadjuvanted recombinant FeLV vaccine and two inactivated FeLV vaccines when subject to consistent virulent FeLV challenge conditions. *Biologicals*. 2017;49:76.

Grosenbaugh DA, Pardo MC. Fifteen-month duration of immunity for the serovar *Grippotyphosa* fraction of a tetravalent canine leptospirosis vaccine. *Vet Rec*. 2018;182:665.

Hascall KL, et al. Prevalence of enteropathogens in dogs attending 3 regional dog parks in Northern California. *J Vet Intern Med*. 2016;30:1838.

Haun N, et al. Healthcare personnel attire and devices as fomites: a systematic review. *Infect Control Hosp Epidemiol*. 2016;37:1367.

Hofmann-Lehmann R, et al. Vaccination against the feline leukaemia virus: outcome and response categories and long-term follow-up. *Vaccine*. 2007;25:5531.

Hosie MJ, et al. Matrix vaccination guidelines: 2015 ABCD recommendations for indoor/outdoor cats, rescue shelter cats and breeding catteries. *J Feline Med Surg*. 2015;17:583.

Huang C, et al. A dual-strain feline calicivirus vaccine stimulates broader cross-neutralisation antibodies than a single-strain vaccine and lessens clinical signs in vaccinated cats when challenged with a homologous feline calicivirus strain associated with virulent systemic disease. *J Feline Med Surg*. 2010;12:129.

Hurley KE, et al. An outbreak of virulent systemic feline calicivirus disease. *J Am Vet Med Assoc*. 2004;224:241.

Jirjis F, et al. Protection against feline leukemia virus challenge for at least 2 years after vaccination with an inactivated feline leukemia virus vaccine. *Vet Ther*. 2010;11:E1.

Kass PH, et al. Multicenter case-control study of risk factors associated with development of vaccine-associated sarcomas in cats. *J Am Vet Med Assoc*. 2003;223:1283.

Kass PH. Prevention of feline injection-site sarcomas: is there a scientific foundation for vaccine recommendations at this time? *Vet Clin North Am Small Anim Pract*. 2018;48:301.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: antimicrobial guidelines working group of the international society for companion animal infectious diseases. *J Vet Intern Med*. 2017;31:279.

Lappin MR, et al. Effects of a single dose of an intranasal feline herpesvirus 1, calicivirus, and panleukopenia vaccine on clinical signs and virus shedding after challenge with virulent feline herpesvirus 1. *J Feline Med Surg*. 2006a;8:158.

Lappin MR, et al. Interstitial nephritis in cats inoculated with Crandall Rees feline kidney cell lysates. *J Feline Med Surg*. 2006b;8:353.

Lappin MR, et al. Investigation of the induction of antibodies against Crandall Rees feline kidney cell lysates and feline renal cell lysates after parenteral administration of vaccines against feline viral rhinotracheitis, calicivirus, and panleukopenia in cats. *Am J Vet Res*. 2005;66:506.

Lappin MR, et al. Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats. *J Am Vet Med Assoc*. 2002;220:38.

Larson LJ, et al. Effect of vaccination with recombinant canine distemper virus vaccine immediately before exposure under shelter-like conditions. *Vet Ther*. 2006;7:113.

Larson LJ, et al. Three-year duration of immunity in dogs vaccinated with a canarypox-vectored recombinant canine distemper virus vaccine. *Vet Ther*. 2007;8:101.

Levy J, et al. American Association of Feline Practitioners' feline retrovirus management guidelines. *J Feline Med Surg*. 2008;10:300.

Littman MP, et al. ACVIM consensus update on Lyme borreliosis in dogs and cats. *J Vet Intern Med*. 2018;32:887.

Moore GE, et al. Adverse events after vaccine administration in cats: 2,560 cases (2002-2005). *J Am Vet Med Assoc*. 2007;231:94.

Moore GE, et al. Adverse events diagnosed within 3 days of vaccine administration in pet dogs. *J Am Vet Med Assoc*. 2005;227:1102.

Moore GE, Glickman LT. A perspective on vaccine guidelines and titer tests for dogs. *J Am Vet Med Assoc*. 2004;224:200.

Mucha D, et al. Lack of association between p53 SNP and FISS in a cat population from Germany. *Vet Comp Oncol*. 2014;12:130.

Newbury S, et al. Prolonged intermittent virus shedding during an outbreak of canine influenza A H3N2 virus infection in dogs in three Chicago area shelters: 16 cases (March to May 2015). *J Am Vet Med Assoc*. 2016;248:1022.

Rodriguez L, et al. A bivalent live-attenuated influenza vaccine for the control and prevention of H3N8 and H3N2 canine influenza viruses. *Vaccine*. 2017;35:4374.

Sánchez-Vizcaíno F, et al. Use of vaccines and factors associated with their uptake variability in dogs, cats and rabbits attending a large sentinel network of veterinary practices across Great Britain. *Epidemiol Infect*. 2018;146:895.

Scherk MA, et al. AAFP feline vaccination advisory panel report. *J Feline Med Surg*. 2013;15(785):2013.

Srivastav A, et al. Comparative vaccine-specific and other injectable-specific risks of injection-site sarcomas in cats. *J Am Vet Med Assoc*. 2012;241:595.

Stull JW, Weese JS. Hospital-associated infections in small animal practice. *Vet Clin North Am Small Anim Pract*. 2015;45:217.

Stull JW, et al. Reducing the risk of pet-associated zoonotic infections. *CMAJ*. 2015;187:736.

Summers SC, et al. Effect of modified live or inactivated feline herpesvirus-1 parenteral vaccines on clinical and laboratory findings following viral challenge. *J Feline Med Surg*. 2017;19:824.

Sykes JE, et al. ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2010;25(1):2010.

Weese JS, Stull J. Respiratory disease outbreak in a veterinary hospital associated with canine parainfluenza virus infection. *Can Vet J*. 2013;54:79.

Westman ME, et al. Determining the feline immunodeficiency virus (FIV) status of FIV-vaccinated cats using point-of-care antibody kits. *Comp Immunol Microbiol Infect Dis*. 2015;42:43.

Whittemore JC, et al. Antibodies against Crandell Rees feline kidney (CRFK) cell line antigens, α-enolase, and annexin A2 in vaccinated and CRFK hyperinoculated cats. *J Vet Intern Med*. 2010;24:306.

Wilson S, et al. Vaccination of dogs with canine parvovirus type 2b (CPV-2b) induces neutralising antibody responses to CPV-2a and CPV-2c. *Vaccine*. 2014;32:5420.

Yao PJ, et al. Incidence rates and risk factors for owner-reported adverse events following vaccination of dogs that did or did not receive a *Leptospira* vaccine. *J Am Vet Med Assoc*. 2015;247:1139.

CHAPTER 94

Polysystemic Bacterial Diseases



CANINE BARTONELLOSIS

Etiology and Epidemiology

Bartonella vinsonii subspecies *berkhoffii* was initially isolated from a dog with endocarditis in North Carolina (Breitschwerdt et al., 1995). *Bartonella vinsonii (berkhoffii)* is thought to be tick-borne but has also been amplified from fleas collected from dogs (Yore et al., 2014). In a recent seroprevalence study of 15,451 dogs, 3.26% of dogs were *Bartonella* spp. seroreactive with *B. henselae* (2.13%), *B. koehlerae* (2.39%), or *B. vinsonii* subsp. *berkhoffii* (1.42%, $P < 0.0001$) organisms (Lashnits et al., 2018). *Bartonella henselae* and *B. koehlerae* are transmitted by fleas. In the seroprevalence study, *Bartonella* spp. antibodies were detected more often in intact males (5.04%) than neutered males (2.87%, $P < 0.0001$) or intact or spayed females (3.22%, $P = 0.0003$). This result and the documentation of *Bartonella* spp. infections in dogs in areas where vector-borne diseases are uncommon like Colorado and Wyoming suggest direct transmission may also occur (Fenimore et al., 2011). Many other *Bartonella* species have been isolated from dogs from which DNA has been amplified from blood or tissues, and include *B. clarridgeiae*, *B. washoensis*, *B. quintana*, *B. rochalimae*, and *B. elizabethae*. Each of these organisms can potentially induce illness in dogs. Dogs infected with a *Bartonella* species are commonly co-infected with other agents such as *Anaplasma* spp. or *Ehrlichia* spp., which may play a role in the pathogenesis of disease.

Clinical Features

Bartonella henselae and *B. vinsonii (berkhoffii)* seem to be the most likely species to be associated with clinical disease in dogs. Clinical findings or syndromes most frequently attributed to *Bartonella* spp. infections of dogs include endocarditis, fever, arrhythmias, hepatitis, granulomatous lymphadenitis, cutaneous vasculitis, rhinitis, polyarthritis, meningoencephalitis, thrombocytopenia, eosinophilia, monocytosis, immune-mediated hemolytic anemia, epistaxis, idiopathic cavitary effusions, and uveitis. *Bartonella* spp. infection should be considered in all dogs, cats, and human beings with evidence of infective endocarditis (Fig. 94.1) particularly if culture negative using routine media (Okaro et al., 2017; Fenimore et al., 2011; Sykes et al., 2006). Recently, ineffective erythropoiesis was detected in a dog positive for *B. henselae* that subsequently responded to antibiotics (Randell et al., 2018). In one study of valvular endocarditis, all dogs with *Bartonella* spp.–associated disease were also seropositive for *Anaplasma phagocytophilum* (MacDonald et al., 2004). Whether the co-infection potentiated the *Bartonella*-associated disease is unknown.

Diagnosis

Serum antibodies can be detected in both healthy and clinically ill dogs, so the presence of antibodies does not always correlate to illness. However, because approximately 50% of dogs with bartonellosis are seronegative, serum antibodies should never be used as the sole diagnostic method in suspect cases (www.galaxydx.com). *Bartonella* spp. can be difficult to amplify from dogs because the organism is frequently present in low numbers. Thus amplification of DNA by polymerase chain reaction (PCR) assay with or without culture is often necessary to confirm infection; blood or affected tissues may also be used for PCR (Duncan et al., 2007; www.galaxydx.com). If positive test results are detected in a clinically ill dog and no other explanation for the illness is obvious, treatment is indicated.

Treatment

Dogs with suspected bartonellosis have failed treatment with doxycycline alone; thus failure to respond to this drug should not exclude the diagnosis. Azithromycin therapy has been successful in some dogs, but it is now recognized that *B. henselae* can become resistant to this drug more quickly than fluoroquinolones (Biswas et al., 2010). Dual therapy is believed to be more effective than monotherapy by some veterinarians, but more information is necessary. Doxycycline at 5 to 10 mg/kg, orally (PO), q12h combined with a veterinary fluoroquinolone like enrofloxacin at 5 mg/kg, PO, q24h is used by most veterinarians working with *Bartonella* spp. infected dogs (Breitschwerdt, 2017). Rifampin used with

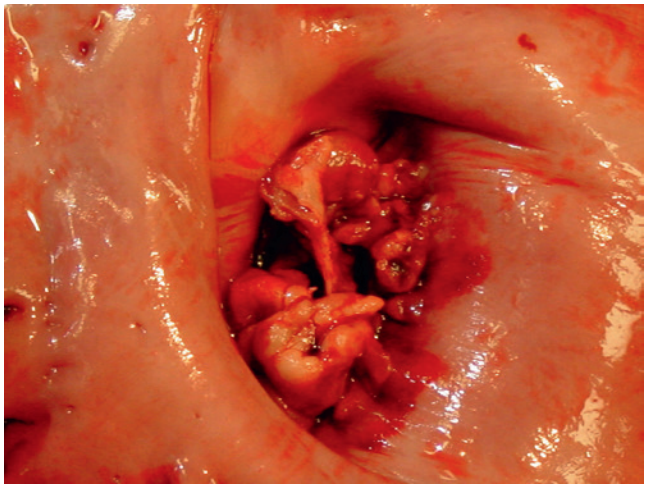


FIG 94.1
Bacterial endocarditis in a dog positive for *B. henselae* DNA in the heart value.

another drug may be required for resistant cases. Dogs with endocarditis should be given an aminoglycoside parenterally for the first week of therapy; amikacin at 20 mg/kg, intravenous (IV), q24h is commonly recommended while evaluating for renal toxicity. No matter which drug is used, a minimum of 4 to 6 weeks of treatment is usually necessary. In one study, successfully treated dogs became seronegative (Breitschwerdt et al., 2004). However, because so many dogs are initially seronegative and the organism can be difficult to grow or amplify from dogs, it is difficult to make definitive recommendations concerning use of diagnostic tests to confirm response to therapy. Thus, resolution of clinical signs and clinicopathologic abnormalities are of paramount importance, and flea and tick control should be maintained to attempt to avoid reinfection.

Zoonotic Aspects and Prevention

Many of the *Bartonella* spp. that have been detected in dogs also infect humans, in particular *B. henselae* and *B. vinsonii (berkhoffii)*. *Bartonella henselae* has been detected in dog saliva, and the cat scratch disease syndrome has been documented in human beings after exposure to dogs. Care should be taken to avoid bites, scratches, or contaminated needle sticks while handling or treating infected dogs. Flea and tick control is likely to lessen transmission of *Bartonella* species between dogs and perhaps from dogs to people. See the Zoonotic Aspects and Prevention section for feline bartonellosis for additional information.

FELINE BARTONELLOSIS

Etiology and Epidemiology

Cats have been proven to be infected by *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. quintana,* and *B. bovis* by culture or DNA amplification (Brunt et al., 2006; Breitschwerdt, 2017). Cats are the main reservoir hosts for *B. henselae* and *B. clarridgeiae,* and are likely the reservoir for *B. koehlerae*. *Ctenocephalides felis* plays a role in the transmission of these three species among cats. *Bartonella henselae* is the most common cause of cat scratch disease, as well as bacillary angiomatosis and peliosis hepatis, common disorders in human beings with acquired immunodeficiency syndrome (Breitschwerdt, 2017). However, multiple other *Bartonella* spp. disease associations have now been recognized, and veterinarian healthcare providers are occupationally at risk (see the Zoonoses subsection). *Bartonella* species have both intraendothelial and intraerythrocytic phases of infection (Fig. 94.2). The intracellular location may relate to the difficulties in permanently eliminating bacteremia and promotes *C. felis* taking up the organism in the blood meal. However, feline *Bartonella* spp. have not been associated with hemolytic anemia in cats, suggesting that this phase of infection is a host evasion mechanism (Ishak et al., 2007).

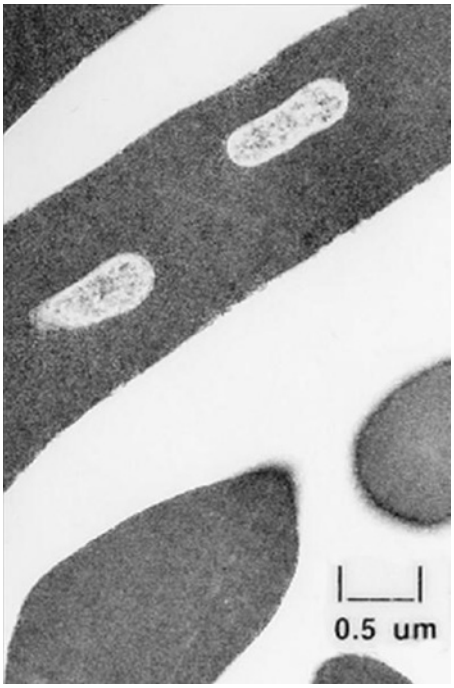


FIG 94.2
Electron micrograph of a feline erythrocyte showing intracellular *Bartonella henselae*. (Courtesy Dr. Dorsey Kordick.)

On the basis of results of seroprevalence studies, culture, or PCR assay, cats are commonly exposed to or infected by *Bartonella* species. Because feline *Bartonella* spp. are mainly transmitted by *C. felis,* prevalence is greatest in cats from regions where fleas are common. For example, although *Bartonella* spp. DNA was not amplified from any sample from cats in Colorado where fleas are rare due to the dry environment, it was commonly amplified from blood (56.9%), skin (31.4%), claws (17.6%), and gingiva (17.6%) of 51 cats housed in Alabama and Florida, where *C. felis* infestation is common (Lappin and Hawley, 2009). Results have been similar in other studies performed around the world.

Bartonella henselae survives in flea feces for days after being passed by infected *C. felis*. Infected flea feces are likely to contaminate cat claws during grooming, and then *Bartonella* species are inoculated into the person when scratched. Open wounds may also be contaminated with infected flea feces. However, *Bartonella* spp. DNA can also be amplified from the mouths of healthy cats and those with gingivostomatitis, so bites and scratches should always be avoided (Quimby et al., 2008; Lappin and Hawley, 2009). Whether clinical disease occurs from *Bartonella* spp. infection depends on a complex interaction of host and organism effects. In general, *Bartonella* spp.-associated illness is not identified in the host-adapted species (e.g., *B. henselae*, *B. clarridgeiae*, and *B. koehlerae* infections in cats) even though large numbers of the organism are detected in blood. In contrast, when *Bartonella* spp. infect non–host-adapted species like dogs and people, illness can occur with extremely low levels of bacteremia.

Clinical Features

Most cats with serologic evidence of exposure to *Bartonella* spp., *Bartonella* spp. cultured from blood, or microbial DNA amplified from blood by PCR assay are clinically normal. However, *Bartonella* spp. infection of cats has also been associated directly or indirectly with a variety of clinical manifestations like fever, lethargy, lymphadenopathy, uveitis, gingivitis, endocarditis, myocarditis, hyperglobulinemia, osteomyelitis, cutaneous vasculitis, and neurologic diseases. Fever and cardiac abnormalities are the most common manifestations in cats infected with *B. henselae* by experimental exposure to infected *C. felis* (Bradley and Lappin, 2010). How often cats become ill from *Bartonella* spp. infections is unknown, and more information is necessary.

It can be difficult to determine which cats have been exposed, and which cats are diseased. *Bartonella* spp. seroprevalence rates in shelter cats can be as high as 93% (Nutter et al., 2004). In another study, the presence of *Bartonella* species antibodies failed to correlate to the presence of most clinical syndromes in ill cats (Breitschwerdt et al., 2005b). In recent studies in the author's laboratory, the prevalence rates for *Bartonella* species antibodies in feline sera were not significantly different for cats with or without seizures (Pearce et al., 2006), cats with or without stomatitis (Dowers and Lappin, 2005), or cats with or without elevations in feline pancreatic lipase immunoreactivity (Bayliss et al., 2009). Why some cats develop *Bartonella*-associated illness and others do not is still not clear. For example, Powell et al. (2002) failed to induce *Toxoplasma gondii* or *Bartonella* species uveitis when *Bartonella* was intravenously inoculated into cats with chronic toxoplasmosis.

Diagnosis

Blood culture, PCR assay on blood, and serologic testing can be used to assess individual cats for *Bartonella* infection. Cats that are culture-negative or PCR-negative and antibody-negative, and cats that are culture-negative or PCR-negative and antibody-positive are probably not a source of flea, cat, or human infection. However, bacteremia can be intermittent, and false-negative culture or PCR results can occur, limiting the predictive value of a single battery of tests. With PCR, false-positive results can occur, and positive results do not necessarily indicate that the organism is alive. Although serologic testing can be used to determine whether an individual cat has been exposed, both seropositive and seronegative cats can be bacteremic, limiting the diagnostic utility of serologic testing when used alone. Thus testing healthy, client-owned cats for *Bartonella* spp. infection is not currently recommended in the United States (Kaplan et al., 2009). Testing should be reserved for cats with suspected clinical bartonellosis.

The combination of serology and PCR assay or culture is available in some laboratories like Antech Diagnostics, North Carolina State University, Galaxy Diagnostics (www.galaxydx.com), and Colorado State University (www.dlab.colostate.edu/). Some cats can have low-level bacteremia, and specialized media combined with PCR may be required to identify the organism (Drummond et al., 2018). If the results of *Bartonella* tests are negative in a clinically ill cat, the organism is not likely the cause of the clinical syndrome unless the infection was peracute and serologic testing was used as the diagnostic test. If the results of *Bartonella* tests are positive, the agent remains on the list of differential diagnoses, but other causes of the clinical syndrome must also be excluded.

The American Association of Feline Practitioners (AAFP) *Bartonella* Panel Report suggests that the diagnosis of clinical bartonellosis include the following combination of findings (Brunt et al., 2006):

- Presence of a syndrome reported to be associated with *Bartonella* spp. infection
- Exclusion of other causes of the clinical syndrome
- Detection of a positive *Bartonella* spp. test (culture, PCR assay, or serology)
- Response to administration of a drug with presumed anti-*Bartonella* activity

However, fulfillment of these criteria does not always prove a definitive diagnosis. The antibiotics used for the treatment of bartonellosis in cats generally have a broad spectrum, are effective for other infecting organisms that can cause syndromes resembling bartonellosis, and can also have antiinflammatory properties.

Treatment

In experimental studies, administration of doxycycline, tetracycline, erythromycin, amoxicillin-clavulanate, or enrofloxacin can limit bacteremia but does not cure infection in all cats. To date, use of antibiotics in healthy cats has not been shown to lessen the risk of cat scratch disease. Thus in the United States, treatment is generally recommended for clinically ill cats (Kaplan et al., 2009). If clinical bartonellosis is suspected, the AAFP Panel Report recommends

doxycycline at 10 mg/kg, PO, daily for 7 days as the initial therapeutic trial (Brunt et al., 2006). In the United States, doxycycline should be formulated into a flavored suspension or given with water to avoid esophagitis leading to esophageal strictures. Using the drug twice daily is also acceptable and may increase the chance of eliminating bacteremia. If a positive response is achieved, continue treatment for 2 weeks past clinical resolution of disease or for a minimum of 28 days. If a poor response is achieved by day 7 or doxycycline is not tolerated and bartonellosis is still considered a valid differential diagnosis, fluoroquinolones should be used as second choices. Enrofloxacin at 5 mg/kg, PO, daily was used in one study of cats infected by exposure to fleas (Bradley and Lappin, 2010). Recently, enrofloxacin has been used less frequently in cats due to the risk of retinal degeneration. Fever suspected to be due to *Bartonella* spp. in one field study seemingly resolved after the administration of doxycycline or orbifloxacin (Lappin et al., 2012). *Bartonella henselae* isolates from people or cats were shown to rapidly develop resistance to azithromycin, so this drug should not be used to treat feline bartonellosis (Biswas et al., 2010). Pradofloxacin is a newer generation quinolone available for use in cats in some countries, and unpublished data suggest that use of the United States formulation of this drug at 7.5 mg/kg, PO, daily may be the preferred drug to treat bartonellosis in cats. *Bartonella* spp.–positive cats that have failed to respond after administration of two different drugs with presumed anti-*Bartonella* activity generally have another cause of the clinical syndrome. There is no clinical utility in rechecking *Bartonella* serologic test or PCR test results in cats after clinical signs resolve because infection is difficult to clear and reinfection is common. Thus, successfully treated cats should have strict flea control maintained.

Zoonotic Aspects and Prevention

The clinical manifestations of bartonellosis in people are more extensive than just cat scratch disease, peliosis hepatis, bacillary angiomatosis, and valvular endocarditis. It is now apparent that immune-competent individuals can develop a number of *Bartonella* spp.–associated chronic inflammatory syndromes, and *Bartonella* spp. infections are an occupational risk for veterinary healthcare providers (Breitschwerdt et al., 2007; Breitschwerdt et al., 2011; Oteo et al., 2017). For example, *Bartonella* spp. infection was commonly confirmed in people with rheumatic symptoms in a Lyme disease–endemic region (Maggi et al., 2012). *Bartonella henselae* may have contributed to the death of two veterinarians (Breitschwerdt et al., 2015).

Veterinarians or others commonly exposed to cats or fleas that develop chronic inflammatory diseases should have *Bartonella* spp. on the list of differential diagnoses. To lessen the likelihood of acquiring a *Bartonella* species infection from a cat, the following adaptations of recommendations to HIV-infected people and other cat owners by the Centers for Disease Control and Prevention and the AAFP have been developed:

- Flea control should be initiated and maintained year round.
- If a family member is immunocompromised and a new cat is to be acquired, adopt a healthy cat older than 1 year and free of fleas.
- Immunocompromised individuals should avoid contact with cats of unknown health status.
- Declawing of cats is generally not required, but claws should be trimmed regularly.
- Bites and scratches should be avoided (including rough play with cats).
- Cat-associated wounds should be washed promptly and thoroughly with soap and water and medical advice sought.
- Although *Bartonella* species have not been shown to be transmitted by saliva, cats should not be allowed to lick open wounds.
- Keep cats indoors to minimize hunting and exposure to fleas and other possible vectors.
- Avoid needle sticks contaminated with blood from potentially infected cats or dogs.

FELINE PLAGUE

Etiology and Epidemiology

Yersinia pestis is the facultatively anaerobic gram-negative coccobacillus that causes plague. The organism is maintained in a sylvan life cycle between rodent fleas and infected rodents, including rock squirrels, ground squirrels, and prairie dogs. However, it has been shown that *C. felis* can be a competent vector, but transmission was less efficient than by a rodent flea in one experimental study (Eisen et al., 2008). Both cats and dogs are susceptible to infection. Antibodies against *Y. pestis* have also been detected in serum of nondomestic felids. Clinical disease is recognized most frequently from spring through early fall, when rodents and rodent fleas are most active. However, a recent unpublished case in Colorado was diagnosed in December of a mild winter. Most of the cases in human beings and cats in the United States have been documented in Colorado, New Mexico, Arizona, California, and Texas. Of the cases of human plague diagnosed from 1977 to 1998, 23 (7.7%) resulted from contact with infected cats (Gage et al., 2000).

Cats and dogs are infected after being bitten by infected rodent fleas, after ingestion of bacteremic rodents, or after inhalation of the organism. After ingestion, the organism replicates in the tonsils and pharyngeal lymph nodes, disseminates in the blood, and results in a neutrophilic inflammatory response and abscess formation in infected tissues. The incubation period is 2 to 6 days after a flea bite and 1 to 3 days after ingestion or inhalation of the organism. Outcomes in experimentally infected cats include death (6 of 16 cats; 38%), transient febrile illness with lymphadenopathy (7 of 16 cats; 44%), or inapparent infection (3 of 16 cats; 19%) (Gasper et al., 1993).

BOX 94.1

Clinical Findings in Cats With *Yersinia pestis* Infection (Plague)

Signalment

All ages, breeds, and gender

History and Physical Examination

Outdoor cats
Male cats
Hunting of rodents or exposure to rodent fleas
Depression
Cervical swellings, draining tracts, lymphadenopathy
Dyspnea or cough

Clinicopathologic and Radiographic Evaluation

Neutrophilia with or without a left shift
Lymphopenia
Neutrophilic lymphadenitis or pneumonitis
Homogenous population of bipolar rods cytologically (lymph node aspirate or airway washings)
Serum antibody titers, either negative (peracute) or positive
Interstitial and alveolar lung disease

Diagnosis

Culture or PCR assay of blood, exudates, tonsillar region, respiratory secretions
Fluorescent antibody identification of organism in exudates
Fourfold increase in antibody titer and appropriate clinical signs

Clinical Features

Bubonic, septicemic, and pneumonic plague can develop in infected human beings, dogs, and cats (Box 94.1). Bubonic plague is the most common form of the disease in cats, but individual cats can show clinical signs of all three syndromes. Most infected cats or dogs are allowed outdoors and have a history of hunting. Anorexia, depression, cervical swelling, dyspnea, and cough are common presenting complaints; fever is detected in most infected cats. Unilateral or bilateral enlarged tonsils, mandibular lymph nodes, and anterior cervical lymph nodes are detected in approximately 50% of infected cats. Cats or dogs with pneumonic plague commonly have respiratory signs and may cough. In a series of 62 suspected dog cases, the most common clinical signs included fever (100%), lethargy (97%), and anorexia (77%); only 23% of the dogs had lymphadenopathy (Nichols et al., 2014).

Diagnosis

Hematologic and serum biochemical abnormalities reflect bacteremia and are not specific for *Y. pestis* infection. Neutrophilic leukocytosis, left shift and lymphopenia, hypoalbuminemia, hyperglobulinemia, hyperglycemia, azotemia, hypokalemia, hypochloremia, hyperbilirubinemia, and increased activities of alkaline phosphatase and alanine transaminase are common. Pneumonic plague causes increased alveolar and diffuse interstitial densities on thoracic radiographs, and consolidated lung lobes may be detected. Cytologic examination of lymph node aspirates reveals lymphoid hyperplasia, neutrophilic infiltrates, and bipolar rods (Fig. 94.3).

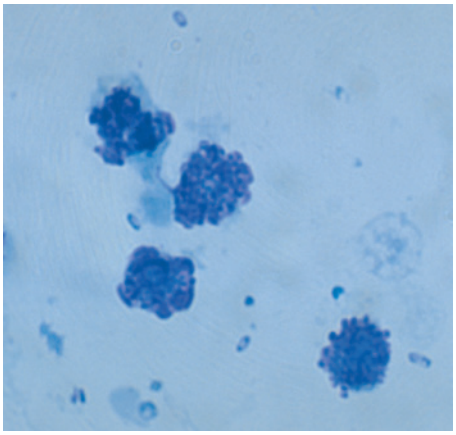


FIG 94.3
Lymph node aspirate from a cat with bubonic plague stained with Wright stain. Bipolar rods are scattered throughout the field.

Cytologic demonstration of bipolar rods on examination of lymph node aspirates, exudates from draining abscesses, or airway washings combined with a history of potential exposure, the presence of rodent fleas, and appropriate clinical signs lead to a presumptive diagnosis of feline plague. Because some cats survive infection and antibodies can be detected in serum for at least 300 days, detection of antibodies alone may indicate only exposure, not clinical infection. However, demonstration of a fourfold increase in antibody titer is consistent with recent infection. A definitive diagnosis is made by culture, fluorescent antibody demonstration of *Y. pestis* in smears of the tonsillar region, lymph node aspirates, exudates from draining abscesses, airway washings, or blood or PCR amplification of *Y. pestis* DNA from blood, fluids, or tissues.

Treatment

Supportive care should be administered as indicated for any bacteremic animal. Cervical lymph node abscesses should be drained and flushed with the clinician wearing gloves, a mask, and a gown. Parenteral antibiotics should be administered until anorexia and fever resolve. Optimal antibiotics for treatment of plague in infected cats in the United States are unknown. Streptomycin administered intramuscularly at 5 mg/kg q12h was used historically but is not widely available. Cats treated with gentamicin intramuscularly or intravenously at 2 to 4 mg/kg q12-24h, or enrofloxacin intramuscularly or intravenously at 5 mg/kg q24h, have resolved

clinical signs. Chloramphenicol administered orally or intravenously at 15 mg/kg q12h can be used in cats with central nervous system signs. Antibiotics should be administered orally for 21 days after the cat has survived the bacteremic phase; doxycycline at 5 mg/kg q12h is an appropriate choice. Care should be taken to avoid doxycycline-associated esophageal strictures in feline cases by giving water after drug administration or liquefying the product. In one study, 90.9% of cats treated with antibiotics survived, whereas only 23.8% of untreated cats survived (Eidson et al., 1991). In a dog case series, 73% of the 62 suspect cases were treated with antibiotics and 97% of the dogs survived (Nichols et al., 2014). The prognosis is believed to be worse for the pneumonic form of *Y. pestis* infection. A recent case seen at the author's institution developed a consolidated lung lobe and died after lobectomy.

Zoonotic Aspects and Prevention

Pets should be housed indoors when possible and not allowed to hunt. Flea control should be used, and the rodent population should be controlled if possible. Sleeping in the same bed with the family dog was associated with plague in one study, which suggests dogs can bring infected fleas into the human environment, and that flea control should be maintained on all pets in the home (Gould et al., 2008). Doxycycline at the doses listed for therapy should be administered for 7 days to animals with potential exposure. Human infection occurs after contact with infected fleas; contact with the tissues or exudates from infected animals, including cats and dog; and from bites and scratches from infected cats. Even though fomite transmission is unlikely, because the organism is sensitive to drying it can survive for weeks to months in infected carcasses and for up to 1 year in infected fleas. Cats and dogs from endemic areas with clinical signs of bacteremia, respiratory tract disease, or cervical draining areas or masses in the spring, summer, and early fall months should immediately be treated for fleas and handled with the clinician wearing gloves, a mask, and a gown until the diagnosis is made or discarded. While hospitalized, as few people as possible should handle infected cats and dogs while in isolation. Exposed personnel should see their physicians to discuss prophylactic antibiotic therapy; antimicrobial-resistant strains of *Y. pestis* are uncommon (Welch et al., 2007). It is believed that cats and dogs are not infectious to human beings after 3 days of antibiotic therapy. Areas where infected cats or dogs are handled should be thoroughly cleaned with routine disinfectants.

LEPTOSPIROSIS

Etiology and Epidemiology

Leptospires are motile, filamentous spirochetes that infect animals and human beings. Leptospirosis can be caused by many different serovars of *Leptospira interrogans* and *Leptospira kirschneri* (Sykes et al., 2011). Seropositive dogs have been detected in many countries, and the most prevalent serovars vary by country and regions within countries (White et al., 2017). In the United States, antibodies against *L. autumnalis, L. bratislava, L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae,* and *L. pomona* have been detected most commonly. One study based on PCR analyses of *Leptospira* spp. DNA in urine from dogs in the United States showed *L. grippotyphosa* in 78 of the 98 positive samples (Harkin and Hays, 2016). Recently, the *L. santarosai* serogroup Sejroe was amplified from healthy dogs in Sao Paulo (Miotto et al., 2018). The *Leptospira* spp. that infect cats are less clear, and cats appear to be more resistant to clinical disease than dogs.

Prevalence and risk factors for cases of canine leptospirosis have been evaluated in several studies. In the United States the number of seropositive dogs increased between 2002 and 2004 (Moore et al., 2006). *Leptospira* spp. exposure can be common in the United States; 8.1% of 33,119 canine serum samples had titers greater than 1:1600 in one study (Gautam et al., 2010). Infection by *Leptospira* spp. occurs in both rural and suburban environments in semitropical areas of the world with alkaline soil conditions. In one study in Kansas, an association between leptospirosis in dogs and urban environments was made, so leptospirosis should be considered in all appropriate clinical situations (Raghavan et al., 2011). Exposure to water outdoors, wetlands, and public open spaces were identified as risk factors in one case-control study (Ghneim et al., 2007). Clinical cases are most commonly diagnosed in the summer and early fall, and numbers of cases often increase in years with heavy rainfall. Infection by host-adapted species results in subclinical infection; the host acts as a reservoir, shedding the organism intermittently.

Infection by non-host-adapted species results in clinical illness. *Leptospira* spp. are passed in urine and enter the body through abraded skin or intact mucous membranes. Transmission also occurs through bite wounds; by venereal contact; transplacentally; and by ingestion of contaminated tissues, soil, water, bedding, food, and other fomites. In an experimental study, *L. pomona* but not *L. bratislava* was successfully transmitted by conjunctival inoculation and resulted in fever and lethargy starting within 7 days (Greenlee et al., 2005). Hosts with preexisting antibody titers usually eliminate the organism quickly and remain subclinically infected. *Leptospira* spp. replicate in multiple tissues of nonimmune hosts or hosts infected by a non–host-adapted species; in the dog, the liver and kidneys develop the highest levels of infection. Inflammation induced by organism replication and production of toxins leads to renal, hepatic, or pulmonary disease. Dogs that are treated or develop appropriate immune responses usually survive. Some animals clear the infection 2 to 3 weeks after exposure without treatment but develop chronic active hepatitis or chronic kidney disease. Cats are generally subclinically affected but may shed the organism into the environment for variable periods after exposure and occasionally develop polyuria, polydipsia, and renal insufficiency (Arbour et al., 2012).

Clinical Findings

Dogs of any age, breed, or gender can develop leptospirosis if not previously immune. Male, middle-aged, herding dogs; hounds; working dogs; and mixed-breed dogs were at greater risk than companion dogs younger than 1 year in one study (Ward et al., 2002). But in a more recent study, small breed dogs were over-represented (Lee et al., 2014). Dogs with peracute clinical disease are usually presented for evaluation of anorexia, depression, generalized muscle hyperesthesia, tachypnea, and vomiting (Box 94.2). Fever, pale mucous membranes, and tachycardia are usually present. Petechiae, ecchymoses, melena, and epistaxis occur frequently from thrombocytopenia and disseminated intravascular coagulation. Peracute infections may rapidly progress to death before marked renal or hepatic disease is recognized.

Fever, depression, and clinical signs or physical examination findings consistent with hemorrhagic syndromes, hepatic disease, renal disease, or a combination of hepatic and renal disease are common in subacutely infected dogs. Conjunctivitis, panuveitis, rhinitis, tonsillitis, cough, and dyspnea occur occasionally. Oliguric or anuric renal failure can develop during the subacute phase. Clinical findings can vary on the basis of the infecting serovar (Goldstein et al., 2006). The pulmonary hemorrhagic syndrome described in people is likely to occur in dogs as well, so leptospirosis should be on the differential list for dogs with dyspnea (Klopfleisch et al., 2010).

Some dogs that survive peracute or subacute infection develop chronic interstitial nephritis or chronic active hepatitis. Polyuria, polydipsia, weight loss, ascites, and signs of hepatic encephalopathy secondary to hepatic insufficiency are the most common manifestations of chronic leptospirosis.

BOX 94.2

Clinical Findings in Dogs With Leptospirosis

Signalment

All ages, breeds, and gender

History

Exposure to appropriate reservoir host or contaminated environment
Urban environment common
Anorexia, depression, lethargy

Physical Examination

Fever
Anterior uveitis
Hemorrhagic tendencies, including melena, epistaxis, petechiae, and ecchymoses
Vomiting, diarrhea
Muscle or meningeal pain
Renomegaly with or without renal pain
Hepatomegaly
Polyuria/polydipsia
Icterus
Coughing or respiratory distress

Clinicopathologic and Imaging Findings

Thrombocytopenia
Leukopenia (acute)
Leukocytosis (subacute)
Azotemia
Suboptimal urine concentrating ability
Pyuria and hematuria without obvious bacteriuria
Hyperbilirubinemia and bilirubinuria
Increased activities of alanine transaminase, aspartate transaminase, alkaline phosphatase, and creatine kinase
Interstitial to alveolar lung disease
Hepatomegaly or renomegaly

Diagnosis

Culture of urine, blood, or tissues
Demonstration of the organism in urine by darkfield or phase-contrast microscopy
Demonstration of organismal DNA in urine, blood, or tissues by PCR
Combination of increasing antibody titer with clinical signs and response to therapy

PCR, Polymerase chain reaction.

Diagnosis

Multiple nonspecific clinicopathologic and imaging abnormalities occur in dogs with leptospirosis and vary depending on the host, the serovar, and whether the disease was peracute, subacute, or chronic. Leukopenia (peracute leptospiremic phase), leukocytosis with or without a left shift, thrombocytopenia, regenerative anemia (from blood loss), or nonregenerative anemia (from chronic renal or hepatic disease) are common hematologic abnormalities. Hyponatremia; hypokalemia; hyperphosphatemia; hypoalbuminemia; hypocalcemia; azotemia; hyperbilirubinemia; decreased total carbon dioxide concentrations; and increased activities of alanine transaminase, alkaline phosphatase, and aspartate transaminase are common serum biochemical abnormalities that develop from renal disease, hepatic disease, gastrointestinal losses, or acidosis. Hyperglobulinemia is detected in some dogs with chronic leptospirosis. Dogs with myositis may have increased creatine kinase activity. Urinalysis abnormalities include bilirubinuria, suboptimal urine specific gravity in the face of azotemia, granular casts, and increased numbers of granulocytes and erythrocytes. The organism is not seen in the urine sediment by light microscopy. Renomegaly, hepatomegaly, and interstitial or alveolar pulmonary infiltrates are common radiographic abnormalities. Mineralization of the renal pelves and cortices can occur with chronic leptospirosis. On histopathologic evaluation of renal tissues, mesangial proliferative glomerulonephritis with or without interstitial nephritis were the most common lesions in one study (Ortega-Pacheco, 2008).

Detection of anti-*Leptospira* antibodies is commonly performed by a microscopic agglutination test (MAT). In some countries, there are also now two commercially available point of care assays (Zoetis Animal Health; IDEXX

Laboratories). One of the commercial kits is optimized to detect immunoglobulin M (IgM) antibodies and in one study was the first to become positive in most dogs during acute infection (Lizer et al., 2018). If MAT is used, because of the wide range of leptospires infecting dogs, as many serovars as possible should be used for screening. *Leptospira bratislava, L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae,* and *L. pomona* are commonly used. Positive titers can result from active infection, previous infection, or vaccination. Antibody titers can be negative in animals with peracute disease; seronegative dogs with classic clinical disease should be retested in 2 to 4 weeks. The serovar with the highest titer is not always the infecting serovar. The highest titer on a convalescent serum sample may be more likely the primary serovar. When the same sera were sent to different laboratories, the results were not always in agreement for the serovar giving the highest titer (Miller et al., 2011), and some vaccinated, client-owned dogs have high titer responses (Martin et al., 2014).

Documentation of seroconversion (negative result becoming positive over time), a single MAT titer greater than 1:3200, or a fourfold increase in antibody titers combined with appropriate clinicopathologic abnormalities and clinical findings, are suggestive of clinical leptospirosis. A definitive diagnosis is made by demonstrating the organism in urine, blood, or tissues. The organism can be seen in urine using darkfield or phase-contrast microscopy, but because of intermittent shedding of small numbers of organisms these procedures can be falsely negative. The organism can be cultured from urine collected by cystocentesis, blood, or renal or hepatic tissue. Materials for culture should be collected before administration of antibiotics, placed in transport media immediately after collection, and transported to the laboratory as quickly as possible. Leptospiremia can be of short duration, and urine shedding of the organism can be intermittent, giving false-negative results. PCR can be used to demonstrate the organism in urine, blood, or tissues (Harkin et al., 2003a, 2003b). In one study of 500 dogs, 41 (8.2%) were PCR-positive for a *Leptospira* spp. in urine, and some of these dogs were clinically normal (Harkin et al., 2003a). None of the PCR-positive dogs was culture-positive, and titers were not always high. *Leptospira* spp. DNA can also be amplified from renal tissues that have no evidence of inflammatory disease (Dash et al., 2018). Recent vaccination should not result in positive PCR assay results (Midence et al., 2012). Antibodies induced by *Leptospira* spp. vaccine did not cross-react with *Borrelia burgdorferi* peptides in one study (Caress et al., 2017).

Treatment

Fluid therapy is required for most dogs; intense diuresis for renal involvement may be required (see Chapter 41). Hemodialysis may increase the probability of survival in dogs with oliguric or anuric renal failure. Dogs should be treated during the initial treatment period with ampicillin administered intravenously at 22 mg/kg q8h. Some quinolones have an effect against *Leptospira* spp. and can be used in combination with penicillins during the acute phase of infection, in particular if other gram-negative organisms are on the differential list. Ampicillin and enrofloxacin were used concurrently in one study, and 83% of infected dogs survived (Adin et al., 2000). Penicillins such as amoxicillin or amoxicillin clavulanate should be administered for 2 weeks. Doxycycline administered orally at 5 mg/kg q12h for 2 weeks should be used to eliminate the renal carrier phase (Sykes et al., 2011).

Zoonotic Aspects and Prevention

All mammalian serovars should be considered potentially zoonotic to human beings. Some human beings have antibodies against canine serovars, suggesting the dog can be a reservoir for human infection (Brod et al., 2005). However, results from studies attempting to associate dog contact with leptospirosis in humans have varied. For example, 0/91 people exposed to dogs with proven leptospirosis were seropositive suggesting the risk was minimal (Barmettler et al., 2011). As leptospirosis is an occupational risk for veterinarians, the organism should be on the list of differential diagnoses if appropriate clinical signs of disease develop (Whitney, 2009). Infected urine, contaminated water, and reservoir hosts should be avoided. Infected dogs should be handled with the clinician wearing gloves. Contaminated surfaces should be cleaned with detergents and disinfected (see Chapter 93).

To lessen risk of exposure, owners should attempt to restrict dogs from drinking potentially contaminated water. Healthy dogs can shed *Leptospira* spp. in urine; 7% of 525 urine samples from dogs in Dublin were positive in one study (Rojas et al., 2010). Thus contact with dog urine should always be avoided. Vaccines available for some serovars reduce the severity of disease and lessen leptospire shedding in urine. Several products containing serovars *L. canicola, L. icterohaemorrhagiae, L. grippotyphosa,* and *L. pomona* are now available and should be used rather than two serovar vaccines to provide the greatest spectrum of protection (see Chapter 93). Numbers of long-term duration of immunity studies are small, but recently, one commercially available product was shown to induce significant protection against *L. grippotyphosa* for 15 months when compared to unvaccinated controls (Grosenbaugh and Pardo, 2018). Dogs in endemic areas should be administered at least two vaccines 2 to 4 weeks apart, and annual boosters are recommended (www.aahanet.org). Canine side effects associated with the current four serovar-containing vaccines are generally transient and mild (Spiri et al., 2017; Yao et al., 2015). In one study, hypersensitivity reactions to *Leptospira* spp. vaccines were estimated at 6.5/10,000 vaccinated dogs (Yao et al., 2015).

MYCOPLASMA AND UREAPLASMA

Etiology and Epidemiology

Mycoplasma spp. and *Ureaplasma* spp. are small, free-living microorganisms that lack a rigid, protective cell wall and

depend on the environment for nourishment. Some *Mycoplasma* spp. and *Ureaplasma* spp. are considered normal flora of mucous membranes. For example, *Mycoplasma* spp. have been isolated from the vagina of 75% of healthy dogs (Doig et al., 1981), the pharynx of 100% of healthy dogs, and the pharynx of 35% of healthy cats (Randolph et al., 1993). The hemotrophic mycoplasmas, *Mycoplasma haemofelis*, *"Candidatus* Mycoplasma haemominutum," *"Candidatus* Mycoplasma turicensis", *Mycoplasma haemocanis,* and *"Candidatus* Mycoplasma haematoparvum" are associated with erythrocytes and are discussed in Chapter 82.

Mycoplasma felis conjunctivitis in cats, *M. felis* upper respiratory tract infection in cats, *Mycoplasma gateae* polyarthritis in cats, and *Mycoplasma cynos* pneumonia in dogs have been induced experimentally. The pathogenic potential for most *Mycoplasma* spp. or *Ureaplasma* spp. is difficult to determine because the organisms can be cultured or amplified from both healthy and sick animals. In one shelter study, *M. cynos* DNA was amplified for 29.2% of healthy dogs suggesting that not all strains are pathogenic (Lavan and Knesl, 2015). For *M. cynos*, genetic heterogeneity has been documented, and some strains may be more pathogenic than others (Mannering et al., 2009).

In many cases *Mycoplasma* spp. or *Ureaplasma* spp. may be colonizing diseased tissues as opportunists as a result of inflammation induced by other causes. Other bacteria or viruses are usually identified concurrently with *Mycoplasma* spp. or *Ureaplasma* spp., making it difficult to determine which agent is inducing disease. *Ureaplasma* spp. have also been cultured from the vagina (40%) and prepuce (10%) of healthy dogs (Doig et al., 1981).

Mycoplasma spp. were isolated in pure culture from 20 of 2900 dogs with clinical signs of urinary tract inflammation (Jang et al., 1984), *Mycoplasma canis* was isolated from 4 of 100 dogs (3 in pure culture) with clinical signs of lower urinary tract disease (Ulgen et al., 2006), and *M. canis* was isolated from nine dogs with clinical signs of urogenital disease (L'Abee-Lund et al., 2003). Some *M. canis* positive dogs were azotemic, suggesting pyelonephritis (Ulgen et al., 2006), and some have been resistant to therapy (L'Abee-Lund et al., 2003).

Multiple studies suggest that some *Mycoplasma* spp. can be primary pathogens of the respiratory tract of dogs. *Mycoplasma* spp. were the only organism cultured from 7 of 93 dogs (Jameson et al., 1995), 5 of 38 dogs (Randolph et al., 1993), and 14 dogs (Chandler et al., 2002) with lower respiratory tract disease. In one study that compared *Mycoplasma* isolates from dogs with and without respiratory disease, *M. cynos* in the lower respiratory tract was statistically associated with respiratory disease (Chalker et al., 2004). In another study, 80% of dogs that developed antibodies to *M. cynos* had respiratory signs of disease (Rycroft et al., 2007).

In a recent study of cats with and without conjunctivitis, the presence of *Mycoplasma* spp. DNA was associated with the presence of conjunctivitis (Low et al., 2007). Both *M. felis* and *M. gateae* have been associated with feline ulcerative keratitis (Gray et al., 2005). *Mycoplasma gateae* and *M. felis* have been detected in cats with polyarthritis. *Mycoplasma* spp. have also been associated with the presence of rhinosinusitis, lower respiratory disease, and pyothorax. In one study of cats with upper respiratory disease in Germany, *M. felis, Mycoplasma canadense, M. cynos, M gateae, Mycoplasma lipophilum, and Mycoplasma hyopharyngis* were identified in clinically ill cats (Hartman et al., 2010).

Clinical Findings

Mycoplasma spp. infection should be considered a potential differential diagnosis for cats presented for evaluation of conjunctivitis, keratitis, sneezing and mucopurulent nasal discharge, coughing, dyspnea, fever, lameness with or without swollen painful joints, subcutaneous abscessation, or abortion. *Mycoplasma* spp. or *Ureaplasma* spp. infections were not associated with lower urinary tract disease of cats in one study (Abou et al., 2006). *Mycoplasma* spp. or *Ureaplasma* spp. infection should be considered a potential differential diagnosis for dogs presented for evaluation of coughing, dyspnea, fever, pollakiuria, hematuria, azotemia, lameness with or without swollen painful joints, mucopurulent vaginal discharge, or infertility. *Mycoplasma* spp. and *Ureaplasma* spp. are generally not recognized cytologically and usually do not grow on aerobic media; infection should be suspected in animals with neutrophilic inflammation without visible bacteria or negative aerobic culture. The index of suspicion for *Mycoplasma* spp. or *Ureaplasma* spp. infection is higher if the animal has neutrophilic inflammation and has been poorly responsive to cell wall–inhibiting antibiotics such as penicillins or cephalosporins.

Diagnosis

The clinicopathologic and imaging findings associated with *Mycoplasma* spp. or *Ureaplasma* spp. infections are similar to those induced by other bacterial infections. Neutrophilia and monocytosis are common in dogs with pneumonia; pyuria and proteinuria occur in dogs with urinary tract disease.

Preputial discharges, vaginal discharges, chronic draining wounds, airway washings, and synovial fluid from animals with *Mycoplasma* spp. or *Ureaplasma* spp. infections have nondegenerate neutrophils as the most common cell type. Dogs with lower respiratory tract disease and pure *Mycoplasma* cultures have alveolar lung patterns that cannot be differentiated from those in dogs with mixed bacterial and *Mycoplasma* cultures. In some dogs and cats with small airway disease evident radiographically, *Mycoplasma* spp. are isolated from the airways in pure culture (Chandler et al., 2002). Joint radiographs of animals with *Mycoplasma*-associated polyarthritis reveal erosive or nonerosive changes (Zeugswetter, 2007).

Specimens for *Mycoplasma* spp. or *Ureaplasma* spp. culture should be plated immediately or transported to the laboratory in Hayflicks broth medium, Amies medium with charcoal, or modified Stuart bacterial transport medium. Specimens should be shipped on ice packs if the transport time is expected to be less than 24 hours and on dry ice if

the transport time is expected to be longer than 24 hours. Most *Mycoplasma* spp. require special media, but in one report *M. canis* grew on regular blood agar plates (L'Abee-Lund et al., 2003). Because the organisms are part of the normal flora, culture of the mucous membranes of healthy animals is never indicated.

Because *Mycoplasma* spp. or *Ureaplasma* spp. can be cultured from healthy animals, interpretation of positive culture results in sick animals is difficult. Most laboratories do not report results of antibiotic susceptibility testing. The disease association is strong if *Mycoplasma* spp. or *Ureaplasma* spp. are isolated in pure culture from tissues from which isolation is unusual (lower airway, uterus, joints). Response to treatment with drugs with known activity against *Mycoplasma* spp. or *Ureaplasma* spp. may help support the diagnosis of disease induced by these agents.

PCR assays are now available for amplification of mycoplasmal DNA (Johnson et al., 2004; Chalker et al., 2004; Low et al., 2007; Zirofsky et al., 2018) in multiple diagnostic laboratories, but they have the same diagnostic limitations as cultures as positive results do not correlate to the presence of disease or response to therapy. Some laboratories use *M. felis* or *M. cynos* specific primers in the PCR assays, which will result in failure to detect other potentially pathogenic species.

Treatment

Tylosin, erythromycin, clindamycin, lincomycin, tetracyclines, chloramphenicol, aminoglycosides, and fluoroquinolones are effective for treatment of *Mycoplasma* spp. or *Ureaplasma* spp. infections (see Chapter 92). Doxycycline administered orally at 10 mg/kg q24h or at 5 mg/kg q12h is generally effective in animals with a competent immune system or without life-threatening disease (Lappin et al., 2017). In animals with mixed infections with gram-negative organisms, life-threatening disease, or suspected tetracycline-resistant strains, fluoroquinolones or azithromycin are good alternate antibiotic choices. One cat with a non-healing bite wound was positive for *M. equigenitalium* or *M. elephantis* DNA and ultimately responded to enrofloxacin and clindamycin (Torres-Henderson et al., 2014). In one study of shelter cats with suspected bacterial upper respiratory infections, the new veterinary fluoroquinolone, pradofloxacin, gave numerically higher response rates than amoxicillin (Spindel et al., 2008). Treatment for 4 to 6 weeks is usually required for lower airway, subcutaneous, or joint infections.

Zoonotic Aspects and Prevention

Although risk of zoonotic transfer is likely minimal, bite wound transmission of *Mycoplasma* spp. from an infected cat to the hand of a human being has been reported (McCabe et al., 1987). Most *Mycoplasma* spp. or *Ureaplasma* spp. infections in dogs and cats are opportunistic and associated with other causes of inflammation; thus they are not likely to be directly contagious from animal to animal unless a pathogenic strain exists. *Mycoplasma* spp. appear to have been associated with respiratory tract disease in dogs and cats as primary pathogens and may be spread from animal to animal, as with *M. pneumoniae* in human beings. Animals with conjunctivitis or respiratory tract disease should be isolated from other animals until clinical signs of disease have resolved (see Chapter 93). *Mycoplasma* spp. and *Ureaplasma* spp. are susceptible to routine disinfectants and rapidly die outside the host.

Suggested Readings

Canine Bartonellosis

Breitschwerdt EB, et al. Endocarditis in a dog due to infection with a novel *Bartonella* subspecies. *J Clin Microbiol*. 1995;33:154.

Breitschwerdt EB, et al. *Bartonella vinsonii* subsp. *berkhoffii* and related members of the alpha subdivision of the Proteobacteria in dogs with cardiac arrhythmias, endocarditis, or myocarditis. *J Clin Microbiol*. 1999;37:3618.

Breitschewerdt EB, et al. Clinicopathological abnormalities and treatment response in 24 dogs seroreactive to *Bartonella vinsonii* (*berkhoffii*) antigens. *J Am Anim Hosp Assoc*. 2004;40:92.

Duncan AW, et al. A combined approach for the enhanced detection and isolation of *Bartonella* species in dog blood samples: pre-enrichment liquid culture followed by PCR and subculture onto agar plates. *J Microbiol Methods*. 2007;69:273.

Fenimore A, et al. *Bartonella* spp. DNA in cardiac tissues from dogs in Colorado and Wyoming. *J Vet Intern Med*. 2011;25:613.

Lashnits E, et al. *Bartonella* seroepidemiology in dogs from North America, 2008-2014. *J Vet Intern Med*. 2018;32:222.

MacDonald KA, et al. A prospective study of canine infective endocarditis in northern California (1999-2001): emergence of *Bartonella* as a prevalent etiologic agent. *J Vet Intern Med*. 2004; 18:56.

Okaro U, et al. *Bartonella* Species, an emerging cause of blood-culture-negative endocarditis. *Clin Microbiol Rev*. 2017;30:709.

Randell MG, et al. *Bartonella henselae* infection in a dog with recalcitrant ineffective erythropoiesis. *Vet Clin Pathol*. 2018;47:45.

Sykes JE, et al. Evaluation of the relationship between causative organisms and clinical characteristics of infective endocarditis in dogs: 71 cases (1992-2005). *J Am Vet Med Assoc*. 2006;228: 1723.

Yore K, et al. Flea species infesting dogs in Florida and *Bartonella* spp. prevalence rates. *Vet Parasitol*. 2014;199:225.

Feline Bartonellosis

Bayliss DB, et al. Serum feline pancreatic lipase immunoreactivity concentration and seroprevalences of antibodies against Toxoplasma gondii and Bartonella species in client-owned cats. *J Feline Med Surg*. 2009;11:663–667.

Biswas S, et al. Comparative activity of pradofloxacin, enrofloxacin, and azithromycin against *Bartonella henselae* isolates collected from cats and a human. *J Clin Microbiol*. 2010;48:617.

Bradbury CA, Lappin MR. Evaluation of topical application of 10% imidacloprid-1% moxidectin to prevent *Bartonella henselae* transmission from cat fleas. *J Am Vet Med Assoc*. 2010;236:869.

Breitschwerdt EB, et al. *Bartonella* species in blood of immunocompetent persons with animal and arthropod contact. *Emerg Inf Dis*. 2007;13:938.

Breitschwerdt EB. Bartonellosis, One Health and all creatures great and small. *Vet Dermatol*. 2017;28:96.

Breitschwerdt EB. Did *Bartonella henselae* contribute to the deaths of two veterinarians? *Parasit Vectors*. 2015;8:317.

Brunt J, et al. Association of Feline Practitioners 2006 panel report on diagnosis, treatment and prevention of *Bartonella* species infections. *J Fel Med Surg*. 2006;8:213.

Dowers KL, Lappin MR. The association of *Bartonella* spp. infection with chronic stomatitis in cats. *J Vet Intern Med*. 2005;19:471.

Drummond MR, et al. Improvement of *Bartonella henselae* DNA detection in cat blood samples by combining molecular and culture methods. *J Clin Microbiol*. 2018;56(5):doi:10.1128/JCM.01732-17.

Ishak AM, et al. Prevalence of *Mycoplasma haemofelis*, '*Candidatus* Mycoplasma haemominutum', *Bartonella* species, *Ehrlichia* species, and *Anaplasma phagocytophilum* DNA in the blood of cats with anemia. *J Feline Med Surg*. 2007;9:1.

Kaplan JE, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents, Recommendations and Reports. *MMWR*. 2009;58(RR04):1.

Lappin MR, et al. Prevalence of *Bartonella* species DNA in the blood of cats with and without fever. *J Fel Med Surg*. 2009;11:141.

Lappin MR, Hawley J. Presence of *Bartonella* species and *Rickettsia* species DNA in the blood, oral cavity, skin and claw beds of cats in the United States. *Vet Dermatol*. 2009;20:509.

Lappin MR, Miller W, Sellins D. Effect of doxycycline or orbifloxacin administration on *Bartonella* spp. and Hemoplasma assay results in naturally exposed cats. *Intern J Appl Res Vet Med*. 2012;10:225.

Maggi RG, et al. *Bartonella* spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region. *Emerg Infect Dis*. 2012;18:783.

Nutter FB, et al. Seroprevalences of antibodies against *Bartonella henselae* and *Toxoplasma gondii* and fecal shedding of *Cryptosporidium* spp., *Giardia* spp., and *Toxocara cati* in feral and domestic cats. *J Am Vet Med Assoc*. 2004;235:1394.

Oteo JA, et al. Prevalence of *Bartonella* spp. by culture, PCR and serology, in veterinary personnel from Spain. *Parasit Vectors*. 2017;10:553.

Pearce L, et al. Prevalence of *Bartonella henselae* specific antibodies in serum of cats with and without clinical signs of central nervous system disease. *J Fel Med Surg*. 2006;8:315.

Powell CC, et al. Inoculation with *Bartonella henselae* followed by feline herpesvirus 1 fails to activate ocular toxoplasmosis in chronically infected cats. *J Fel Med Surg*. 2002;4:107.

Quimby JM, et al. Evaluation of the association of *Bartonella* species, feline herpesvirus 1, feline calicivirus, feline leukemia virus and feline immunodeficiency virus with chronic feline gingivostomatitis. *J Feline Med Surg*. 2008;10:66.

Eidson M, et al. Clinical, clinicopathologic, and pathologic features of plague in cats: 119 cases (1977-1988). *J Am Vet Med Assoc*. 1991;199:1191.

Feline Plague

Eisen RJ, et al. Early-phase transmission of *Yersinia pestis* by cat fleas (*Ctenocephalides felis*) and their potential role as vectors in a plague-endemic region of Uganda. *Am J Trop Med Hyg*. 2008;78:949.

Gage KL, et al. Cases of cat-associated human plague in the Western US, 1977-1998. *Clin Infect Dis*. 2000;30:893.

Gasper PW, et al. Plague *(Yersinia pestis)* in cats: description of experimentally induced disease. *J Med Entomol*. 1993;30:20.

Gould LH, et al. Dog-associated risk factors for human plague. *Zoonoses Public Health*. 2008;55:448.

Kassem AM, et al. Notes from the field: Plague in Domestic Cats - Idaho, 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:1378–1379.

McElroy KM, et al. Flea-associated zoonotic diseases of cats in the USA: bartonellosis, flea-borne rickettsioses, and plague. *Trends Parasitol*. 2010;26:197–204.

Nichols MC, et al. *Yersinia pestis* infection in dogs: 62 cases (2003-2011). *J Am Vet Med Assoc*. 2014;244:1176.

Pennisi MG, et al. *Yersinia pestis* infection in cats: ABCD guidelines on prevention and management. *J Feline Med Surg*. 2013;15:582.

Orloski KA, et al. *Yersinia pestis* infection in three dogs. *J Am Vet Med Assoc*. 1995;207:316.

Welch TJ, et al. Multiple antimicrobial resistance in plague: an emerging public health risk. *PLoS ONE*. 2007;2:e309.

Wendte JM, et al. In vitro efficacy of antibiotics commonly used to treat human plague against intracellular Yersinia pestis. *Antimicrob Agents Chemother*. 2011;55:3752.

Leptospirosis

Adin CA, et al. Treatment and outcome of dogs with leptospirosis: 36 cases (1990-1998). *J Am Vet Med Assoc*. 2000;216:371.

Arbour J, et al. Clinical leptospirosis in three cats (2001-2009). *J Am Anim Hosp Assoc*. 2012;48:256.

Barmettler R, et al. Assessment of exposure to *Leptospira* serovars in veterinary staff and dog owners in contact with infected dogs. *J Am Vet Med Assoc*. 2011;238:183.

Brod CS, et al. Evidence of dog as a reservoir for human leptospirosis: a serovar isolation, molecular characterization and its use in a serological survey. *Rev Soc Bras Med Trop*. 2005;38:294.

Caress AL, Moroff S, Lappin MR. *Leptospira* spp. vaccinal antibodies do not react with *Borrelia burgdorferi* peptides used in the AccuPlex 4. *J Vet Diagn Invest*. 2017;29:788–790.

Dash BR, et al. Molecular detection of *Leptospira* spp. from canine kidney tissues and its association with renal lesions. *Vet World*. 2018;11:530–534.

Gautam R, et al. Detection of antibodies against *Leptospira* serovars via microscopic agglutination tests in dogs in the United States, 2000-2007. *J Am Vet Med Assoc*. 2010;237:293.

Ghneim GS, et al. Use of a case-control study and geographic information systems to determine environmental and demographic risk factors for canine leptospirosis. *Vet Res*. 2007;38:37.

Goldstein RE, et al. Influence of infecting serogroup on clinical features of leptospirosis in dogs. *J Vet Intern Med*. 2006;20:489.

Greenlee JJ, et al. Experimental canine leptospirosis caused by *Leptospira interrogans* serovars *pomona* and *Bratislava*. *Am J Vet Res*. 2005;66:1816.

Grosenbaugh DA, Pardo MC. Fifteen-month duration of immunity for the serovar Grippotyphosa fraction of a tetravalent canine leptospirosis vaccine. *Vet Rec*. 2018;182:665.

Harkin KR, et al. Comparison of polymerase chain reaction assay, bacteriologic culture, and serologic testing in assessment of prevalence of urinary shedding of leptospires in dogs. *J Am Vet Med Assoc*. 2003a;222:1230.

Harkin KR, et al. Clinical application of a polymerase chain reaction assay for diagnosis of leptospirosis in dogs. *J Am Vet Med Assoc*. 2003b;222:1224.

Harkin KR, Hays MP. Variable-number tandem-repeat analysis of leptospiral DNA isolated from canine urine samples molecularly confirmed to contain pathogenic leptospires. *J Am Vet Med Assoc*. 2016;249:399–405.

Klopfleisch R, et al. An emerging pulmonary haemorrhagic syndrome in dogs: similar to the human leptospiral pulmonary haemorrhagic syndrome? *Vet Med Int*. 2010;2010:928541.

Lee HS, et al. Signalment changes in canine leptospirosis between 1970 and 2009. *J Vet Intern Med*. 2014;28:294–299.

Lizer J, et al. Evaluation of 3 serological tests for early detection of *Leptospira*-specific antibodies in experimentally infected dogs. *J Vet Intern Med*. 2018;32:201–207.

Markovich JE, et al. The prevalence of leptospiral antibodies in free roaming cats in Worcester County, Massachusetts. *J Vet Intern Med*. 2012;26:688.

Martin LE, et al. Vaccine-associated *Leptospira* antibodies in client-owned dogs. *J Vet Intern Med*. 2014;28:789–792.

Midence JN, et al. Effects of recent *Leptospira* vaccination on whole blood real-time PCR testing in healthy client-owned dogs. *J Vet Intern Med*. 2012;26:149.

Miotto BA, et al. Prospective study of canine leptospirosis in shelter and stray dog populations: identification of chronic carriers and different *Leptospira* species infecting dogs. *PLoS ONE*. 2018;13.

Miller MD, et al. Variability in results of the microscopic agglutination test in dogs with clinical leptospirosis and dogs vaccinated against leptospirosis. *J Vet Intern Med*. 2011;25:426.

Moore GE, et al. Canine leptospirosis, United States, 2002-2004. *Emerg Infect Dis*. 2006;12:501.

Ortega-Pacheco A, et al. Frequency and type of renal lesions in dogs naturally infected with leptospira species. *Ann N Y Acad Sci*. 2008;1149:270.

Raghavan R, et al. Evaluations of land cover risk factors for canine leptospirosis: 94 cases (2002-2009). *Prev Vet Med*. 2011;101:241.

Rojas P, et al. Detection and quantification of leptospires in urine of dogs: a maintenance host for the zoonotic disease leptospirosis. *Eur J Clin Microbiol Infect Dis*. 2010;29:1305.

Shropshire SB, et al. Evaluation of the *Leptospira* species microscopic agglutination test in experimentally vaccinated cats and Leptospira species seropositivity in aged azotemic client-owned cats. *J Feline Med Surg*. 2016;18:768–772.

Spiri AM, et al. Clinical, serological and echocardiographic examination of healthy field dogs before and after vaccination with a commercial tetravalent leptospirosis vaccine. *BMC Vet Res*. 2017;13:138.

Sykes JE, et al. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25:1.

Ward MP, et al. Prevalence of and risk factors for leptospirosis among dogs in the United States and Canada: 677 cases (1970-1998). *J Am Vet Med Assoc*. 2002;220:53.

White AM, et al. Hotspots of canine leptospirosis in the United States of America. *Vet J*. 2017;222:29–35.

Whitney EA, et al. Prevalence of and risk factors for serum antibodies against Leptospira serovars in US veterinarians. *J Am Vet Med Assoc*. 2009;234:938.

Yao PJ, et al. Incidence rates and risk factors for owner-reported adverse events following vaccination of dogs that did or did not receive a Leptospira vaccine. *Am Vet Med Assoc*. 2015;247:1139–1145.

Mycoplasma and Ureaplasma

Abou N, et al. PCR-based detection reveals no causative role for *Mycoplasma* and *Ureaplasma* in feline lower urinary tract disease. *Vet Microbiol*. 2006;116:246.

Chalker VJ, et al. Mycoplasmas associated with canine infectious respiratory disease. *Microbiol*. 2004;150:3491.

Chandler JC, et al. Mycoplasmal respiratory infections in small animals: 17 cases (1988-1999). *J Am Anim Hosp Assoc*. 2002;38:111.

Doig PA, et al. The genital *Mycoplasma* and *Ureaplasma* flora of healthy and diseased dogs. *Can J Comp Med*. 1981;45:233.

Foster SF, et al. Pneumonia associated with *Mycoplasma* spp. in three cats. *Aust Vet J*. 1998;76:460.

Gray LD, et al. Clinical use of 16S rRNA gene sequencing to identify *Mycoplasma felis* and *M. gateae* associated with feline ulcerative keratitis. *J Clin Microbiol*. 2005;43:3431.

Hartmann AD, et al. Detection of bacterial and viral organisms from the conjunctiva of cats with conjunctivitis and upper respiratory tract disease. *J Feline Med Surg*. 2010;12:775.

Jameson PH, et al. Comparison of clinical signs, diagnostic findings, organisms isolated, and clinical outcome in dogs with bacterial pneumonia: 93 cases (1986-1991). *J Am Vet Med Assoc*. 1995;206:206.

Jang SS, et al. *Mycoplasma* as a cause of canine urinary tract infection. *J Am Vet Med Assoc*. 1984;185:45.

Johnson LR, et al. A comparison of routine culture with polymerase chain reaction technology for the detection of *Mycoplasma* species in feline nasal samples. *J Vet Diagn Invest*. 2004;16:347.

Johnson LR, et al. Assessment of infectious organisms associated with chronic rhinosinusitis in cats. *J Am Vet Med Assoc*. 2005;227:579.

L'Abee-Lund TM, et al. *Mycoplasma canis* and urogenital disease in dogs in Norway. *Vet Rec*. 2003;153:231.

Lappin MR, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. *J Vet Intern Med*. 2017;31:279.

Lavan R, Knesl O. Prevalence of canine infectious respiratory pathogens in asymptomatic dogs presented at US animal shelters. *J Small Anim Pract*. 2015;56:572.

Low HC, et al. Prevalence of feline herpesvirus 1, *Chlamydophila felis*, and *Mycoplasma* spp DNA in conjunctival cells collected from cats with and without conjunctivitis. *Am J Vet Res*. 2007;68:643.

Mannering SA, et al. Strain typing of *Mycoplasma cynos* isolates from dogs with respiratory disease. *Vet Microbiol*. 2009;135:292.

McCabe SJ. Mycoplasma infection of a hand acquired from a cat. *J Hand Surg Am*. 1987;2:1085–1088.

Randolph JF, et al. Prevalence of mycoplasmal and ureaplasmal recovery from tracheobronchial lavages and prevalence of mycoplasmal recovery from pharyngeal swab specimens in dogs with or without pulmonary disease. *Am J Vet Res*. 1993;54:387.

Rycroft AN, et al. Serological evidence of *Mycoplasma cynos* infection in canine infectious respiratory disease. *Vet Microbiol*. 2007;120:358.

Spindel ME, et al. Evaluation of pradofloxacin for the treatment of feline rhinitis. *J Feline Med Surg*. 2008;10:472.

Torres-Henderson C, et al. Pilot study to evaluate the role of *Mycoplasma* species in cat bite abscesses. *J Feline Med Surg*. 2014;16:997.

Ulgen M, et al. Urinary tract infections due to *Mycoplasma canis* in dogs. *J Vet Med Am Physiol Pathol Clin Med*. 2006;53:379.

Veir JK, et al. Prevalence of selected infectious organisms and comparison of two anatomic sampling sites in shelter cats with upper respiratory tract disease. *J Feline Med Surg*. 2008;10:551.

Zeugswetter F, et al. Erosive polyarthritis associated with *Mycoplasma gateae* in a cat. *J Feline Med Surg*. 2007;9:226.

Zirofsky D, et al. Feline herpesvirus 1 and *Mycoplasma* spp. conventional PCR assay results from conjunctival samples from shelter cats with suspected acute ocular infections. *Topics in Companion Animal Medicine*. 2018;33:45.

CHAPTER 95

Polysystemic Rickettsial Diseases



The most common rickettsial agents causing illness in dogs and cats are in the families Anaplasmataceae (*Anaplasma* spp., *Ehrlichia* spp., and *Neorickettsia* spp.) and Rickettsiaceae (*Rickettsia* spp.) The organisms in the *Anaplasma, Ehrlichia,* and *Neorickettsia* genera are classified genetically and by cell tropism (monocytotropic, granulocytotropic, or thrombocytotropic). The organisms of most importance to dogs and cats in the United States discussed in this chapter include *A. phagocytophilum, A. platys, E. canis, E. chaffeensis, E. ewingii, N. risticii, R. felis*, and *R. rickettsii* (Table 95.1). Prevalence rates in many countries have been determined for most agents; world maps are maintained by the Companion Vector Borne Disease group sponsored by Bayer Animal Health (http://www.cvbd.org/en/occurrence-maps/world-map/). Maps showing prevalence rates for some of the agents in the United States are published by the Companion Animal Parasite Council (www.capcvet.org). It is common for dogs and cats to be exposed to more than one vector-borne agent (Yancey et al., 2014).

CANINE GRANULOCYTOTROPIC ANAPLASMOSIS

Etiology and Epidemiology

Anaplasma phagocytophilum (previously known as *E. equi*, *E. phagocytophila*, canine granulocytic *Ehrlichia*, and human granulocytic ehrlichiosis agent) is known to infect a variety of animals, including small mammals, mountain lions, coyotes, sheep, cattle, deer, dogs, horses, and human beings. Small mammals and deer are natural reservoirs. The distribution of *A. phagocytophilum* is defined by the range of *Ixodes* ticks and in the United States is most common in California, Wisconsin, Minnesota, and the Northeastern states. This agent is common in some other areas of the world including parts of Europe, Asia, and Africa. In one study of more than 4 million canine sera tested for antibodies against *A. phagocytophilum* spp., the Northeast and upper Midwest states were most likely to have positive dogs (McMahan et al., 2016). *Borrelia burgdorferi* is also transmitted by *Ixodes* ticks, so co-infections can occur. The vector must be attached for approximately 24 to 48 hours to transmit the agent. Clinical signs usually develop approximately 1 to 2 weeks after infection. Neutrophils (and rarely other leukocytes) phagocytize the organism, and once intracellular, *A. phagocytophilum* prevents phagolysosome fusion. This mechanism allows multiplication within the phagosome, which gives the appearance of morula in neutrophils under light microscopy (Fig. 95.1). The exact pathogenesis of disease is still undetermined, and why some dogs but not others develop clinical signs of disease is unclear. However, the disease-inducing potential could be related in part to strain differences (De Arcangeli et al., 2018; Rejmanek et al., 2012).

Clinical Features

Although experimentally inoculated dogs can be PCR-positive for *A. phagocytophilum* DNA for weeks after exposure to infected *Ixodes* spp., clinical disease syndromes appear to occur primarily during the acute phase of infection. Infection has been associated most commonly with nonspecific signs of fever, lethargy, and inappetence. Stiffness and lameness consistent with musculoskeletal pain are also common, and *A. phagocytophilum* has been associated with polyarthritis (Fig. 95.2). Vomiting, diarrhea, difficult breathing, cough, lymphadenopathy, hepatosplenomegaly, and central nervous system (CNS) signs (seizures and ataxia) have also been reported. Dogs can be chronic subclinical carriers, so exacerbation of disease could occur in some dogs. However, chronic disease syndromes such as those associated with *E. canis* infection are not well documented. In a recent study of dogs with neurologic diseases in Sweden, serologic evidence of exposure to *A. phagocytophilum* and *B. burgdorferi* was common, but neither organism was linked to the presence of neurologic disease (Jaderlund et al., 2007). In one study of valvular endocarditis, all dogs with *Bartonella* spp.–associated disease were also seropositive for *A. phagocytophilum* (MacDonald et al., 2004). Whether the co-infection potentiated the *Bartonella*-associated disease is unknown. Epistaxis, which occurs with *E. canis*, *R. rickettsii*, and *Bartonella* spp. infections in some dogs, has also been reported.

TABLE 95.1

***Ehrlichia* spp., *Anaplasma* spp., and *Rickettsia* spp. of Primary Significance to Dogs or Cats**

GENUS AND SPECIES	SMALL ANIMAL HOST	CELL TROPISM	PRIMARY VECTOR	PRIMARY CLINICAL SYNDROMES
Anaplasma phagocytophilum	Dog and cat	Granulocytotropic	*Ixodes* spp.	Fever, polyarthritis
Anaplasma platys	Dog and cat	Thrombocytotropic	*Rhipicephalus sanguineus*	Fever, thrombocytopenia, uveitis
Ehrlichia canis	Dog and cat	Monocytotropic	*Rhipicephalus sanguineus; Dermacentor variabilis*	Fever and diverse manifestations
Ehrlichia chaffeensis	Dog and cat	Monocytotropic	*Amblyomma americanum, Dermacentor variabilis*	Subclinical; unclear in natural infections
Ehrlichia ewingii	Dog and cat	Granulocytotropic	*Amblyomma americanum*	Polyarthritis, fever, meningitis
Rickettsia rickettsii	Dog and cat		*Dermacentor* spp., *Amblyomma americanum, Rhipicephalus sanguineus*	Fever and diverse manifestations

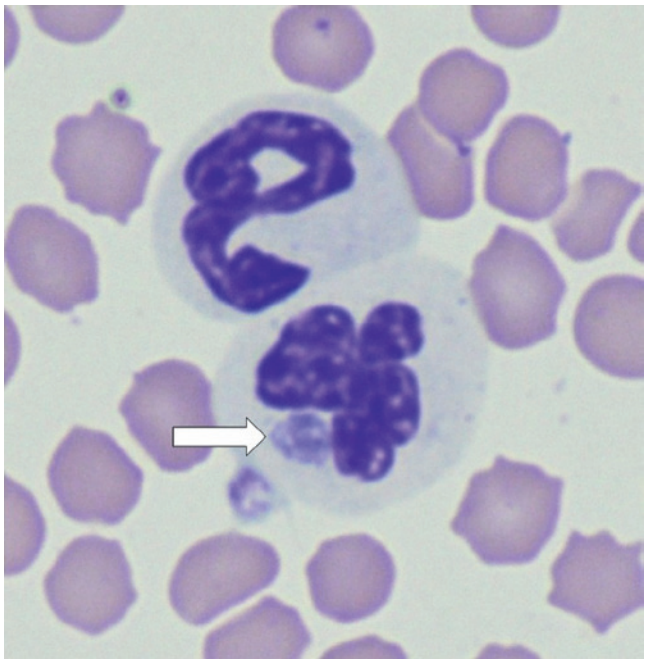


FIG 95.1
Anaplasma phagocytophilum morulae in a neutrophil of an experimentally infected cat.

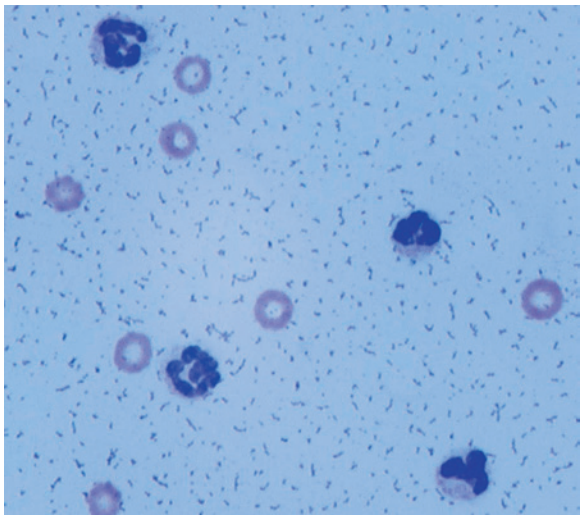


FIG 95.2
Suppurative changes consistent with polyarthritis induced by *Ehrlichia canis, E. ewingii,* or *Anaplasma phagocytophilum* infection in dogs.

Diagnosis

Morula of *A. phagocytophilum* can be detected in neutrophils of some clinically affected dogs, so infection can be strongly suspected after performance of a complete blood count (CBC) or evaluation of synovial fluid from a joint tap (see Fig. 95.2). Other CBC abnormalities recognized in some dogs include thrombocytopenia, hemolytic anemia (rarely), leukopenia, eosinopenia, lymphocytosis, and monocytosis. Reported biochemical panel and urinalysis abnormalities are mild and nonspecific. The morulae cannot be distinguished from those of *E. ewingii,* but the geographic range of the infections varies between the organisms; the travel history can help rank the differentials (see the Canine granulocytic ehrlichiosis section in this chapter).

There are multiple serum antibody tests around the world. The most common point-of-care assay that detects antibodies against *A. phagocytophilum* (SNAP 4Dx Plus, IDEXX, Westbrook, ME) also detects antibodies against *A. platys*. Many other service laboratories offer *A. phagocytophilum* antibody testing (Moroff et al., 2014). Antibody assay results can be falsely negative in acute cases, so a convalescent test 2 to 3 weeks later may be required to confirm exposure. If

an assay is being used that detects antibodies against both *A. phagocytophilum* and *A. platys*, antibodies that are detected in a dog in a region that is not endemic for *Ixodes* spp. are likely against *A. platys*. Polymerase chain reaction (PCR) assays performed on blood collected in ethylenediamine tetraacetic acid (EDTA) can be used to confirm infection and can be used to differentiate *A. phagocytophilum* infection from other infections. In one study of 19 dogs infected by *A. phagocytophilum* after infestation by wild-caught *I. scapularis*, PCR results were positive before detection of antibodies in any of the three antibody assays tested (Moroff et al., 2014).

Most dogs infected by *A. phagocytophilum* have subclinical infections and do not need to be treated. Most dogs with granulocytic anaplasmosis only have an acute phase, exposure rates in endemic areas are high, and the disease syndromes associated with infection have multiple other causes. Thus antibody test results and PCR assay results alone cannot be used to prove clinical disease associated with *A. phagocytophilum* infection. For example, although *A. phagocytophilum* is known to cause thrombocytopenia and polyarthritis in some dogs, one study failed to show an association between *A. phagocytophilum* PCR assay or serologic test results in dogs with polyarthritis or thrombocytopenia (Foley et al., 2007). Veterinarians should recognize that a clinically ill dog positive for *A. phagocytophilum* antibodies or DNA but is not responding to appropriate therapy could have another cause of the clinical syndrome, and the diagnostic workup should be continued.

Treatment

Doxycycline administered at 5 mg/kg orally (PO), q12h or at 10 mg/kg PO q24h for at least 10 days is recommended by most clinicians for the treatment of canine granulocytotropic anaplasmosis. Most dogs respond to therapy within hours to days of initiating therapy. In one group of experimentally infected dogs, administration of doxycycline did not result in decreasing antibody levels and so following antibody titers as an indication of response to therapy is likely not of clinical benefit (Chandrashekar et al., 2017). After 28 days of doxycycline administration, there was no evidence of persistent infection in one study (Yancey et al., 2018).

Zoonotic Aspects and Prevention

Anaplasma phagocytophilum infects people and dogs, and so is zoonotic. Human infections are most likely acquired by direct tick transmission, but handling infected blood and carcasses can also lead to infection. Care should also be taken when handling ticks. Infection can be avoided by tick control or prophylactic use of tetracyclines when visiting endemic areas. In at least two studies, use of acaricides prevented transmission of *A. phagocytophilum* to dogs (Honsberger et al., 2016). Dogs appear to be susceptible to reinfection, so tick control should be maintained at all times in endemic areas. Dogs used for blood donors that reside in endemic areas should be screened for *A. phagocytophilum* infections by serology and PCR assay; the American College of Veterinary Internal Medicine (ACVIM) optimally recommends using only dogs that are negative in both tests (Wardrop et al., 2016). However, if PCR assay cannot be performed, the minimal standard recommended was to use only seronegative dogs as donors.

FELINE GRANULOCYTOTROPIC ANAPLASMOSIS

Etiology and Epidemiology

As in dogs, *A. phagocytophilum* is transmitted by *Ixodes* ticks, so infections of cats are likely to be most common in these areas. Cats can be infected by *A. phagocytophilum* infection after being infested with wild-caught *I. scapularis* from Rhode Island (Lappin et al., 2015). Although rodents are commonly infected with *A. phagocytophilum,* whether ingestion or direct contact with rodents plays a role in *A. phagocytophilum* infection of cats is currently unknown. DNA of *A. phagocytophilum* can be amplified from ticks collected from cats (Duplan et al., 2018) and has been amplified from blood in naturally exposed cats with or without clinical illness in multiple countries (Adaszek et al., 2013; Bjoersdorff et al., 1999; Galemore et al., 2018; Hegarty et al., 2015; Lappin et al., 2004; Savidge et al., 2016). Cats living in endemic areas are commonly seropositive (Galemore et al., 2018; Hoyt et al., 2018). Although the pathogenesis of disease associated with *A. phagocytophilum* in cats is unknown, it is likely similar to that for dogs and human beings.

Clinical Features

Fever, anorexia, and lethargy are the most common clinical abnormalities in cats with granulocytic anaplasmosis. Ticks may or may not currently infest infected cats. Overall, clinical signs associated with *A. phagocytophilum* infection in cats are mild and resolve quickly after initiating doxycycline or minocycline therapy. Subclinical infections are the most common manifestation, like in dogs. In one study of feral cats in Massachusetts, there was no association being positive for *A. phagocytophilum* infection and anemia or thrombocytopenia in cats (Galemore et al., 2018).

Diagnosis

Approximately 50% of cats with proven clinical infections induced by *A. phagocytophilum* have a mild thrombocytopenia (66,000-118,000/μL). Neutrophilia with a left shift, lymphocytosis, lymphopenia, and hyperglobulinemia have been detected in some cats. Morulae (see Fig. 95.1) can be detected in experimentally and naturally exposed cats (Lappin et al., 2015; Savidge et al., 2016). Clinical abnormalities resolve quickly after doxycycline treatment is initiated. Biochemical and urinalysis abnormalities are uncommon. Some commercial laboratories offer serologic testing. Infected cats are negative for antibodies against *E. canis,* so *A. phagocytophilum* IFA slides should be used. Approximately 30% of cats with proven clinical infections induced by *A. phagocytophilum* are

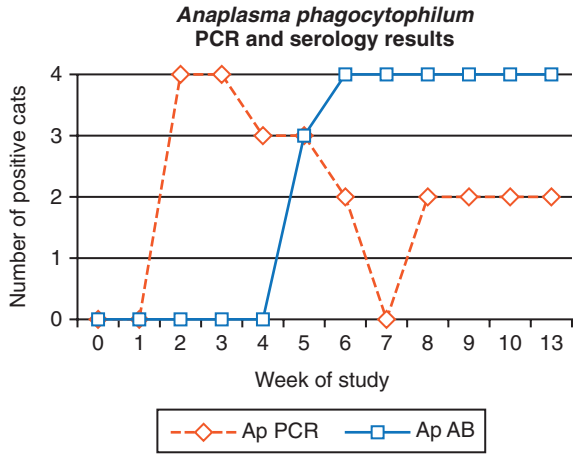


FIG 95.3
Serologic and polymerase chain reaction assay test results over time in cats infected with *Anaplasma phagocytophilum* by exposure to wild-caught *Ixodes scapularis* ticks. The four cats were exposed to wild-caught Ixodes scapularis ticks on Day 0 of the study. *AB,* Antibodies detected by the SNAP 4DX; *Ap, A. phagocytophilum; PCR,* polymerase chain reaction.

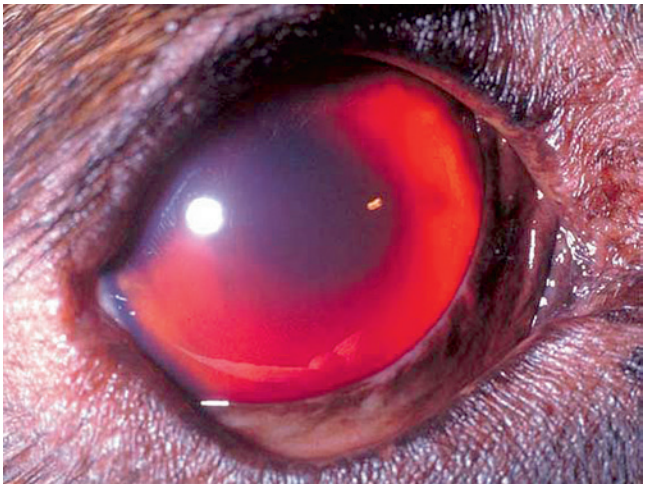


FIG 95.4
Bilateral anterior uveitis in a dog consistent with *E. canis*–associated inflammation. (Courtesy Dr. Cynthia Powell, Colorado State University.)

seronegative when first assessed serologically, but all proven cases to date have ultimately seroconverted. *Anaplasma phagocytophilum* DNA can be amplified from blood before development of detectable serum antibodies, so a single negative antibody result in an acutely infected cat does not exclude infection. Therefore cats with suspected anaplasmosis may need convalescent serum samples to prove infection. Alternately, antibody testing could be combined with PCR testing of whole blood in acute cases (Lappin et al., 2015). In a recent study of cats ($n = 4$) exposed to wild-caught *Ixodes scapularis* ticks from Rhode Island, all cats developed antibodies that were detectable in a commercially available kit labeled for use with canine serum (SNAP 4DX, IDEXX) and became PCR-positive (Lappin et al., 2015). However, none of the cats developed measurable clinical signs of disease or complete blood cell abnormalities (Fig. 95.3).

Treatment

Supportive care should be administered as needed. Several antibiotics have been administered to naturally infected cats, but most cats became clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence was not reported (Adaszek et al., 2013; Bjoersdorff et al., 1999; Lappin et al., 2004; Savidge et al., 2016). Although clinically normal, two cats were still PCR-positive 17 days and 90 days after treatment (of 21-30 days' duration), respectively, which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating the organism from the body (Lappin et al., 2004).

Zoonotic Aspects and Prevention

See the section on canine granulocytic anaplasmosis for a discussion of zoonotic aspects. To prevent *A. phagocytophilum* infection in cats, acaricidal products approved for use on cats should be used. As for dogs, cats used for blood donors that reside in endemic areas should be screened for *A. phagocytophilum* infections by serology and PCR assay; the ACVIM optimally recommends using only cats that are negative in both tests (Wardrop et al., 2016). However, if PCR assay cannot be performed, the minimal standard recommended was to use only seronegative cats as donors.

CANINE THROMBOCYTOTROPIC ANAPLASMOSIS

Etiology and Epidemiology

Anaplasma platys forms morulae in circulating platelets, and this syndrome has been referred to as *canine infectious cyclic thrombocytopenia.* Infected dogs have been detected primarily in the south and southeastern United States, Australia, Africa, Caribbean Islands, the Middle East, South America, and parts of Europe. Inclusions morphologically similar to *A. platys* have been detected in one cat in Brazil, and other cats have been positive for *A. platys* DNA in blood (Hegarty et al., 2015; Lima et al., 2010; Qurollo et al., 2014; Zobba et al., 2015). However, whether this agent is associated with significant disease in cats is unknown. *Anaplasma platys* DNA has been amplified from ticks, particularly *Rhipicephalus* spp. (Foongladda et al., 2011; Geurden et al., 2018), and trans-stadial transmission has been documented in this tick (Aktas and Ozubek, 2018). High co-infection rates with *E. canis* also support the hypothesis that *Rhipicephalus* spp. ticks are the vectors of *A. platys* (Yabsley et al., 2008).

After intravenous inoculation, the incubation period is 8 to 15 days. Although cyclic thrombocytopenia and parasitemia can occur at 10- to 14-day intervals, organism numbers and severity of thrombocytopenia may lessen over time.

Later in infection, thrombocytopenia can be severe, but the organism may not be recognized cytologically or by PCR with blood (Eddlestone et al., 2007). In these experimentally infected dogs, microbial DNA could be amplified from bone marrow and splenic aspirates. Anemia and thrombocytopenia in dogs experimentally infected with either *A. platys* and/or *E. canis* were more persistent in the co-infected dogs (Gaunt et al., 2010).

Clinical Features

Dogs with *A. platys* infections in the United States are usually subclinically infected or have mild fever. More severely affected dogs have exhibited fever, uveitis, and clinical evidence of bleeding, including ecchymosis, petechia, epistaxis, melena, gingival bleeding, retinal hemorrhage, and hematoma formation. Co-infection with other tick-borne agents such as *E. canis* and *Babesia* spp. is common and may reflect a shared vector. Fatalities have been reported in the Mediterranean basin, suggested that some strains are more pathogenic than others (Bouzouraa et al., 2016).

Diagnosis

Anemia, thrombocytopenia, and neutrophilic leukocytosis can occur. Morulae may or may not be present within platelets. In endemic areas *A. platys* infection, alone or in combination with other tick-borne agents, should be suspected in dogs with anemia or thrombocytopenia. Cross-reactivity with *E. canis* is thought to be minimal, but *A. platys* antibodies are detected in some serologic assays for *A. phagocytophilum*, including one commercially available kit (SNAP 4DX Plus; Chandrashekar et al., 2010). Agreement between different tests for *A. phagocytophilum* and *A. platys* antibodies are not 100% (Liu et al., 2018). Antibody assay results can be falsely negative in acute cases, so a convalescent test 2 to 3 weeks later may be required to confirm exposure. PCR assays performed on blood collected in EDTA can be used to confirm infection and differentiate *A. platys* infections from other infections, and microbial DNA can also be amplified from healthy dogs and can be negative in clinically ill dogs (Eddlestone et al., 2007). Most dogs infected by *A. platys* have subclinical infections, most infected dogs only have an acute phase, exposure rates in endemic areas are high, and the disease syndromes associated with infection have multiple other causes. Thus antibody test results and PCR assay results alone cannot be used to prove clinical disease associated with *A. platys* infection.

Treatment

The doxycycline and tetracycline treatment protocols discussed for *A. phagocytophilum* infections of dogs should also be effective for *A. platys* infections. If co-infection with *E. canis* exists, treatment duration should be at least 4 weeks (Neer et al., 2002). In one study of dogs that were experimentally inoculated, PCR-positive test results for *A. platys* or *E. canis* remained negative after doxycycline administration in spite of attempted immune suppression (Gaunt et al., 2010).

Zoonotic Aspects and Prevention

The strategies discussed for control of *A. phagocytophilum* infection of dogs should also be effective for *A. platys*. *Anaplasma platys* DNA has been amplified from the blood of human beings, so tick control should always be maintained (Breitschwerdt et al., 2014)

CANINE MONOCYTOTROPIC EHRLICHIOSIS

Etiology and Epidemiology

Organisms that are associated with monocytotropic ehrlichiosis in naturally infected dogs include *E. canis, E. chaffeensis,* and *Neorickettsia risticii* var *atypicalis*. Cases with *E. canis* and *E. chaffeensis* are detected most frequently and will be discussed herein. An individual dog can be infected by more than one ehrlichial agent, and co-infection with other tick-borne pathogens is common.

Ehrlichia canis is the most common of these agents and causes the most severe clinical disease; it is maintained in the environment from passage from ticks to dogs. *Rhipicephalus sanguineus* and *Dermacentor variabilis* are the known vectors. The organism is not passed transovarially in the tick, so unexposed ticks must feed on a rickettsemic dog in the acute phase to become infected and perpetuate the disease (Ipek et al., 2018). Dogs seropositive for *E. canis* have been identified in most regions of the world and most of the United States, but the majority of cases occur in areas with high concentrations of *R. sanguineus,* such as the Southwest and Gulf Coast. There are different genogroups within *E. canis,* which may partially explain differences in pathogenicity (Nambooppha et al., 2018).

Ehrlichia chaffeensis is a cause of human mononuclear ehrlichiosis. White-tailed deer, voles, coyotes, and opossums are reservoirs, and *Amblyomma americanum, D. variabilis,* and some *Ixodes* ticks are vectors. Infections by *E. chaffeensis* are detected primarily in the southeastern United States. Clinical manifestations in dogs are currently being detailed (Breitschwerdt et al., 1998; Zhang et al., 2003) and appear to be rare. In experimentally infected dogs, fever is common (Nair et al., 2016). In one study of dogs infected by natural exposure to ticks in Oklahoma, clinical abnormalities were not detected in the dogs that became positive for *E. chaffeensis* (Starkey et al., 2014). In two large serological surveys of 8662 and 6582 dog serum samples in North America and the Caribbean, antibody prevalence rates for *E. canis* and *E. chaffeensis* were approximately 1% and 3%, respectively (Beall et al., 2012; Qurollo et al., 2014). As little is known about clinical disease associated with *E. chaffeensis*, the following discussion focuses on *E. canis*.

Ehrlichia canis infection causes acute, subclinical, and chronic phases of disease. Infected mononuclear cells marginate in small vessels or migrate into endothelial tissues, inducing vasculitis during the acute phase. The acute phase begins 1 to 3 weeks after infection and lasts 2 to 4 weeks; most immunocompetent dogs survive. The subclinical phase

lasts months to years in naturally infected dogs. Although some dogs clear the organism during the subclinical phase, the organism persists intracellularly in some, leading to the chronic phase of infection. Many of the clinical and clinicopathologic abnormalities that develop during the chronic phase are from immune reactions against the intracellular organism. The variable duration of the subclinical phase of disease explains why *E. canis* infection does not have a distinct seasonal incidence as does Rocky Mountain spotted fever (RMSF). However, acute-phase disease is recognized most frequently in the spring and summer when the vectors are most active. The pathogenesis of acute and chronic ehrlichiosis is complex and composed of both agent and host effects.

Clinical Features

Clinical disease from ehrlichial infection can occur in any dog, but its severity varies depending on the organism, host factors, and presence of co-infections like *A. platys* and *Bartonella* spp. Virulence is thought to vary with different field strains of *E. canis*. Dogs with depressed cell-mediated immunity develop severe disease. However, *E. canis* itself did not cause immunosuppression in young, experimentally infected dogs within the first several months of infection (Hess et al., 2006).

Clinical findings in dogs with *E. canis* infections vary with the timing of infection (Table 95.2). The clinical manifestations of acute-phase disease are quite similar to those of RMSF as a result of the development of vasculitis. Ticks are most commonly found on dogs during the acute phase of infection. Fever can occur in both clinical phases of infection but is more common in dogs with acute ehrlichiosis. Petechiae or other evidence of bleeding noted during the acute phase is generally caused by a combination of mild thrombocytopenia (consumption or immune-mediated destruction) and vasculitis; thrombocytopenia (consumption, immune-mediated destruction, sequestration, decreased production), vasculitis, and platelet function abnormalities (Brandao et al., 2006) occur in the chronic phase. The thrombocytopenia in the acute phase is generally not severe enough to result in spontaneous bleeding, so bleeding may be primarily from vasculitis and decreased platelet function. Some dogs with *E. canis* infection induced experimentally show activated platelets, which may lessen the tendency to bleed in some dogs (Shropshire et al., 2018).

Pale mucous membranes usually only occur in the chronic phase during the development of pancytopenia. Hepatomegaly, splenomegaly, and lymphadenopathy are from chronic immune stimulation (i.e., lymphoreticular hyperplasia) and are detected most frequently in dogs in the chronic phase. Interstitial or alveolar edema secondary to vasculitis or inflammation, pulmonary parenchymal hemorrhage secondary to vasculitis or thrombocytopenia, or secondary infections from neutropenia are mechanisms resulting in dyspnea or cough in some dogs with ehrlichiosis. Pulmonary hypertension may occur in some dogs with chronic disease (Locatelli et al., 2012). Polyuria, polydipsia, and proteinuria are reported in some dogs that develop renal insufficiency.

TABLE 95.2

Clinical Abnormalities Associated With *Ehrlichia canis* Infection in Dogs

STAGE OF INFECTION	ABNORMALITIES
Acute	Fever Serous or purulent oculonasal discharge Anorexia Weight loss Dyspnea Lymphadenopathy Tick infestation often evident
Subclinical	No clinical abnormalities Ticks often not present
Chronic	Ticks often not present Depression Weight loss Pale mucous membranes Abdominal pain Evidence of hemorrhage: epistaxis, retinal hemorrhage, etc. Lymphadenopathy Splenomegaly Dyspnea, increased lung sounds, interstitial or alveolar lung infiltrates Ocular: perivascular retinitis, hyphema, retinal detachments, anterior uveitis, corneal edema Central nervous system: meningeal pain, paresis, cranial nerve deficits, seizures Hepatomegaly Arrhythmias and pulse deficits Polyuria and polydipsia Stiffness and swollen, painful joints

Stiffness, exercise intolerance, and swollen, painful joints occur in some dogs with suppurative polyarthritis (see Fig. 95.2). Most dogs with polyarthritis from which the organism has been demonstrated have been infected with *E. ewingii* or *A. phagocytophilum*. Ophthalmic manifestations of disease are common; tortuous retinal vessels, perivascular retinal infiltrates, retinal hemorrhage, anterior uveitis (see Fig. 95.4), and exudative retinal detachment occur (Komnenou et al., 2007). CNS signs can include depression, pain, ataxia, paresis, nystagmus, and seizures.

Diagnosis

Clinicopathologic and radiographic abnormalities consistent with *E. canis* infection are summarized in Table 95.3. Neutropenia may occur during acute-phase vasculitis and after bone marrow suppression in the chronic phase. Chronic immune stimulation causes monocytosis and lymphocytosis; lymphocytes often have cytoplasmic azurophilic

TABLE 95.3

Clinicopathologic Abnormalities Associated With *Ehrlichia canis* Infection in Dogs

STAGE OF INFECTION	ABNORMALITIES
Acute	Thrombocytopenia Leukopenia followed by neutrophilic leukocytosis and monocytosis Morulae Low-grade, nonregenerative anemia unless hemorrhage has occurred Variable *Ehrlichia* titer PCR-positive
Subclinical	Hyperglobulinemia Thrombocytopenia Neutropenia Lymphocytosis Monocytosis Positive *Ehrlichia* titer PCR-positive
Chronic	Monocytosis Lymphocytosis Thrombocytopenia Nonregenerative anemia Hyperglobulinemia Hypocellular bone marrow Bone marrow/spleen plasmacytosis Hypoalbuminemia Proteinuria Polyclonal or immunoglobulin G monoclonal gammopathy Cerebrospinal fluid mononuclear cell pleocytosis Nonseptic, suppurative polyarthritis Rare azotemia Increased alanine aminotransferase and alkaline phosphatase activities Positive *Ehrlichia* titer Variable PCR positive

PCR, Polymerase chain reaction.

granules (i.e., large granular lymphocytes). *Ehrlichia canis* infection results in changes in lymphocyte subsets in dogs, sometimes mimicking chronic lymphocytic leukemia (i.e., clonal proliferation); further data are needed to determine the clinical significance of these findings (Villaescusa et al., 2012). Regenerative anemia is from blood loss (acute and chronic phases); normocytic, normochromic nonregenerative anemia is from bone marrow suppression or anemia of chronic disease (chronic phase). Thrombocytopenia can occur with either acute or chronic ehrlichiosis but is generally more severe in the chronic phase disease. Thrombocytopathies from hyperglobulinemia potentiate bleeding in some dogs with chronic ehrlichiosis. Chronic ehrlichiosis is classically associated with pancytopenia, but any combination

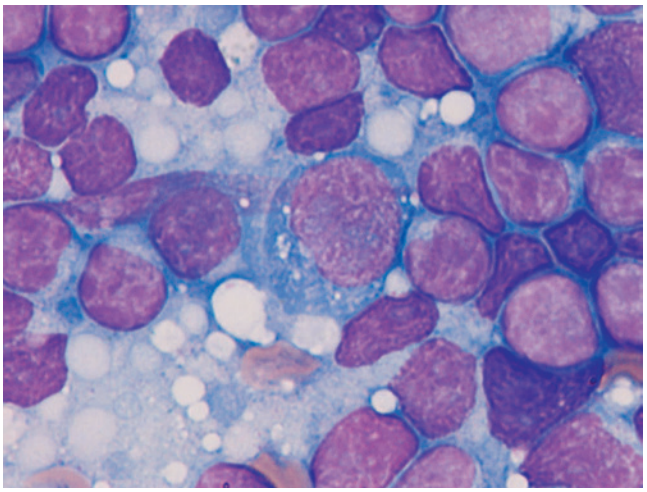


FIG 95.5
Lymph node cytology from a dog with chronic *Ehrlichia canis* infection.

of neutropenia, thrombocytopenia, and anemia can occur. Changes in bone marrow cell lines associated with ehrlichiosis vary from hypercellular (acute phase) to hypocellular (chronic phase). Bone marrow plasmacytosis is common in dogs with subclinical and chronic ehrlichiosis, and the disease can be confused with multiple myeloma, particularly in dogs with monoclonal gammopathies. However, dogs with ehrlichiosis are typically normocalcemic and do not have lytic bone lesions.

Hypoalbuminemia in the acute phase is probably caused by third spacing of albumin in tissues because of vasculitis or due to the acute phase response (i.e., albumin is a negative acute phase protein [APP]), whereas in the chronic-phase disease it is caused by glomerular loss from immune complex deposition or chronic immunostimulation (i.e., monoclonal or polyclonal gammopathy). Prerenal azotemia can occur with acute or chronic disease; renal azotemia develops in some dogs with severe glomerulonephritis from chronic ehrlichiosis. The combination of hyperglobulinemia and hypoalbuminemia is consistent with subclinical or chronic ehrlichiosis. Polyclonal gammopathies are most common, but monoclonal (e.g., immunoglobulin G) gammopathies can also occur. Serum cardiac troponin I concentration is increased in dogs with ehrlichiosis compared with healthy controls, but concentrations did not correlate to clinical outcome (Koutinas et al., 2012). The positive APP C-reactive protein (CRP), serum amyloid A (SAA), and haptoglobin (Hp) and the negative APP albumin concentrations were measured in 27 dogs with nonmyelosuppressive chronic monocytropic ehrlichiosis, 29 dogs with myelosuppressive chronic monocytropic ehrlichiosis, and 7 healthy dogs. The APP levels correlated to type of clinical syndrome but not to clinical outcome (Mylonakis et al., 2011a).

Aspirates of enlarged lymph nodes and spleen reveal reactive lymphoreticular and plasma cell hyperplasia (Fig. 95.5). In one study, plasma cells were more commonly detected in

lymph nodes of dogs with chronic monocytotropic ehrlichiosis than other causes of lymphadenopathy (Mylonakis et al., 2011b). Polyarthritis due to *E. canis* was not detected in one experimental study (Theodorou et al., 2015). If nondegenerate neutrophils are detected in synovial fluid from dogs with polyarthritis, *E. ewingii* and *A. phagocytophilum* may be the more likely causes. Bone marrow aspirates in dogs with chronic ehrlichiosis typically reveal myeloid, erythroid, and megakaryocytic hypoplasia in association with lymphoid and plasma cell hyperplasia. However, myelofibrosis was not detected in one study of 10 affected dogs (Mylonakis et al., 2010). Morulae from *E. canis* are rarely detected in the cytoplasm of mononuclear cells. Ehrlichiosis generally causes mononuclear pleocytosis and increased protein concentrations in cerebrospinal fluid. Antiplatelet antibodies, antinuclear antibodies, antierythrocyte antibodies (by direct Coombs test), and rheumatoid factors are detected in some dogs with ehrlichiosis, leading to an inappropriate diagnosis of primary immune-mediated disease (Smith et al., 2004).

No pathognomonic radiographic signs appear in dogs with ehrlichiosis. The polyarthritis is nonerosive, and dogs with respiratory signs most commonly have increased pulmonary interstitial markings, but alveolar patterns can occur.

Identification of morulae in cells documents *Ehrlichia* infection, but it is uncommon with monocytotropic strains. Examination of buffy coat smears or blood smears made from blood collected from an ear margin vessel may increase the chances of finding morulae. Some *Ehrlichia* spp. can be grown on cultured cells, but the procedure is low yield and expensive and so is not clinically useful.

Most commercial laboratories (using IFAs) and point-of-care diagnostic tests use reagents that detect antibodies against *E. canis* in serum. These tests are generally used as the first screening procedures in dogs suspected to have ehrlichiosis. If serum antibodies against *E. canis* are detected in a dog with clinical findings consistent with ehrlichiosis, a presumptive diagnosis of canine ehrlichiosis infection should be made and appropriate treatment begun. However, detection of antibodies alone is not diagnostic of ehrlichiosis because many dogs are subclinically infected. In addition, negative test results do not totally exclude ehrlichiosis from the list of differential diagnoses because clinical disease can be detected before seroconversion and not all *Ehrlichia* spp. induce antibodies that are consistently detected in all *E. canis* assays. If not stated by the company, veterinarians should contact specific test providers to determine whether the assay to be used detected antibodies against *E. canis, E. chaffeensis*, and *E. ewingii*.

PCR assays are now available commercially and can be used to detect organism-specific DNA in peripheral blood. It can be performed on joint fluid, aqueous humor, cerebrospinal fluid, and tissues. Blood PCR assay results can be positive before seroconversion in some experimentally inoculated dogs and positive results document infection, whereas positive serologic tests only document exposure (Moroff et al., 2014). Because antibiotic treatment rapidly induces negative blood PCR results, the clinician should draw the blood sample for testing and place it in an EDTA tube before treatment. In one recent study tissues (lymph nodes, spleen, liver, bone marrow, and blood) from naturally infected dogs were assayed by PCR. Blood and lymph nodes were the most likely to be positive but were falsely negative in approximately 30% of the samples (Gal et al., 2007). In one study, PCR performed on blood and splenic aspirates were equivalent for making the diagnosis of *E. canis* infection (Faria et al., 2010). Repeated testing with serology and PCR assays may be required to accurately determine the infection status of some individual dogs (Kidd et al., 2017) and is recommended in general for most vector borne diseases (Maggi et al., 2014).

Treatment

Supportive care should be provided as indicated. Several different tetracycline, doxycycline, chloramphenicol, and imidocarb diproprionate protocols have been used. The ACVIM Infectious Disease Study Group currently recommends doxycycline (10 mg/kg PO q24h for at least 28 days). Doxycycline administered at 5 mg/kg, PO, q12h has also been studied and can be effective. In one study of experimentally infected dogs, ticks still could acquire *E. canis* from feeding on dogs previously treated with doxycycline for 14 days (Schaefer et al., 2007). In an experimental study, minocycline at 10 mg/kg, PO, twice daily for 28 days had similar results to doxycycline at 10 mg/kg, PO, once daily for 28 days (Jenkins et al., 2018). Whether *E. canis* infection persists appears to vary in part on the basis of when treatment is initiated. For example, experimentally infected dogs treated during the acute or subclinical phases became PCR-negative as clinical parameters improved, but dogs treated during the chronic phase were intermittently PCR-positive after treatment (McClure et al., 2010).

Clinical signs and thrombocytopenia should rapidly resolve. If clinical abnormalities are not resolving within 7 days, other differential diagnoses should be considered. Results of studies that used imidocarb diproprionate (5-7 mg/kg intramuscular (IM) or SC repeated in 14 days) to treat canine ehrlichiosis have been variable. Some patients develop pain at the injection site, salivation, oculonasal discharge, diarrhea, tremors, and dyspnea after administration of this drug. Quinolones are not effective for the treatment of *E. canis* infections in dogs.

Positive antibody titers have been detected for up to 31 months after therapy in some naturally infected dogs. Dogs with low (<1:1024) antibody titers generally revert to negative by 1 year after therapy. Dogs with antibody titers greater than 1:1024 often maintain positive antibody titers after therapy. Whether these dogs are persistent carriers of the organism is undetermined. On the basis of these findings antibody titers are considered to be ineffective for monitoring response to therapy. Monitoring resolution of thrombocytopenia and hyperglobulinemia as markers of therapeutic elimination of the organism may be more effective.

Results of studies have been variable on whether ehrlichial infections are cleared by treatment and repeated infections

can occur. Thus whether to treat seropositive healthy dogs is controversial. Arguments for and against testing or treating healthy dogs were reviewed by the ACVIM Infectious Disease Study Group (Neer et al., 2002). The primary reason to treat a seropositive healthy dog is to try to eliminate infection before development of chronic-phase disease. However, treatment of healthy dogs is controversial for at least six reasons: (1) whether treatment halts progression to the chronic phase is unknown; (2) not all seropositive dogs are infected; (3) not all seropositive dogs progress to the chronic phase; (4) whether treatment eliminates infection is unknown; (5) even if infection is eliminated, reinfection can occur; and (6) treatment of healthy carriers may result in antimicrobial resistance. Because further data are necessary to make definitive recommendations, owners should be given the pros and cons and asked to make treatment decisions.

The prognosis is good for dogs with acute ehrlichiosis, and it is variable to guarded for those with chronic ehrlichiosis. Fever, petechiae, vomiting, diarrhea, epistaxis, and thrombocytopenia often resolve within days after initiation of therapy in acute cases. Bone marrow suppression from chronic-phase ehrlichiosis may not respond for weeks to months, if at all. Anabolic steroids and other bone marrow stimulants can be administered but are unlikely to be effective because precursor cells are often lacking. Immune-mediated events resulting in the destruction of red blood cells or platelets are likely to occur with ehrlichiosis, leading to the recommendation to administer antiinflammatory or immunosuppressive doses of glucocorticoids to acutely affected animals. Prednisone (2.2 mg/kg PO divided q12h during the first 3 to 4 days after diagnosis) may be beneficial in some cases, but controlled data are lacking.

Zoonotic Aspects and Prevention

Dogs and human beings are both infected by *E. canis* and *E. chaffeensis*. Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play a role in the human disease by bringing vectors into the human environment. Ticks should be removed and handled with care. Tick control should be maintained at all times; administration of fipronil was shown to lessen transmission in one study (Davoust et al., 2003). In another study, administration of imidacloprid 10% and permethrin 50% to young dogs lessened prevalence of *E. canis* infections by 94.6% (Otranto et al., 2010). Because *E. canis* is not passed transovarially in the tick, it can be eliminated in the environment by tick control or by treating all dogs through a generation of ticks. *Ehrlichia canis* can be transmitted within 3 hours of tick attachment so use of products that repel or very quickly kill the ticks may be superior to products with a slower kill rate (Jongejan et al., 2016). *Rhipicephalus* can only transmit *E. canis* for approximately 155 days; if tick control is not feasible tetracycline can be administered (6.6 mg/kg PO daily for 200 days). During this time, infected dogs will not infect new ticks, and previously infected ticks will lose the ability to transmit the organism. Doxycycline given at 100 mg/dog/day was used successfully as a chemopreventative (Davoust et al., 2005). Dogs used for blood donors should be screened for *E. canis* infections by serology and PCR assay; the ACVIM optimally recommends using only dogs that are negative in both tests (Wardrop et al., 2016). However, if PCR assay cannot be performed, the minimal standard recommended was to use only seronegative dogs as donors.

Some countries have published guidelines to be used by veterinarians to aid in the management of ehrlichiosis and anaplasmosis (Neer et al., 2002; Sainz et al., 2015).

FELINE MONOCYTOTROPIC EHRLICHIOSIS

Etiology and Epidemiology

Ehrlichia-like bodies or morulae have been detected in peripheral lymphocytes or monocytes of naturally exposed cats in a number of countries, including the United States, Kenya, France, Brazil, and Thailand. DNA consistent with *E. canis* has been amplified from blood of naturally infected cats in multiple surveys (Aguirre et al., 2004; Braga et al., 2013; Braga et al., 2012; Breitschwerdt et al., 2002; de Oliveira et al., 2009; Hegarty et al., 2015). In Brazil, cats at high risk for *R. sanguineus* infestation had a PCR-positive rate for *E. canis* DNA of 9.4% (Braga et al., 2014). In addition, *E. chaffeensis* DNA has been amplified from the blood of naturally exposed cats in the United States (Hegarty et al., 2015). In Europe, *Ehrlichia canis* DNA has been amplified from ticks collected from some cats (Pennisi et al., 2015). In the United States, *Amblyomma americanum* removed from cats were shown to occasionally contain DNA of *E. chaffeensis* (Little et al., 2018). Cats have also been shown to have antibodies that react to specific peptides of *E. canis* and *E. chaffeensis* (Hegarty et al., 2015). These studies document that cats can be exposed to mononuclear *Ehrlichia* spp. and become infected. However, other studies of cats in endemic areas (Arizona, Florida, Louisiana) have failed to amplify *Ehrlichia* spp. DNA from the blood of cats (Eberhardt et al., 2006; Levy et al., 2011; Luria et al., 2004;). In one study of naturally exposed cats, *E. canis* DNA was amplified from the blood, but antibodies were never detected (Breitschwerdt et al., 2002). Pathogenesis of disease associated with monocytotropic ehrlichiosis in cats is unknown but is likely to be similar to that for *E. canis* infection of dogs. Guidelines for cats with *Ehrlichia* spp. infections have been published in Europe (Pennisi et al., 2017).

Clinical Features

All ages of cats have been infected; most cats were domestic short-haired, and both males and females have been affected. Anorexia, fever, inappetence, lethargy, weight loss, hyperesthesia or joint pain, pale mucous membranes, splenomegaly, dyspnea, and lymphadenopathy were the most common historic and physical examination abnormalities. Dyspnea, petechiae, retinal detachments, vitreous hemorrhages, and

pale mucous membranes were other reported physical examination abnormalities. Concurrent diseases are rarely reported but have included hemoplasmas (previously *Haemobartonella felis*), *Cryptococcus neoformans*, feline leukemia virus and feline immunodeficiency virus infections, and lymphoma.

Diagnosis

Anemia is common and usually nonregenerative. Leukopenia; leukocytosis characterized by neutrophilia, lymphocytosis, and monocytosis; and intermittent thrombocytopenia have been reported in some cats. Bone marrow evaluation of cats with cytopenias has revealed primarily hypoplasia of the affected cell line. However, one cat had bone marrow cytologic characteristics consistent with myeloid leukemia (Breitschwerdt et al., 2002). Hyperglobulinemia was reported in multiple cats; protein electrophoresis usually reveals a polyclonal gammopathy. An epidemiologic link has been made between the presence of *Ehrlichia* spp. antibodies in serum and monoclonal gammopathy (Stubbs et al., 2000). On the basis of the cases reported to date, ehrlichiosis should be considered on the list of differential diagnoses for cats with unexplained leukocytosis (primarily lymphocytosis), cytopenias, and hyperglobulinemia. Biochemical abnormalities were infrequently reported in cats with suspected monocytotropic ehrlichiosis and were nonspecific. The three cats with *E. canis*–like DNA in the blood also had antinuclear antibodies, similar to results reported for infected dogs (Breitschwerdt et al., 2002).

Some cats with suspected clinical ehrlichiosis seroreacted to *E. canis* or *N. risticii* morulae in indirect fluorescent antibody assays. Antibodies that seroreact to more than one *Ehrlichia* spp. are sometimes detected in cat sera. Some cats with *E. canis*–like DNA in blood were seronegative (Breitschwerdt et al., 2002), so suspect cases should be screened concurrently by PCR assays. Information concerning accuracy of results from commercial kits optimized for the detection of *E. canis* antibodies in canine serum when used with feline serum is not currently available. Positive serologic test results occur in both healthy and clinically ill cats, so a diagnosis of clinical ehrlichiosis should not be based on serologic test results alone. A tentative diagnosis of clinical feline ehrlichiosis can be based on the combination of positive serologic test results or PCR assay results, clinical signs of disease consistent with *Ehrlichia* infection, exclusion of other causes of the disease syndrome, and response to anti-*Ehrlichia* drugs.

Treatment

Clinical improvement after therapy with tetracycline, doxycycline, or imidocarb dipropionate was reported for most cats. However, for some cats a positive response to therapy was a criterion for the diagnosis of ehrlichiosis. As for dogs, administration of doxycycline at 5 mg/kg, PO, q12h or 10 mg/kg, PO, q24h should be effective. Doxycycline has been associated with esophageal strictures and so should be formulated into a liquid for use in cats or followed by at least 2 mL of a liquid (Bennett et al., 2010). Optimal treatment duration is unknown, but 28 days is generally recommended provided there is resolution of clinical and laboratory abnormalities. For cats with treatment failure or those intolerant of doxycycline, imidocarb diproprionate can be given safely (5 mg/kg IM or SC twice, 14 days apart). Salivation and pain at the injection site are the common adverse effects, and imidocarb efficacy is in question for the treatment of canine monocytotropic ehrlichiosis (Eddlestone et al., 2007).

Zoonotic Aspects and Prevention

Although cats and human beings can both be infected by *E. canis* and *E. chaffeensis,* direct transmission is not known to occur. Care should be taken when removing ticks, and arthropod control should be maintained at all time for cats, particularly if allowed outdoors.

CANINE GRANULOCYTOTROPIC EHRLICHIOSIS

Etiology and Epidemiology

Ehrlichia ewingii forms morulae in neutrophils and eosinophils, and has been detected in dogs and human beings that reside in the central region, as well as the Southern and Southeastern United States. In one seroprevalence study of dogs in North America and the Caribbean, positive dogs were most common in Oklahoma (14.3%) and North Carolina (10.3%) (Qurollo et al., 2014). *Ehrlichia ewingii* has been detected most commonly in *A. americanum* (Wright et al., 2014), and deer are reservoirs (Yabsley et al., 2002). In one study of dogs naturally exposed to ticks in Oklahoma, all 10 dogs became positive for *E. ewingii* DNA, but clinical abnormalities were not detected (Starkey et al., 2014). The incubation period after tick exposure is approximately 13 days. Pathogenesis of disease is unknown but is likely to be similar to other *Ehrlichia* spp. In general, clinical signs of *E. ewingii* infection are less severe than those of *E. canis*. Concurrent disease or infections may play a role in the pathogenesis of *E. ewingii* infection.

Clinical Features

Nonspecific signs of *E. ewingii* infection include fever, lethargy, anorexia, depression, and signs consistent with polyarthritis, such as stiffness. Other clinical signs include vomiting, diarrhea, and peripheral edema and neurologic signs such as ataxia, paresis, and vestibular disease. Clinical signs can be mild, self-limited, or inapparent (Goodman et al., 2003). Similar to *R. rickettsii*, acute disease seems to be most common, so *E. ewingii* infection should be highest on the list of differential diagnoses from the spring through autumn when *A. americanum* is most active.

Diagnosis

Suppurative polyarthritis is most common. Other clinicopathologic findings typically associated with acute *E. canis* infection (see Table 95.3), such as mild to moderate

thrombocytopenia and anemia, also occur. Morulae can be detected in neutrophils and eosinophils in peripheral blood and in neutrophils from synovial fluid. However, presence of morulae is transient and so easily missed cytologically. A peptide-based, *E. ewingii* serologic assay is now available (O'Connor et al., 2010; SNAP 4DX Plus, IDEXX Laboratories, Portland, ME). However, because antibodies can be detected in healthy as well as diseased dogs, presence of *E. ewingii*–specific antibodies cannot be used alone to diagnose clinical granulocytotropic ehrlichiosis. If not stated by the company, veterinarians should contact specific test providers to determine whether the assay to be used detected antibodies against *E. canis, E. chaffeensis*, and *E. ewingii*.

Some dogs with acute disease will have negative test results on presentation, so a convalescent test to shown seroconversion is required for diagnosis. PCR assays are now used to differentiate between members of the *Ehrlichia*, *Anaplasma*, and *Neorickettsia* genera, and should be performed on blood collected in EDTA before administration of antibiotics in acute cases or those negative for specific antibodies. However, healthy dogs can be positive for *E. ewingii* DNA in blood so positive test results do not prove the clinical syndrome was from the infection (Starkey et al., 2014).

Treatment

Supportive care should be provided as indicated. The tetracycline, doxycycline, and chloramphenicol protocols recommended for *E. canis* infections are generally effective. Doxycycline administered at 5 mg/kg PO q12h or at 10 mg/kg PO q24h for at least 14 days is recommended by most clinicians for the treatment of canine granulocytotropic ehrlichiosis. However, few data from the field are available that document treatment efficacy of these protocols.

Zoonotic Aspects and Prevention

Dogs and human beings are both infected by *E. canis*, *E. ewingii*, and *E. chaffeensis* (Buller et al., 1999). Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play a role in the human disease by bringing vectors into the human environment. Ticks should be removed and handled with care. The ACVIM recommended to optimally use only seronegative and PCR-negative dogs as blood donors, particularly in areas endemic for *Amblyomma americanum* (Wardrop et al., 2016). Whether to treat healthy, seropositive dogs has pros and cons similar to those for *E. canis* infections of healthy dogs but is probably not needed (see the Canine Monocytotropic Ehrlichiosis section).

ROCKY MOUNTAIN SPOTTED FEVER

Etiology and Epidemiology

In the United States, the spotted fever group (SFG) organism most likely to be associated with clinical disease in dogs is *R. rickettsii*, the cause of RMSF. Other SFG organisms like *R. parkeri* and *R. felis* are known to infect dogs, but disease associations are less apparent (see the Other Rickettsial Infections section). In one survey of ticks in Missouri, *R. amblyommatis* was the predominant SFG species, and it was detected in *Amblyomma americanum*, *Dermacentor variabilis*, and *Ixodes scapularis* (Santanello et al., 2018). Other members of the SFG that infect dogs may induce antibodies that cross react with *R. rickettsii* (see Diagnosis later), which may lessen the risk of developing RMSF (Santanello et al., 2018). Canine RMSF is recognized predominantly in the Southeastern states from April through September when the tick vectors are most active. *Dermacentor andersoni* (American wood tick), *Dermacentor variabilis* (American dog tick), and *A. americanum* (Lone Star tick) are the principal vectors, host, and reservoir of *R. rickettsii.* A reemergence of RMSF in the southwestern states has recently occurred, and *R. sanguineous* ticks are the vector (Demma et al., 2005, 2006; Nicholson et al., 2006). *Rickettsia rickettsii* has also been detected in *R. sanguineous* in California, and infection of this tick has been confirmed experimentally (Piranda et al., 2011; Wikswo et al., 2007). Strains of *R. rickettsii* that infect dogs and human beings are closely related genetically (Kidd et al., 2006). Seroprevalence rates for antibodies against SPG organisms are high in endemic areas. In one study of dogs in the southeastern United States 14.1% and 29.7% of healthy and clinically ill dogs, respectively, had antibodies that reacted to *R. rickettsii* (Solano-Gallego et al., 2004).

The organism is maintained in nature in a cycle between ticks and small mammals such as voles, ground squirrels, and chipmunks, and it is transmitted transovarially in some ticks, so nymphs and larvae can be infected without feeding. *Rickettsia rickettsii* replicates in endothelial tissues (causing vasculitis) and can lead to diverse and sometimes severe clinical manifestations of disease as soon as 2 to 3 days after exposure. Antiplatelet antibodies can be detected in many infected dogs, suggesting an immune-mediated component to the thrombocytopenia that is frequently present (Grindem et al., 1999). The course of RMSF in dogs experimentally by tick infestation was recently described (Levin et al., 2014). Although seropositive cats have been detected, whether clinical illness occurs is unclear (Bayliss et al., 2009; Case et al., 2006).

Clinical Features

Any dog not previously exposed to *R. rickettsii* can develop RMSF. The tick frequently feeds on and leaves the dog before the development of clinical signs. In one study, only 5 of 30 owners knew their dogs had been infested by ticks (Gasser et al., 2001). After infection, the majority of dogs are subclinical; some develop acute disease with a clinical course of approximately 14 days. No age or sex predilection exists.

In dogs infected with *R. rickettsii* after tick infestation, the most significant findings were fever (starting 3-7 days after infestation), lethargy, anorexia, ocular lesions, tremors, skin rash, thrombocytopenia and leukocytosis (Levin et al., 2014). In naturally occurring cases, interstitial pulmonary disease, dyspnea, and cough have been reported as well as vomiting or diarrhea. Because the disease is generally acute,

lymphadenopathy and splenomegaly are not as common as in dogs with ehrlichiosis. Petechiae, epistaxis, subconjunctival hemorrhage, hyphema, anterior uveitis, iris hemorrhage, retinal petechiae, and retinal edema occur frequently. Cutaneous manifestations can include hyperemia, petechiae, edema, and dermal necrosis. Hemorrhage likely results from vasculitis, thrombocytopenia from consumption of platelets at sites of vasculitis, thrombocytopenia from immune destruction, and, in some dogs, disseminated intravascular coagulation. CNS signs include vestibular lesions (nystagmus, ataxia, head tilt); seizures; paresis; tremors; changes in mentation; and hyperesthesia (Mikszewski and Vite, 2005). Fatal RMSF is generally secondary to cardiac arrhythmias and shock, pulmonary disease, acute renal failure, or severe CNS disease.

Diagnosis

Clinicopathologic and radiographic abnormalities are common but do not definitively document RMSF. Neutrophilic leukocytosis, with or without a left shift and toxic cells, is found in most clinically affected dogs. Platelet counts are variable, but in one study 14 of 30 dogs had less than 75,000 platelets/μL without evidence of disseminated intravascular coagulation (Gasser et al., 2001). Leukocytosis and thrombocytopenia were the most common laboratory findings in experimentally infected dogs (Levin et al., 2015). In some naturally infected dogs, hemostatic abnormalities consistent with disseminated intravascular coagulation occur. Anemia occurs in some dogs, primarily from blood loss. Increased activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, as well as hypoalbuminemia, occur frequently. Because *R. rickettsii* does not result in chronic intracellular infection as does ehrlichiosis, hyperglobulinemia is rare. Renal insufficiency in some dogs causes azotemia and metabolic acidosis. Serum sodium, chloride, and potassium concentrations decrease in many dogs with gastrointestinal tract signs or renal insufficiency. Compared with dogs with chronic ehrlichiosis, chronic proteinuria from glomerulonephritis is rare. Positive direct Coombs test results occur in some dogs.

CNS inflammation usually causes increased protein concentrations and neutrophilic pleocytosis in cerebrospinal fluid; some dogs may have mononuclear cell pleocytosis or mixed inflammation. No pathognomonic radiographic abnormalities are associated with RMSF, but both experimentally and naturally infected dogs commonly develop unstructured pulmonary interstitial patterns.

A presumptive diagnosis of canine RMSF can be based on the combination of appropriate clinical, historic, and clinicopathologic evidence of disease; serologic test results; exclusion of other causes of the clinical abnormalities; and response to antirickettsial drugs. Documentation of seroconversion or an increasing titer 2 to 3 weeks after initial serologic testing suggests recent infection. Positive serum antibody test results alone do not prove RMSF because subclinical infection is common. In addition, positive serum antibody tests do not document infection by *R. rickettsii* because infection with nonpathogenic SFG agents can induce cross-reacting antibodies. Demonstration of *R. rickettsii* by inoculating affected tissues or blood into susceptible laboratory animals or by documenting the organism in endothelial cells by using direct fluorescent antibody staining leads to a definitive diagnosis of RMSF but is not clinically practical. PCR assay can be used to document the presence of *R. rickettsii* DNA in blood, other fluids, or tissues and document infection. But results from naturally occurring cases are rarely positive in PCR panels. In experimentally infected dogs, *R. rickettsii* DNA was inconsistently amplified from the blood of the dogs one to four times between day 5 and 13 after tick infestation (Levin et al., 2015). As with other vector-borne testing recommendations, the combination of serology and PCR assay should be used in dogs with suspected RMSF (Maggi et al., 2014).

Treatment

Supportive care for gastrointestinal tract fluid and electrolyte losses, renal disease, disseminated intravascular coagulation, and anemia should be provided as indicated. Overzealous fluid therapy may worsen respiratory or CNS manifestations of disease if vasculitis is severe.

Tetracycline derivatives, chloramphenicol, and quinolones are the antirickettsial drugs used most frequently. Doxycycline (5-10 mg/kg PO q12h for 21-28 days) is the preferred treatment. In one study of experimentally infected dogs, treatment for 16 days resulted in temporary clinical improvement in one dog that then relapsed (Levin et al., 2014). In one study of 30 dogs with RMSF, all dogs survived and no apparent differences in response rate occurred among tetracycline, doxycycline, chloramphenicol, or enrofloxacin (Gasser et al., 2001). Fever, depression, and thrombocytopenia often begin to resolve within 24 to 48 hours after starting therapy. Administration of prednisolone at anti-inflammatory or immunosuppressive doses in combination with doxycycline did not potentiate RMSF in experimentally infected dogs. The prognosis for canine RMSF is fair; it has been estimated that death occurs in less than 5% of affected dogs.

Zoonotic Aspects and Prevention

Because RMSF has not been reported twice in the same dog, permanent immunity is likely. Providing strict tick control can prevent infection. Human beings probably do not acquire *R. rickettsii* from contact with dogs, but dogs may increase human exposure to RMSF by bringing ticks into the human environment. People can also be infected when removing ticks with activated *R. rickettsii* from the dog by hand. Two dogs and the owner all died of RMSF in one study (Elchos and Goddard, 2003). As in dogs, RMSF in people is most commonly diagnosed from April to September when most of the tick vectors are most active. However, in areas endemic for *R. rickettsii* and *Rhipicephalus sanguineus*, RMSF could be diagnosed year round. RMSF can be fatal in some infected people, particularly if treatment is not started soon after clinical signs are recognized (Drexler et al., 2017; Helmick et al., 1984).

OTHER RICKETTSIAL INFECTIONS

Rickettsia felis was originally detected in a commercial cat flea *(Ctenocephalides felis)* colony and has been shown to belong in the SFG. Fever, headache, myalgia, and macular rash in human beings have been attributed to *R. felis* infection around the world (Angelakis et al., 2016). *Rickettsia felis* has been amplified from fleas collected from dogs or cats around the world including Australia, France, Israel, New Zealand, Thailand, the United Kingdom, and the United States. For example, in one study of 92 pairs of cat blood and flea extracts from Alabama, Maryland, and Texas, 62 (67.4%) of flea extracts and none of the cat blood samples were positive for *R. felis* DNA (Hawley et al., 2007). Recently, it has been suggested that dogs may prove to be important in the biology of *R. felis* (Hii et al., 2011). Because clinical illness in cats or dogs has not been documented, optimal treatment is unknown. However, on the basis of results for RMSF in dogs, doxycycline or a fluoroquinolone would be logical choices. Prevention in cats and dogs should include flea control, which may lessen exposure to people.

Rickettsia massiliae was amplified from *R. sanguineus* ticks in an area of southern California (Beeler et al., 2011). A clinical syndrome thought to be RMSF had been recognized in two dogs on the property. Antibodies against *R. massiliae, Rickettsia rhipicephali,* and *R. rickettsii* were detected by IFA in all four dogs, but each was negative for rickettsial DNA in blood by PCR. *Rhipicephalus sanguineus* collected from dogs and cats in Hungary, France, Italy, Belgium (dogs only), and Germany (cats only) were found to be positive for three *Rickettsia* species (*R. massiliae, R. raoultii,* and *R. rhipicephali*) as well as *A. platys* and *Hepatozoon canis* (Geurden et al., 2018). *Rickettsia conorii* causes Mediterranean Spotted Fever and has been associated with fever in southern Italy (Solano-Gallego, 2015). SFG *Rickettsia* DNA was amplified from *Dermacenter* collected from cats (Little et al., 2018). Further research is needed to determine disease association amongst these other SPG organisms and dogs or cats. However, on the basis of results for RMSF in dogs, doxycycline or a fluoroquinolone would be logical treatment choices. Prevention in cats and dogs should include flea and tick control, which may lessen exposure to people.

Neorickettsia helminthoeca (salmon poisoning) causes enteric signs of disease in dogs from the Pacific Northwest. *Coxiella burnetii* infection is associated with parturient or aborting cats and is primarily a zoonotic disease (see Chapter 99).

Suggested Readings

Canine Granulocytotropic Anaplasmosis

Blagburn BL, et al. Use of imidacloprid-permethrin to prevent transmission of Anaplasma phagocytophilum from naturally infected Ixodes scapularis ticks to dogs. *Vet Ther*. 2004;5:212.

Chandrashekar R, et al. Serologic responses to peptides of *Anaplasma phagocytophilum* and *Borrelia burgdorferi* in dogs infested with wild-caught Ixodes scapularis. *Vet J*. 2017;226:6.

De Arcangeli S, et al. *Anaplasma phagocytophilum* infection in thrombocytopenic dogs. *Vet Ital*. 2018;54:73.

Foley J, et al. Association between polyarthritis and thrombocytopenia and increased prevalence of vector borne pathogens in Californian dogs. *Vet Rec*. 2007;160:159.

Foley JE, et al. Spatial distribution of seropositivity to the causative agent of granulocytic ehrlichiosis in dogs in California. *Am J Vet Res*. 1599;62:2001.

Honsberger NA, et al. Efficacy of sarolaner in the prevention of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* transmission from infected *Ixodes scapularis* to dogs. *Vet Parasitol*. 2016;222:67.

Jaderlund KH, et al. Seroprevalence of *Borrelia burgdorferi* sensu lato and *Anaplasma phagocytophilum* in dogs with neurological signs. *Vet Rec*. 2007;160:825.

MacDonald KA, et al. A prospective study of canine infective endocarditis in northern California (1999-2001): emergence of Bartonella as a prevalent etiologic agent. *J Vet Intern Med*. 2004;18:56.

McMahan CS, et al. Factors associated with *Anaplasma* spp. seroprevalence among dogs in the United States. *Parasit Vectors*. 2016;9:169.

Moroff S, et al. Detection of antibodies against *Anaplasma phagocytophilum* in dogs using an automated fluorescence based system. *Vet J*. 2014;202:348.

Rejmanek D, et al. Molecular characterization reveals distinct genospecies of Anaplasma phagocytophilum from diverse North American hosts. *J Med Microbiol*. 2012;61:204.

Wardrop KJ, et al. Update on canine and feline blood donor screening for blood-borne pathogens. *J Vet Intern Med*. 2016;30:15.

Yancey CB, et al. Doxycycline treatment efficacy in dogs with naturally occurring *Anaplasma phagocytophilum* infection. *J Small Anim Pract*. 2018;59:286.

Yancey CB, et al. Regional seroreactivity and vector-borne disease co-exposures in dogs in the United States from 2004-2010: utility of canine surveillance. *Vector Borne Zoonotic Dis*. 2014;14:724.

Feline Granulocytotropic Anaplasmosis

Adaszek Ł, et al. Three clinical cases of *Anaplasma phagocytophilum* infection in cats in Poland. *J Feline Med Surg*. 2013;15:333–337.

Billeter SA, et al. Prevalence of Anaplasma phagocytophilum in domestic felines in the United States. *Vet Parasitol*. 2007;147:194.

Bjoersdorff A, et al. Feline granulocytic ehrlichiosis—a report of a new clinical entity and characterization of the new infectious agent. *J Small Anim Pract*. 1999;40:20.

Duplan F, et al. *Anaplasma phagocytophilum*, *Bartonella* spp., haemoplasma species and *Hepatozoon* spp. in ticks infesting cats: a large-scale survey. *Parasit Vectors*. 2018;11(1):201.

Galemore ER, Labato MA, O'Neil E. Prevalence of Anaplasma phagocytophilum infection in feral cats in Massachusetts. *JFMS Open Rep*. 2018;4(1):2055116917753804.

Geurden T, et al. Detection of tick-borne pathogens in ticks from dogs and cats in different European countries. *Ticks Tick Borne Dis*. 2018;pii: S1877-959X(18)30119-5.

Hegarty BC, et al. Serological and molecular analysis of feline vector-borne anaplasmosis and ehrlichiosis using species-specific peptides and PCR. *Parasit Vectors*. 2015;8:320.

Hoyt K, et al. Evidence for clinical anaplasmosis and borreliosis in cats in Maine. *Top Companion Anim Med*. 2018;33:40.

Lappin MR, et al. Molecular and serologic evidence of *Anaplasma phagocytophilum* infection in cats in North America. *J Am Vet Med Assoc*. 2004;225:893.

Lappin MR, et al. Evidence of infection of cats by *Borrelia burgdorferi* and *Anaplasma phagocytophilum* after exposure to wild-caught adult *Ixodes scapularis*. *J Vet Diagn Invest*. 2015;27:522.

Savidge C, et al. Anaplasma phagocytophilum infection of domestic cats: 16 cases from the northeastern USA. *J Feline Med Surg*. 2016;18:85.

Canine Thrombocytotropic Anaplasmosis

Aktas M, Ozubek S. Molecular evidence for trans-stadial transmission of *Anaplasma platys* by *Rhipicephalus sanguineus* sensu lato under field conditions. *Med Vet Entomol*. 2018;32:78.

Bouzouraa T, et al. Clinical and laboratory features of canine *Anaplasma platys* infection in 32 naturally infected dogs in the Mediterranean basin. *Ticks Tick Borne Dis*. 2016;7:1256.

Breitschwerdt EB, et al. Intravascular persistence of *Anaplasma platys*, *Ehrlichia chaffeensis*, and *Ehrlichia ewingii* DNA in the blood of a dog and two family members. *Parasit Vectors*. 2014;7:298.

Chandrashekar R, et al. Performance of a commercially available in-clinic ELISA for the detection of antibodies against *Anaplasma phagocytophilum*, *Ehrlichia canis*, and *Borrelia burgdorferi* and *Dirofilaria immitis* antigen in dogs. *Am J Vet Res*. 2010;71:1443.

Eddlestone SM, et al. PCR detection of *Anaplasma platys* in blood and tissue of dogs during acute phase of experimental infection. *Exp Parasitol*. 2007;115:205.

Foongladda S, et al. *Rickettsia*, *Ehrlichia*, *Anaplasma*, and *Bartonella* in ticks and fleas from dogs and cats in Bangkok. *Vector Borne Zoonotic Dis*. 2011;11:1335.

Gaunt S, et al. Experimental infection and co-infection of dogs with *Anaplasma platys* and Ehrlichia canis: hematologic, serologic and molecular findings. *Parasit Vectors*. 2010;3:33.

Lima MLF, et al. Molecular detection of *Anaplasma platys* in a naturally-infected cat in Brazil. *Braz J Microbiol*. 2010;41:381.

Liu J, et al. Sensitivity and specificity levels of two rapid assays for antibodies to *Anaplasma* spp. in dogs. *J Vet Diagn Invest*. 2018;30:290.

Qurollo BA, et al. Co-infection with *Anaplasma platys*, *Bartonella henselae*, *Bartonella koehlerae* and '*Candidatus* Mycoplasma haemominutum' in a cat diagnosed with splenic plasmacytosis and multiple myeloma. *J Feline Med Surg*. 2014;16:713.

Yabsley MJ, et al. Prevalence of *Ehrlichia canis*, *Anaplasma platys*, *Babesia canis vogeli*, *Hepatozoon canis*, *Bartonella vinsonii berkhoffii,* and *Rickettsia* spp. in dogs from Grenada. *Vet Parasitol*. 2008;151:279.

Zobba R, et al. Cell tropism and molecular epidemiology of *Anaplasma platys*-like strains in cats. *Ticks Tick Borne Dis*. 2015;6:272.

Canine Monocytotropic Ehrlichiosis

Abbate JM, et al. Six-month field efficacy and safety of the combined treatment of dogs with Frontline Tri-Act® and NexGard Spectra®. *Parasit Vectors*. 2018;11:425.

Beall MJ, et al. Seroprevalence of *Ehrlichia canis*, *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in dogs in North America. *Parasit Vectors*. 2012;5:29.

Brandao LP, et al. Platelet aggregation studies in acute experimental canine ehrlichiosis. *Vet Clin Pathol*. 2006;35:78.

Davoust B, et al. Assay of fipronil efficacy to prevent canine monocytic ehrlichiosis in endemic areas. *Vet Parasitol*. 2003;112:91.

Davoust B, et al. Validation of chemoprevention of canine monocytic ehrlichiosis with doxycycline. *Vet Microbiol*. 2005;107:279.

Faria JL, et al. *Ehrlichia canis* morulae and DNA detection in whole blood and spleen aspiration samples. *Rev Bras Parasitol Vet*. 2010;19:98.

Gal A, et al. Detection of *Ehrlichia canis* by PCR in different tissues obtained during necropsy from dogs surveyed for naturally occurring canine monocytic ehrlichiosis. *Vet J*. 2007;[Epub ahead of print].

Harrus S, et al. Comparison of simultaneous splenic sample PCR with blood sample PCR for diagnosis and treatment of experimental *Ehrlichia canis* infection. *Antimicrob Agents Chemother*. 2004;48:4888.

Hess PR, et al. Experimental *Ehrlichia canis* infection in the dog does not cause immunosuppression. *Vet Immunol Immunopathol*. 2006;109:117.

Ipek NDS, et al. Molecular evidence for transstadial transmission of *Ehrlichia canis* by *Rhipicephalus sanguineus* sensu lato under field conditions. *J Med Entomol*. 2018;55:440.

Jenkins S, et al. Efficacy of minocycline in naturally occurring nonacute *Ehrlichia canis* infection in dogs. *J Vet Intern Med*. 2018;32:217.

Jongejan F, et al. Comparative efficacy of oral administrated afoxolaner (NexGard™) and fluralaner (Bravecto™) with topically applied permethrin/imidacloprid (Advantix(®)) against transmission of *Ehrlichia canis* by infected *Rhipicephalus sanguineus* ticks to dogs. *Parasit Vectors*. 2016;9:348.

Kidd L, et al. Prevalence of vector-borne pathogens in Southern California dogs with clinical and laboratory abnormalities consistent with immune-mediated disease. *J Vet Intern Med*. 2017;31:1081.

Komnenou AA, et al. Ocular manifestations of natural canine monocytic ehrlichiosis (Ehrlichia canis): a retrospective study of 90 cases. *Vet Ophthalmol*. 2007;10:137.

Koutinas CK, et al. Serum cardiac troponin I concentrations in naturally occurring myelosuppressive and non-myelosuppressive canine monocytic ehrlichiosis. *Vet J*. 2012;[Epub ahead of print].

Locatelli C, et al. Pulmonary hypertension associated with *Ehrlichia canis* infection in a dog. *Vet Rec*. 2012;170:676.

Maggi RG, et al. Comparison of serological and molecular panels for diagnosis of vector-borne diseases in dogs. *Parasit Vectors*. 2014;7:127.

McClure JC, et al. Efficacy of a doxycycline treatment regimen initiated during three different phases of experimental ehrlichiosis. *Antimicrob Agents Chemother*. 2010;54:5012.

Moroff S, et al. Use of an automated system for detection of canine serum antibodies against Ehrlichia canis glycoprotein 36. *J Vet Diagn Invest*. 2014;26:558.

Mylonakis ME, et al. Absence of myelofibrosis in dogs with myelosuppression induced by *Ehrlichia canis* infection. *J Comp Pathol*. 2010;142:328.

Mylonakis ME, et al. Cytologic patterns of lymphadenopathy in canine monocytic ehrlichiosis. *Vet Clin Pathol*. 2011b;40:78.

Mylonakis ME, et al. Serum acute phase proteins as clinical phase indicators and outcome predictors in naturally occurring canine monocytic ehrlichiosis. *J Vet Intern Med*. 2011a;25:811.

Nair AD, et al. Comparative experimental infection study in dogs with *Ehrlichia canis, E. chaffeensis, Anaplasma platys* and *A. phagocytophilum*. *PLoS ONE*. 2016;11(2):e0148239. doi:10.1371/journal.pone.0148239. eCollection.

Nambooppha B, et al. Two different genogroups of *Ehrlichia canis* from dogs in Thailand using immunodominant protein genes. *Infect Genet Evol*. 2018;63:116.

Neer TM, et al. Consensus statement on ehrlichial disease of small animals from the Infectious Disease Study Group of the ACVIM. *J Vet Intern Med*. 2002;16:309.

Otranto D, et al. Prevention of endemic canine vector-borne diseases using imidacloprid 10% and permethrin 50% in young dogs: a longitudinal field study. *Vet Parasitol*. 2010;172:323.

Qurollo BA, et al. A serological survey of tick-borne pathogens in dogs in North America and the Caribbean as assessed by *Anaplasma phagocytophilum, A. platys, Ehrlichia canis, E. chaffeensis, E. ewingii*, and *Borrelia burgdorferi* species-specific peptides. *Infect Ecol Epidemiol*. 2014;doi:10.3402/iee.v4.24699. eCollection.

Sainz Á, et al. Guideline for veterinary practitioners on canine ehrlichiosis and anaplasmosis in Europe. *Parasit Vectors*. 2015;8:75.

Schaefer JJ, et al. Tick acquisition of *Ehrlichia canis* from dogs treated with doxycycline hyclate. *Antimicrob Agents Chemother*. 2007;51:3394.

Shropshire S, Olver C, Lappin M. Characteristics of hemostasis during experimental *Ehrlichia canis* infection. *J Vet Intern Med*. 2018;doi:10.1111/jvim.15130. [Epub ahead of print].

Smith BE, et al. Antinuclear antibodies can be detected in dog sera reactive to *Bartonella vinsonii* subsp. *berkhoffii, Ehrlichia canis*, or *Leishmania infantum* antigens. *J Vet Intern Med*. 2004;18:47.

Starkey LA, et al. Development of antibodies to and PCR detection of *Ehrlichia* spp. in dogs following natural tick exposure. *Vet Microbiol*. 2014;173:379.

Theodorou K, et al. Synovial fluid cytology in experimental acute canine monocytic ehrlichiosis (Ehrlichia canis). *Vet Microbiol*. 2015;177:224.

Villaescusa A, et al. Evaluation of peripheral blood lymphocyte subsets in family-owned dogs naturally infected by Ehrlichia canis. *Comp Immunol Microbiol Infect Dis*. 2012;35:391.

Zhang XF, et al. Experimental *Ehrlichia chaffeensis* infection in beagles. *J Med Microbiol*. 2003;52:1021.

Feline Monocytotropic Ehrlichiosis

Aguirre E, et al. Assessment of feline ehrlichiosis in central Spain using serology and a polymerase chain reaction technique. *Ann N Y Acad Sci*. 2004;1026:103–135.

Beaufils JP, et al. Ehrlichiosis in cats. A retrospective study of 21 cases. *Pratique Medicale Chirurgicale de l'Animal de Compagnie*. 1999;34:587.

Bennett AD, et al. A comparative study evaluating the esophageal transit time of eight healthy cats when pilled with the FlavoRx pill glide versus pill delivery treats. *J Feline Med Surg*. 2010;12:286.

Bouloy RP, et al. Clinical ehrlichiosis in a cat. *J Am Vet Med Assoc*. 1994;204:1475.

Braga ÍA, et al. Detection of Ehrlichia canis in domestic cats in the central-western region of Brazil. *Braz J Microbiol*. 2014;45:641–645.

Braga IA, et al. Hematological values associated to the serological and molecular diagnostic in cats suspected of Ehrlichia canis infection. *Rev Bras Parasitol Vet*. 2013;22:470–474.

Braga Mdo S, et al. Molecular and serological detection of *Ehrlichia* spp. in cats on São Luís Island, Maranhão, Brazil. *Rev Bras Parasitol Vet*. 2012;21:37.

Breitschwerdt E, et al. Molecular evidence of *Ehrlichia canis* infection in cats from North America. *J Vet Intern Med*. 2002;16:642.

de Oliveira LS, et al. Molecular detection of *Ehrlichia canis* in cats in Brazil. *Clin Microbiol Infect*. 2009;2:53.

Eberhardt JE, et al. Prevalence of select infectious disease agents in cats from Arizona. *J Feline Med Surg*. 2006;8:164.

Levy JK, et al. Prevalence of infectious diseases in cats and dogs rescued following Hurricane Katrina. *J Am Vet Med Assoc*. 2011;238:311.

Luria BJ, et al. Prevalence of infectious diseases in feral cats in Northern Florida. *J Feline Med Surg*. 2004;6:287.

Pennisi MG, et al. Ticks and associated pathogens collected from cats in Sicily and Calabria (Italy). *Parasit Vectors*. 2015;8:512.

Stubbs CJ, et al. Feline ehrlichiosis; literature review and serologic survey. *Compend Contin Educ*. 2000;22:307.

Canine Granulocytotropic Ehrlichiosis

Buller RS, et al. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. *N Engl J Med*. 1999;341:148.

Goodman RA, et al. Molecular identification of *Ehrlichia ewingii* infection in dogs: 15 cases (1997-2001). *J Am Vet Med Assoc*. 2003;222:1102.

O'Connor TP, et al. Evaluation of peptide- and recombinant protein-based assays for detection of anti-*Ehrlichia ewingii* antibodies in experimentally and naturally infected dogs. *Am J Vet Res*. 2010;71:1195.

Wright CL, et al. Prevalence of *Ehrlichia chaffeensis* and *Ehrlichia ewingii* in *Amblyomma americanum* and *Dermacentor variabilis* collected from southeastern Virginia, 2010-2011. *Ticks Tick Borne Dis*. 2014;5:978.

Yabsley MJ, et al. *Ehrlichia ewingii* infection in white-tail deer (Odocoileus virginian us). *Emerg Infect Dis*. 2002;8:668.

Rocky Mountain Spotted Fever

Angelakis E, et al. *Rickettsia felis*: the complex journey of an emergent human pathogen. *Trends Parasitol*. 2016;32:554.

Bayliss DB, et al. Prevalence of Rickettsia species antibodies and Rickettsia species DNA in the blood of cats with and without fever. *J Feline Med Surg*. 2009;11:266.

Beeler E, et al. A focus of dogs and Rickettsia massiliae-infected Rhipicephalus sanguineus in California. *Am J Trop Med Hyg*. 2011;84:244.

Case JB, et al. Serological survey of vector-borne zoonotic pathogens in pet cats and cats from animal shelters and feral colonies. *J Feline Med Surg*. 2006;8:111.

Demma LJ, et al. Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *N Engl J Med*. 2005;353:587.

Demma LJ, et al. Serologic evidence for exposure to Rickettsia rickettsii in eastern Ariz8ona and recent emergence of Rocky Mountain spotted fever in this region. *Vector Borne Zoonotic Dis*. 2006;6:423.

Drexler NA, et al. Fatal Rocky Mountain spotted fever along the United States-Mexico border, 2013-2016. *Emerg Infect Dis*. 2017;23:1621.

Elchos BN, Goddard J. Implications of presumptive fatal Rocky Mountain spotted fever in two dogs and their owner. *J Am Vet Med Assoc*. 2003;223:1450.

Gasser AM, et al. Canine Rocky Mountain spotted fever: a retrospective study of 30 cases. *J Am Anim Hosp Assoc*. 2001;37:41.

Geurden T, et al. Detection of tick-borne pathogens in ticks from dogs and cats in different European countries. *Ticks Tick Borne Dis*. 2018;doi:10.1016/j.ttbdis.2018.06.013. [Epub ahead of print]; pii: S1877-959X(18)30119-5.

Grindem CB, et al. Platelet-associated immunoglobulin (antiplatelet antibody) in canine Rocky Mountain spotted fever and ehrlichiosis. *J Am Anim Hosp Assoc*. 1999;35:56.

Hawley JR, et al. Prevalence of Rickettsia felis DNA in the blood of cats and their fleas in the United States. *J Feline Med Surg*. 2007;9:258.

Helmick CG, et al. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis*. 1984;150:480.

Hii SF, et al. Molecular evidence supports the role of dogs as potential reservoirs for Rickettsia felis. *Vector Borne Zoonotic Dis*. 2011;11:1007.

Kidd L, et al. Molecular characterization of *Rickettsia rickettsii* infecting dogs and people in North Carolina. *Ann N Y Acad Sci*. 2006;1078:400.

Levin ML, et al. Clinical presentation, convalescence, and relapse of rocky mountain spotted fever in dogs experimentally infected via tick bite. *PLoS ONE*. 2014;9:e115105.

Little SE, et al. Ticks from cats in the United States: patterns of infestation and infection with pathogens. *Vet Parasitol*. 2018;257:15.

Mikszewski JS, Vite CH. Central nervous system dysfunction associated with Rocky Mountain spotted fever infection in five dogs. *J Am Anim Hosp Assoc*. 2005;41:259.

Nicholson WL, et al. Spotted fever group rickettsial infection in dogs from eastern Arizona: how long has it been there? *Ann N Y Acad Sci*. 2006;1078:519.

Pennisi MG, et al. Anaplasma, Ehrlichia and Rickettsia species infections in cats: European guidelines from the ABCD on prevention and management. *J Feline Med Surg*. 2017;19:542.

Piranda EM, et al. Experimental infection of *Rhipicephalus sanguineus* ticks with the bacterium Rickettsia rickettsii, using experimentally infected dogs. *Vector Borne Zoonotic Dis*. 2011;11:29.

Santanello C, et al. Spotted fever group Rickettsiae in ticks from Missouri. *Ticks Tick Borne Dis*. 2018;doi:10.1016/j.ttbdis.2018.06.008. pii: S1877-959X(17)30536-8.

Solano-Gallego L, et al. Acute febrile illness is associated with *Rickettsia* spp infection in dogs. *Parasit Vectors*. 2015;8:216.

Solano-Gallego L, et al. *Bartonella henselae* IgG antibodies are prevalent in dogs from southeastern USA. *Vet Res*. 2004;35:585.

Wikswo ME, et al. Detection of *Rickettsia rickettsii* and *Bartonella henselae* in Rhipicephalus sanguineus ticks from California. *J Med Entomol*. 2007;44:158.

CHAPTER 96

Polysystemic Viral Diseases



Many viruses infect dogs and cats. Several, including canine distemper virus (CDV), some feline coronaviruses, feline immunodeficiency virus (FIV), and feline leukemia virus (FeLV) can cause systemic signs of disease. See other chapters for discussions of viral diseases primarily associated with disease of specific organ systems.

CANINE DISTEMPER VIRUS

Etiology and Epidemiology

CDV induces disease predominantly in terrestrial carnivores, but many other species, including seals, ferrets, skunks, badgers, porpoises, and exotic Felidae, have been infected by either CDV or related morbilliviruses. Virulence of the CDV strains varies by genetic lineage. Strains of CDV occurring in dogs in North America now vary genetically from isolates evaluated in the 1900s, and there are now antigenic variants that may affect current vaccine efficacy (Anis et al., 2018; Kapil et al., 2008). In addition, more than one strain of CDV can be present in the same area (Wostenberg et al., 2018). The virus replicates in lymphoid, nervous, and epithelial tissues, and is shed in respiratory exudates, feces, saliva, urine, and conjunctival exudates for up to 60 to 90 days after natural infection. After inhalation, the virus is engulfed by macrophages and within 24 hours is carried by the lymphatics to tonsillar, pharyngeal, and bronchial lymph nodes, where replication occurs. Central nervous system (CNS) and epithelial tissues are infected approximately 8 to 9 days after initial infection.

The degree of clinical illness and the tissues involved vary depending on the strain of the virus and the immune status of the host. Nonimmune dogs of any age are susceptible, but the disease is most common in puppies between 3 and 6 months of age. Massive replication of the virus in the epithelial cells of the respiratory tract, gastrointestinal system, and genitourinary system occurs in dogs with poor immune responses by postinfection days 9 to 14; these dogs usually die from polysystemic disease. In dogs with moderate immune responses by postinfection days 9 to 14, the virus replicates in epithelial tissues and may result in clinical signs of disease. Dogs with good cell-mediated responses and virus-neutralizing antibody titers by postinfection day 14 clear the virus from most tissues and may not be clinically affected. Most infected dogs develop CNS infection, but clinical signs of CNS disease occur only in dogs with low or no antibody response. Acute demyelination results from restrictive infection of oligodendrogliocytes and subsequent necrosis; chronic demyelination is caused by immune-mediated mechanisms, including antimyelin antibodies and CDV immune complex formation and removal.

Clinical Features

Many clinically affected dogs are unvaccinated, failed to receive colostrum from an immune bitch, were inappropriately vaccinated, or are immunosuppressed and also have a history of exposure to infected animals. Owners generally present affected dogs for evaluation of depression, malaise, oculonasal discharge, cough, vomiting, diarrhea, or CNS signs. Dogs with poor immune responses generally have the most severe signs and progress rapidly to life-threatening disease. Some partially immune dogs have only mild respiratory disease, presumptively diagnosed as canine infectious respiratory disease complex. Tonsillar enlargement, fever, and mucopurulent ocular discharge are common physical examination findings. Increased bronchial sounds, crackles, and wheezes are usually auscultated in dogs with bronchopneumonia.

Hyperesthesia, seizures, cerebellar or vestibular disease, paresis, and chorea myoclonus are common CNS signs that generally develop within 21 days of recovery from systemic disease (Table 96.1). CNS disease is generally progressive and carries a poor prognosis; it can develop in some dogs that never had systemic signs of disease recognized. Old dog encephalitis is a chronic, progressive panencephalitis in dogs older than 6 years thought to be attributable to CDV infection in which microglial proliferation and neuronal degeneration in the cerebral cortex result in depression, circling, head pressing, and visual deficits (see Chapter 64 for more information on CNS distemper).

TABLE 96.1

Clinical Manifestations of CDV Infection

In utero infection	Stillbirth Abortion Fading puppy syndrome in the neonatal period CNS signs at birth
Gastrointestinal tract disease	Vomiting Small-bowel diarrhea
Respiratory tract disease	Mucoid to mucopurulent nasal discharge Sneezing Coughing with increased bronchovesicular sounds or crackles on auscultation Dyspnea
Ocular disease	Retinochoroiditis, medallion lesions (see Fig. 96.1), optic neuritis Keratoconjunctivitis sicca Mucopurulent ocular discharge
Neurologic Disease	
Spinal cord disease	Paresis and ataxia
Central vestibular disease	Head tilt, nystagmus, other cranial nerve and conscious proprioception deficits
Cerebellar disease	Ataxia, head bobbing, hypermetria
Cerebral disease	Generalized or partial seizures ("chewing gum fits") Depression Unilateral or bilateral blindness
Chorea myoclonus	Rhythmic jerking of single muscles or muscle groups
Miscellaneous	Fever Anorexia Tonsillar enlargement Dehydration Pustular dermatosis Hyperkeratosis of the nose and footpads Enamel hypoplasia in surviving puppies

CDV, Canine distemper virus; *CNS,* central nervous system.

Ocular abnormalities associated with CDV infection include anterior uveitis, optic neuritis with resultant blindness and dilated pupils, and retinochoroiditis. The combination of retinochoroiditis and encephalitis is detected in approximately 40% of affected dogs. Keratoconjunctivitis sicca and hyperreflective retinal scars called *medallion lesions* occur in some dogs with chronic infection (Fig. 96.1).

Other less common syndromes have been attributed to CDV infection. Dogs infected before the development of permanent dentition usually have enamel hypoplasia.

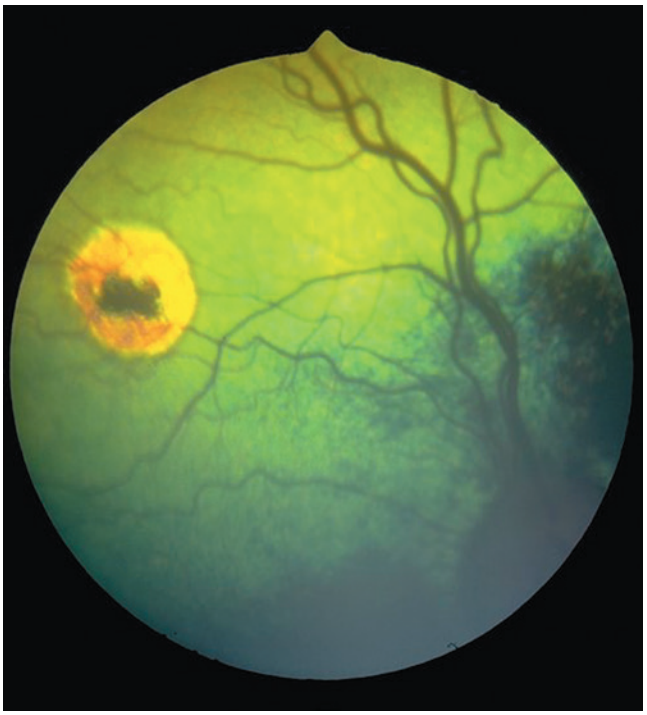


FIG 96.1
Medallion lesions resulting from canine distemper virus infection. (Courtesy Dr. Cynthia Powell, Colorado State University, Fort Collins.)

Hyperkeratosis of the nose and footpads and pustular dermatitis are the most common dermatologic abnormalities. Puppies infected transplacentally can be stillborn, aborted, or born with CNS disease.

Diagnosis

The combination of clinical findings and routine clinicopathologic and radiographic evaluation usually leads to a presumptive diagnosis of CDV infection. Lymphopenia and mild thrombocytopenia are consistent hematologic abnormalities. Interstitial and alveolar pulmonary infiltrates are common radiographic findings in dogs with respiratory disease. Although some dogs with CNS infection have normal cerebrospinal fluid (CSF) analyses, most have mononuclear cell pleocytosis and increased protein concentrations. The ratio of serum/CSF immunoglobulin G (IgG) and albumin is commonly high in dogs with encephalitis, but this only documents inflammation of the CNS, not CDV infection.

Measurement of serum or CSF antibody titers can aid in the diagnosis of CDV infection. Documentation of a fourfold increase in the serum IgG titer over a 2- to 3-week period or detection of IgM antibodies in serum is consistent with recent infection or recent vaccination but does not prove clinical disease. CSF antibody titers to CDV are increased in some dogs with encephalitis. False-positive results can occur in CSF samples contaminated with blood. If CSF antibody titers are greater than those in serum, the

antibody in the CSF had to be produced locally and is consistent with CNS CDV infection. If increased CSF protein concentrations, mononuclear pleocytosis, and antibodies against CDV are detected in a CSF sample not contaminated with peripheral blood, a presumptive diagnosis of CDV encephalitis can be made.

Definitive diagnosis of CDV infection requires demonstration of viral inclusions by cytologic examination, direct fluorescent antibody (DFA) staining of cytologic or histopathologic specimens, histopathologic evaluation, virus isolation, or reverse transcriptase polymerase chain reaction (RT-PCR) documentation of CDV RNA in peripheral blood, CSF, or conjunctival scrapings. Viral inclusions are rarely found in erythrocytes, leukocytes, and leukocyte precursors of infected dogs. Inclusions are generally present for only 2 to 9 days after infection and therefore often are not present when clinical signs occur. Inclusions may be easier to find in smears made from buffy coats or bone marrow aspirates than in those made from peripheral blood. Viral particles can be detected by DFA in cells from the tonsils, respiratory tree, urinary tract, conjunctival scrapings, and CSF for 5 to 21 days after infection. In areas molecular assays are expensive or not available, DFA assays can be performed with a moderate sensitivity (79%) when compared with molecular assays (Athanasiou et al., 2018). However, false-positive results have been detected occasionally in DFA performed on conjunctival cells from specific pathogen-free puppies, so results of these tests should be interpreted cautiously (Burton et al., 2008). Recent administration of modified-live CDV-containing vaccines can lead to positive results in DFA and some RT-PCR assays so vaccination history is important to consider with assessing the results of these assays. It is possible to differentiate wild strains and vaccine strains of CDV by RT-PCR; veterinarians should ask the preferred service laboratory whether the assay being used can provide this discrimination (Yi et al., 2012).

Treatment

Although a number of substances like ribraviron, interferon alpha, and caffeic acid inhibit CDV in vitro, therapy for CDV infection is nonspecific and supportive (Carvalho et al., 2014). Secondary bacterial infections of the gastrointestinal tract and respiratory system are common and, if indicated, should be treated as indicated. Anticonvulsants are administered as needed to control seizures (see Chapter 62), but chorea myoclonus has no known effective treatment. Glucocorticoid administration may be beneficial in some dogs with CNS disease from chronic CDV infection, but it is contraindicated in acutely infected dogs. The prognosis for dogs with CNS distemper is poor.

Prevention and Zoonotic Aspects

The CDV survives in exudates only for approximately 1 hour at body temperature and 3 hours at room temperature and is susceptible to most routine hospital disinfectants. Dogs with gastrointestinal or respiratory signs of disease should be housed in isolation to avoid aerosolization to susceptible populations. Care should be taken to avoid transmission by contaminated fomites (see Chapter 93). All puppies should be administered at least three CPV-2, CAV-2, and CDV-containing vaccines, every 3 to 4 weeks, between 6 and 16 weeks of age, with the last booster administered at 16 weeks of age (see Chapter 93). Administration of a final dose at 18 to 20 weeks of age should be considered for dogs residing in high-risk environments. Modified-live CDV vaccines and the recombinant CDV (rCDV) vaccine are considered effective by the AAHA task force (https://www.aaha.org/guidelines/canine_vaccination_guidelines.aspx). The rCDV vaccine can be used to break through maternal antibodies that can block CDV vaccines. In one recent study, almost all vaccinated dogs in a shelter achieved protective serum antibody titers within 13 to 15 days after receiving a modified live CDV vaccine (Litster et al., 2012a). Vaccines should be boosted at 1 year of age. After the 1-year booster, repeat boosters are not needed again for a minimum of 3 years and protection after challenge has been documented for more than 4 years (Jensen et al., 2015). Serologic studies have shown that vaccination induces long-term protection against CDV (Killey et al., 2018).

Disease from CDV infection has occurred in some vaccinated dogs and rarely is attributed to modified-live virus vaccination. Clinical disease in vaccinated dogs develops if the host was immunocompromised, infected with the virus before vaccination, had vaccine-suppressive levels of maternal antibodies, or was incompletely vaccinated. Alternately, the vaccine may have been inactivated by improper handling or may not have protected against all field strains of CDV (Anis et al., 2018). Distemper virus encephalitis develops after modified-live vaccination of some dogs co-infected with canine parvovirus; administration of modified-live CDV vaccines should be delayed in dogs with clinical signs of disease consistent with parvovirus infection. Mild, transient thrombocytopenia can be induced by modified CDV vaccination but has not been associated with spontaneous bleeding unless the patient has an underlying subclinical coagulopathy. No proven public health risks are associated with CDV.

Serum antibody titers that predict resistance to challenge with CDV are known. Samples can be submitted to a validated laboratory for assessment of vaccination needs. Alternately, in some countries, assays designed to be used in the clinic are available and have been used to assess animals for CDV susceptibility in outbreak situations or for individual pet dogs (Gray et al., 2012; Litster et al., 2012ab). Some vaccinated dogs are negative for CDV antibodies 3 years after vaccination, depending on the assay used (Mahon et al., 2017). These findings support the use of serology in determining CDV vaccination need, which can be used yearly in lieu of vaccination to determine when the titer goes below protection levels. Serology can also be used to determine areas within a community that are the likely source of dogs in CDV outbreaks and drive targeted vaccination programs and lessen the potential for local outbreaks (Spindel et al., 2018).

FELINE CORONAVIRUS

Etiology and Epidemiology

Coronaviruses causing disease in cats include feline infectious peritonitis virus (FIPV) and feline enteric coronavirus (FECV). The virology and immunopathogenesis of feline coronaviruses has been reviewed (Pedersen et al., 2014a). Enteric infection generally results in mild gastrointestinal signs; systemic infection can induce a clinical syndrome with diverse manifestations commonly referred to as feline infectious perinotitis (FIP). Most current work suggests that the mutations associated with the FIPV strains are in the 3c and spike protein genes (Bank-Wolf et al., 2014; Lewis et al., 2015; Rottier et al., 2005). Enteric coronaviruses are commonly shed in feces and are highly contagious. By RT-PCR testing, coronaviruses can be detected in feces as early as 3 days after infection. In studies of FECV-infected, closed cat colonies, almost every cat becomes infected. In one study of 155 pet cats with naturally occurring FECV infection, viral RNA was shed continuously ($n = 18$) or intermittently ($n = 44$) in the feces of some cats (Addie et al., 2001). Others were initially shedding viral RNA and then ceased shedding ($n = 56$), and some were resistant to infection ($n = 4$). The cats that stopped viral shedding were susceptible to reinfection. Viral RNA was detected in the ileum, colon, and rectum of cats with persistent shedding.

Most cases of FIP develop in multiple-cat households or catteries. Theoretically, the effusive form of disease develops in cats with poor cell-mediated immune responses; the noneffusive form ("dry") develops in cats with partial cell-mediated immunity. The effusive form of disease is an immune complex vasculitis characterized by leakage of protein-rich fluid into the pleural space, the peritoneal cavity, the pericardial space, and the subcapsular space of the kidneys. In the noneffusive form pyogranulomatous or granulomatous lesions develop in multiple tissues, particularly the eyes, brain, kidneys, omentum, and liver. Some affected cats have characteristics of both forms of FIP. Using reverse transcriptase quantitative PCR (RT-qPCR) assay and immunohistochemical staining, it was shown that experimentally inoculated cats have FIPV genomic RNA mainly in macrophages in diseased tissues and effusions (Pedersen et al., 2015).

Clinical disease associated with FIP virus may be influenced by a number of factors, including the virulence of the strain, the dose of the virus, the route of infection, the immune status of the host, genetically determined host factors, the presence of other concurrent infections, and whether the cat had been previously exposed to a coronavirus. Some breeds, including British Shorthair, Devon Rex, and Abyssinian, appear to be predisposed to the development of FIP in some studies (Pedersen et al., 2014a; Pesteanu-Somogyi et al., 2006; Worthing et al., 2012;). However, it has been difficult to determine the genetic basis for increased susceptibility or resistance (Pedersen et al., 2014c). In a study of 40 of 111 cats that survived experimental inoculation with FIPV, there was no sex association, but resistance increased after 6 months of age (Pedersen et al., 2014c). FeLV infection and respiratory tract infection increase the risk for FIP, suggesting that the immune status of the host is important in determining the development of clinical disease. Cats concurrently infected with FIV shed 10 to 100 times more FECV in stool than FIV-naive cats. Previous exposure to non-FIP-inducing feline coronaviruses before challenge with virulent FIPV can result in acceleration of the disease process (Pedersen et al., 2014c). Experimentally infected, coronavirus seropositive kittens can develop accelerated FIP compared with seronegative kittens when exposed to FIPV. This antibody-dependent enhancement of virus infectivity occurs because macrophages are more effectively infected by virus complexed with antibody than by virus alone, but this phenomenon appears to be rare in naturally infected cats.

Clinical Features

Enteric replication of coronaviruses commonly results in fever, vomiting, and mucoid diarrhea. With FECV infection, clinical signs are self-limiting and generally respond to supportive care within days. Fulminant FIP can occur in cats of any age but is generally recognized in cats younger than 5 years; most cases are younger than 1 year. Intact males are over-represented in some studies. In cattery outbreaks, usually only one or two kittens in a litter are clinically affected. This may relate to poor transmissibility of strains capable of inducing FIP. Anorexia, weight loss, and general malaise are common presenting complaints (Box 96.1). Icterus, ocular inflammation, abdominal distension, dyspnea, or CNS abnormalities are occasionally noted by the owner.

Fever and weight loss are common. Pale mucous membranes or petechiae are noted in some cats. FIP is one of the most common causes of icterus in cats younger than 2 years; liver size can be normal or enlarged, and the margins are usually irregular. Abdominal distension is common, a fluid wave can often be balloted, and occasionally masses (pyogranulomas or lymphadenopathy) can be palpated in the omentum, mesentery, or intestines. A solitary ileocecocolic or colonic mass, resulting in obstruction leading to vomiting and diarrhea, occurs in some cats (Harvey et al., 1996). Kidneys can be small (chronic disease) or large (acute disease or subcapsular effusion); renal margins are usually irregular. Pleural effusion can result in dyspnea and a restrictive breathing pattern (shallow and rapid), as well as muffled heart and lung sounds. Male cats sometimes have scrotal enlargement from fluid accumulation.

Anterior uveitis and chorioretinitis occur most frequently with the noneffusive form of the disease and can be its only manifestation. Pyogranulomatous disease can develop anywhere in the CNS, leading to a variety of neurologic signs that include seizures, posterior paresis, and nystagmus. Seizures secondary to FIP are a poor prognostic indicator (Timmann et al., 2008).

Feline coronaviruses have been suggested as a cause of failure to conceive, abortion, stillbirth, and congenital defects, as well as the fading kitten syndrome (kitten mortality complex). However, one epidemiologic study failed to

BOX 96.1

Clinical Findings Suggestive of FIP in Cats

Signalment and History

Cats < 5 years or >10 years of age
Purebred cat
Purchased from a cattery or housed in a multiple-cat household
Previous history of a mild, self-limiting gastrointestinal or respiratory disease
Serologic evidence of infection by FeLV
Nonspecific signs of anorexia, weight loss, or depression
Seizures, nystagmus, or ataxia
Acute, fulminant course in cats with effusive disease
Chronic, intermittent course in cats with noneffusive disease

Physical Examination

Fever
Weight loss
Pale mucous membranes with or without petechiae
Dyspnea with a restrictive breathing pattern
Muffled heart or lung sounds
Abdominal distension with a fluid wave with or without scrotal swelling
Abdominal mass from focal intestinal granuloma or lymphadenopathy
Icterus with or without hepatomegaly
Chorioretinitis or iridocyclitis
Multifocal neurologic abnormalities
Irregularly marginated kidneys with or without renomegaly
Splenomegaly

Clinicopathologic Abnormalities

Nonregenerative anemia
Neutrophilic leukocytosis with or without a left shift
Lymphopenia
Hyperglobulinemia characterized as a polyclonal gammopathy; rare monoclonal gammopathies
Nonseptic, pyogranulomatous exudate in pleural space, peritoneal cavity, or pericardial space
Increased protein concentrations and neutrophilic pleocytosis in CSF
Positive coronavirus antibody titer in the majority (especially noneffusive)
Pyogranulomatous or granulomatous inflammation in perivascular location on histologic examination of tissues
Positive results of immunofluorescence or RT-PCR performed on pleural or peritoneal exudate

CSF, Cerebrospinal fluid; *FeLV,* feline leukemia virus; *FIP,* feline infectious peritonitis; *RT-PCR,* reverse transcriptase polymerase chain reaction.

link feline coronavirus with reproductive failure or neonatal kitten death.

Diagnosis

Multiple hematologic, serum biochemical, urinalysis, diagnostic imaging, and CSF abnormalities develop in cats with FIP. There have been multiple review articles and case series evaluating diagnostic procedures (Pedersen 2014b; Stranieri et al., 2018; Tasker et al., 2018). Other than histopathology, the positive predictive values of tests used to aid in the diagnosis of FIP are less than 100%. A presumptive diagnosis of FIP is usually based on the combination of clinical and clinicopathologic findings.

Normocytic, normochromic, nonregenerative anemia; neutrophilic leukocytosis; and lymphopenia are common. Disseminated intravascular coagulation resulting in thrombocytopenia and, rarely, hemolytic anemia occurs in cats with FIP. Hyperglobulinemia is one of the most common abnormalities and occurs in up to 89% of cases. Hyperglobulinemia can be detected with or without hypoalbuminemia (Riemer et al., 2016). In some studies, the ratio of albumin to globulins of <0.4 was supportive of a diagnosis of FIP, and a ratio >0.8 excluded the diagnosis. Polyclonal gammopathies from increases in α_2-globulin and γ-globulin concentrations are most commonly detected; monoclonal gammopathies are rare. A number of acute phase proteins like α_1-acid glycoprotein have been evaluated in the blood of cats with and without FIP. In one small study of 12 cats with FIP, serum concentrations of α_1-acid glycoprotein had high sensitivity (100%) and specificity for the diagnosis of FIP (Giori et al., 2011). Most of these findings are consistent with chronic inflammation and do not prove FIP.

Hyperbilirubinemia with variable increases in alanine aminotransferase and alkaline phosphatase activities occurs in some cats with hepatic disease. Prerenal azotemia, renal azotemia, and proteinuria are the most common renal abnormalities. Radiographs can reveal pleural, pericardial, or peritoneal effusions; hepatomegaly; or renomegaly. Mesenteric lymphadenopathy may result in mass lesions in some cats. Ultrasonography can be used to confirm the presence of abdominal fluid in cats with minimal fluid volumes and to evaluate the pancreas, liver, lymph nodes, and kidneys (Lewis and O'Brien, 2010). Protein concentrations and nucleated cell counts (neutrophils predominate in most cases) are commonly increased in CSF from cats with CNS involvement. Although high coronavirus antibody titers are common in the CSF of cats with neurologic FIP, the antibodies appear to be derived from blood and, as the authors of one study concluded, were of equivocal value (Boettcher et al., 2007).

Feline coronavirus antibody tests that were available at the time were evaluated and how to use the results of the assays in feline practice were reviewed (Addie et al., 2015). There are multiple potential reasons to use coronavirus antibody tests, particularly in breeding catteries. In the diagnosis of clinical FIP, the greatest clinical value of coronavirus antibody tests is the detection of a negative

result. If the test used is very sensitive, a negative test result helps exclude the diagnosis of FIP because most cats with effusive or noneffusive disease are serum antibody-positive. However, cats with FIP are occasionally serologically negative because of rapidly progressive disease, with a delayed rise in titer, disappearance of antibody in terminal stages of the disease, or immune complex formation. Positive coronavirus serologic test results are more difficult to use for a number of reasons. Infection of cats by any coronavirus can cause cross-reacting antibodies; therefore a positive antibody titer does not diagnose FIP, protect against disease, or predict when a cat may develop clinical FIP. Presence of maternal antibodies can confuse the diagnosis in very young kittens. However, this is age dependent as maternal antibodies decline to undetectable concentrations by 4 to 6 weeks of age; kittens infected in the postnatal period become seropositive at 8 to 14 weeks of age. Because coronavirus antibody tests are not standardized, results from different laboratories commonly do not correlate (Addie et al., 2015).

Immunocytochemistry has been developed to detect coronavirus antigen in CSF, aqueous humor, and effusions (Doenges et al., 2016; Felten et al., 2017; Felten et al., 2018). The assay can be very sensitive, but the specificity is low in most studies because some cats without FIP can be positive. Immunohistochemistry documenting the presence of coronavirus in tissues concurrently with characteristic histopathologic findings can be used to prove the diagnosis of FIP (Harvey et al., 1996).

Because virus isolation is not practical clinically, RT-qPCR is used most frequently to amplify coronaviruses in feces, blood, effusions, CSF, aqueous humor, and tissues. Multiple different molecular targets have been employed with varying sensitivity and specificity. Use of these assays on blood or feces generally do not differentiate FIPV from FECV and so positive results to not prove FIP. Use of these assays on effusions appear to have the most clinical utility. If effusions are not present, use of an RT-qPCR on circulating peripheral blood mononuclear cells was more sensitive than use of serum (Doenges et al., 2017). In cats with neurologic and/or ocular signs, the sensitivity of a real-time RT-PCR on CSF was 85.7% in one study (Doenges et al., 2016)

Effusions from cats with FIP are sterile, colorless to straw-colored, may contain fibrin strands, and may clot when exposed to air (Fig. 96.2). The protein concentration on fluid analysis commonly ranges from 3.5 g/dL to 12 g/dL and is generally higher than that associated with other diseases. Mixed inflammatory cell populations of lymphocytes, macrophages, and neutrophils occur most commonly; neutrophils predominate in most cases, but in some cats macrophages are the primary cell type seen. In some cats, the coronavirus antibody titers are greater in the effusion than in serum. Measurement of protein concentrations in effusions and calculation of the albumin/globulin ratio (AGR) can aid in the diagnosis of effusive FIP. In one study, an AGR of 0.5 had a positive predictive value of 89%, and an AGR of 1.0 had a negative predictive value of 91%. Coronavirus antigens are commonly detected by immunocytochemistry in the effusions of cats with FIP, but the sensitivity is less than 100% as antigens have also been detected in the effusions of some cats with other diseases (Felten et al., 2017). If molecular assays are available, they should be performed on cats with effusions consistent with FIP becasue viral RNA can be amplified from effusions in most cats with FIP by RT-qPCR and is unlikely to be amplified from effusions from other causes.

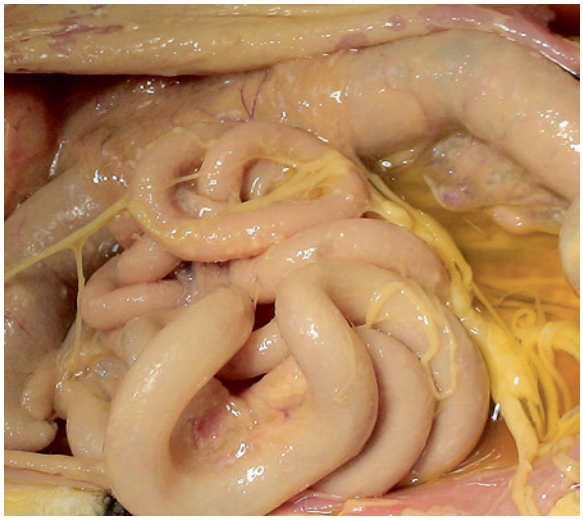


FIG 96.2
Abdominal effusion consistent with the effusive form of feline infectious peritonitis identified on necropsy of an affected cat.

The most definitive diagnosis of FIP is based on combination of characteristic histopathologic findings with the presence of coronavirus by virus isolation, immunocytochemical or immunohistochemical staining, or amplification of viral RNA in effusions, other fluids like CSF or aqueous humor or tissues by RT-qPCR.

Treatment

Because an antemortem diagnosis of FIP is difficult to make, assessment of studies reporting successful treatment is virtually impossible. Treatments for FIP have been reviewed, and there is no protocol that is consistently effective (Hartmann and Ritz, 2008; Pedersen et al., 2014b). A small percentage of cats have spontaneous remission, adding to the confusion concerning therapeutic response. Supportive care, including correction of electrolyte and fluid balance abnormalities, and lessening stress should be provided to cats with FIP as needed.

Feline coronaviruses are dependent on 3C-like protease for replication (Kim et al., 2015). The use of one 3C-like protease inhibitor showed promise in the treatment of FIP but is not currently on the market (Pedersen et al., 2017). In vitro inhibition of FIP virus replication has also been demonstrated with a number of drugs, including ribavirin, human interferon-α, feline fibroblastic interferon-β, adenine arabinoside, and amphotericin B. However, to date no

uniformly successful antiviral treatment has been developed, and the drugs typically have potentially serious adverse effects. Cyclosporine A inhibits replication of feline coronaviruses in vitro, but it is currently unknown whether this drug can be used successfully as a treatment of FIP (Tanaka et al., 2012). Small interfering RNA (siRNA) can be synthesized and target different regions of the coronavirus genome to inhibit viral replication in vitro and is another potential future treatment modality (McDonagh et al., 2011).

Because disease from FIP is secondary to immune-mediated reactions against the virus, modulation of the inflammatory reaction is the principal form of palliative therapy. Low-dose prednisolone (1-2 mg/kg orally [PO] q24h) may lessen clinical manifestations of noneffusive FIP. However, the use of immunosuppressive drugs is controversial because cats with FIP have impaired immune responses. Prednisolone and feline recombinant interferon were used in combination for the treatment of both effusive and noneffusive FIP in small numbers of cats (Ishida et al., 2004). In that study, four cats with effusive disease believed to be from FIP virus had prolonged remission. It is impossible to determine whether the effect was from the prednisolone or interferon because both drugs were administered to all cats. In another study, administration of interferon-ω was ineffective for the treatment of FIP (Ritz et al., 2007). In the future, veterinarians may be able lessen inflammation and disease induced by FIP by administering anti-feline tumor necrosis factor monoclonal antibodies (Doki et al., 2016). Immune modulation with polyprenyl immunostimulant may induce beneficial effects in some cats with noneffusive FIP (Legendre and Bartges, 2009; Legendre et al., 2017).

Antibiotics do not have primary antiviral effects but may be indicated for the treatment of secondary bacterial infection. Other supportive care treatments such as anabolic steroids (stanozolol, 1 mg PO q12h), aspirin (10 mg/kg PO q48-72h), and ascorbic acid (125 mg PO q12h) have also been recommended for the treatment of FIP. Most cats with systemic clinical signs of FIP die or require euthanasia within days to months of diagnosis. The effusive form of disease carries a grave prognosis. The drug propentofylline, used to treat vasculitis, was evaluated in a placebo-controlled study of naturally infected cats with effusive disease. However, the propentofylline protocol assessed did not improve the quality of life or lessen the effusion (Fischer et al., 2011). Depending on the organ system involved and the severity of polysystemic clinical signs, cats with noneffusive FIP have variable survival times. Cats with only ocular FIP may respond to antiinflammatory treatment or enucleation of the affected eye(s) and have a better prognosis than cats with systemic FIP.

Prevention and Zoonotic Aspects

Prevention of coronavirus infections is best accomplished by avoiding exposure to the virus. Although viral particles coronaviruses can survive in dried secretions for up to 7 weeks, routine disinfectants inactivate the viruses. Some cats eliminate FECA coronavirus infections, and not all cats exposed to FIPV develop the syndrome of FIP. However, some research cats that survived FIPV infection on primary exposure developed FIP on subsequent inoculation suggesting that immunity is not permanent (Addie et al., 2001; Pedersen et al., 2014a). Although the genetics of FIPV resistance is complex, cats with progeny that died of FIP should be avoided for use for breeding programs in pedigreed catteries (Pedersen et al., 2014).

An intranasally administered, mutant strain of coronavirus that induces mucosal immune response but minimal systemic immune response is available in some countries (Primucell FIP, Zoetis Animal Health). This strain does not induce FIP; the majority of cats with adverse effects have exhibited only mild signs associated with placement of liquid in the nares, and the vaccine does not appear to potentiate antibody-dependent enhancement of virus infectivity when administered to previously seropositive cats. The vaccine appears to be effective in at least some cats, but whether it protects against all field strains, mutations, or recombinants is unknown, so it is considered as noncore by the American Association of Feline Practitioners (see Chapter 93). Zoonotic transfer of FIP virus or FECV to human beings has not been documented.

FELINE IMMUNODEFICIENCY VIRUS

Etiology and Epidemiology

FIV is an exogenous, single-strand RNA virus in the family Retroviridae, subfamily Lentivirinae. The virus is morphologically similar to the human immunodeficiency virus (HIV), but it is antigenically distinct. Like FeLV, FIV produces reverse transcriptase to catalyze the insertion of viral RNA into the host genome. Multiple clades of the virus exist, and some isolates have differing biologic behavior. For example, immune deficiency is induced much more quickly by some isolates, and clinical diseases such as uveitis are induced by some but not all isolates. The prevalence of FIV antibodies in United States and Canada was 3.6% in a 2017 study (Burling et al., 2017), which is higher than the 2.5% in a study reported in 2006 (Levy et al., 2006). Regional variations in prevalence rates for both FIV and FeLV exist (Chhetri et al., 2013).

FIV replicates readily in the oral lymphoid tissues (Miller et al., 2017). Aggressive biting behavior is thought to be the primary route of transmission of FIV; older, male, outdoor cats with clinical signs of disease are most commonly infected. Plasma viral loads increase as the FIV disease severity increases (Kann et al., 2014). Vertical transmission appears to be unlikely to occur based on a study of group housed shelter cats (Litster et al., 2014). FIV is present in semen and can be transmitted by artificial insemination. Transplacental and perinatal transmission occurs from infected queens to kittens. Arthropod transmission appears to be unlikely. Transmission by routes other than biting is less common because high levels of viremia are of short duration. FIV infection of cats has worldwide distribution,

and prevalence rates vary greatly by region and the lifestyle of the cats tested. FIV replicates in several cell types, including T lymphocytes ($CD4^+$ and $CD8^+$), B lymphocytes, macrophages, and astrocytes. The primary phase of infection occurs as the virus disseminates throughout the body, initially leading to low-grade fever, neutropenia, and generalized reactive lymphadenopathy. A subclinical, latent period of variable length then develops; the length of this period is related in part to the strain of virus and the age of the cat when infected. The median ages of healthy, naturally infected cats and clinically ill naturally infected cats are approximately 3 years and 10 years, respectively, suggesting a latent period of years for most strains of FIV. Chronic experimental and naturally occurring infection results in a slow decline in circulating $CD4^+$ lymphocyte numbers, response to mitogens, and decreased production of cytokines associated with cell-mediated immunity, such as interleukin (IL)-2 and IL-10; neutrophil function and natural killer cell function are also affected. Humeral immune responses are often intact, and a polyclonal gammopathy develops from nonspecific B-lymphocyte activation. Within months to years, an immune deficiency stage similar to acquired immunodeficiency syndrome (AIDS) in human beings develops. Coinfection with FeLV potentiates the primary and immune deficiency phases of FIV. However, co-infection with *Mycoplasma haemofelis, Toxoplasma gondii,* feline herpesvirus, and feline calicivirus, as well as immunization, failed to potentiate FIV-associated immunodeficiency in research studies. However, FIV antibodies and hemoplasma infections are associated in some studies, which may just reflect that both agents are transmitted directly (Sarvani et al., 2018). Recently, *Felis catus* gammaherpesvirus has been be detected in FIV-infected cats, and the role co-infection with the two viruses plays in pathogenesis or progression of disease is being studied (McLuckie et al., 2017). Infection with FIV may be associated with T-cell lymphomas (Murphy et al., 2018). Many cats with FIV antibodies survive for years after diagnosis, and in one study, there was no difference in long-term survival between cats that were or were not FIV infected (Liem et al., 2013). However, cats with FeLV infection or FeLV and FIV co-infections had significantly shorter life spans than cats infected with FIV alone (Spada et al., 2018). The oral and rectal microbiota of FIV-infected cats varies from healthy controls, which may relate to chronic diarrhea and stomatitis that develops in some infected cats (Weese et al., 2015ab).

Clinical Features

Clinical signs of infection with FIV can arise from direct viral effects or secondary infections that ensue after the development of immunodeficiency (Table 96.2). Most of the clinical syndromes diagnosed in FIV-seropositive cats also occur in FIV-naïve cats, which makes proving disease causation difficult during the subclinical stage of infection. A positive FIV antibody test does not prove immunodeficiency or disease from FIV and does not necessarily indicate a poor prognosis. The only way to determine accurately whether an FIV-seropositive cat with a concurrent infectious disease has a poor prognosis is to treat the concurrent infection.

Primary (acute) FIV infection is characterized by fever and generalized lymphadenopathy. Owners commonly present FIV-infected cats in the immunodeficiency stage for evaluation of nonspecific signs such as anorexia, weight loss, and depression or for evaluation of abnormalities associated with specific organ systems. When a clinical syndrome is diagnosed in a cat seropositive for FIV, the workup should include diagnostic tests for other potential causes (see Table 96.2).

Clinical syndromes reportedly from primary viral effects include chronic small-bowel diarrhea, nonregenerative anemia, thrombocytopenia, neutropenia, lymphadenopathy, pars planitis (inflammation in the anterior vitreous humor), anterior uveitis, glomerulonephritis, renal insufficiency, and hyperglobulinemia. Oral cavity inflammatory diseases occur in both FIV and FeLV infected cats (Kornya et al., 2014). In one report of naturally infected cats, FIV was associated with proteinuria but not renal azotemia (Baxter et al., 2012). In another study, proteinuria and low specific gravity were common in FIV-positive cats (Taffin et al., 2017). FIV may play a role in the development of hypertrophic cardiomyopathy in some cats (Rolim et al., 2016). However, secondary infections associated with myocarditis like *T. gondii* and *Bartonella* spp. should also always be excluded in these cases. Behavioral abnormalities, with dementia, hiding, rage, inappropriate elimination, and roaming, are neurologic manifestations of FIV infection. Seizures, nystagmus, ataxia, and peripheral nerve abnormalities may occasionally be attributable to primary viral effects, but secondary infections associated with neurologic disease like *T. gondii* should always be excluded as well (Power et al., 2018). Lymphoid malignancies, myeloproliferative diseases, and several carcinomas and sarcomas have been detected in FIV-infected, FeLV-naïve cats, suggesting a potential association between FIV and malignancy; FIV-infected cats are at higher risk for the development of lymphoma (Magden et al., 2011; Murphy et al., 2018).

Diagnosis

Neutropenia, thrombocytopenia, and nonregenerative anemia are common hematologic abnormalities associated with FIV infection. Monocytosis and lymphocytosis occur in some cats and may be caused by the virus or chronic infection with opportunistic pathogens. Cytologic examination of bone marrow aspirates may reveal maturation arrest (i.e., myelodysplasia), lymphoma, or leukemia. A progressive decline in $CD4^+$ lymphocytes, a plateau or progressive increase in $CD8^+$ lymphocytes, and an inversion of the $CD4^+$/$CD8^+$ ratio occurs in experimentally infected cats over time. A multitude of serum biochemical abnormalities is possible depending on what FIV-associated syndrome is occurring. Polyclonal gammopathy can occur in some FIV-infected cats. No pathognomonic imaging abnormalities are associated with FIV infection.

TABLE 96.2

Clinical Syndromes Associated With FIV Infection and Possible Opportunistic Agents

CLINICAL SYNDROME	PRIMARY VIRAL EFFECT	OPPORTUNISTIC AGENTS
Dermatologic/otitis externa	None	Bacterial; atypical *Mycobacterium; Otodectes cynotis; Demodex cati; Notoedres cati;* dermatophytosis; *Cryptococcus neoformans;* cowpox
Gastrointestinal	Yes; small-bowel diarrhea	*Cryptosporidium* spp.; *Cystoisospora* spp.; *Giardia* spp.; *Salmonella* spp.; *Campylobacter spp.* others
Glomerulonephritis	Yes	Bacterial; FeLV, FIP, SLE
Hematologic	Yes; nonregenerative anemia; neutropenia; thrombocytopenia	*Mycoplasma haemofelis*; FeLV; *Bartonella henselae?*
Myocarditis; hypertropic cardiomyopathy	Yes	*Bartonella* spp., *T. gondii*
Neoplasia	Yes; myeloproliferative disorders and lymphoma	FeLV
Neurologic	Yes; behavioral abnormalities	*Toxoplasma gondii; C. neoformans*; FIP; FeLV, *B. henselae?*
Ocular	Yes; pars planitis, anterior uveitis	*T. gondii;* FIP; *C. neoformans,* FHV-1, *B. henselae*
Pneumonia/pneumonitis	None	Bacterial; *T. gondii; C. neoformans*
Pyothorax	None	Bacterial
Renal failure	Yes	Bacterial; FIP; FeLV
Stomatitis	None	Calicivirus; overgrowth of bacteria flora; candidiasis, *B henselae?*
Upper respiratory tract	None	FHV-1; calicivirus; overgrowth of bacterial flora; *Cryptococcus neoformans*
Urinary tract infection	None	Bacterial

FeLV, Feline leukemia virus; *FHV-1,* feline herpesvirus type 1; *FIP,* feline infectious peritonitis; *FIV,* feline immunodeficiency virus; *SLE,* systemic lupus erythematosus.

Antibodies against FIV are detected in serum in clinical practice most frequently by enzyme-linked immunosorbent assay (ELISA). Saliva can be used instead of serum in fractious cats or in facilities that do not have a veterinarian available at all times (Westman et al., 2016a). Test results for FIV antibody can vary amongst test kits (Levy et al., 2017; Westman et al., 2017). Whether antibodies induced by the FIV vaccine available in some countries also varies by test kit (Westman et al., 2017). Results of PCR or virus isolation can be used to distinguish a previously vaccinated cat if the history is not known (Nichols et al., 2017). Clinical signs can occur before seroconversion in some cats, and some infected cats never seroconvert; thus false-negative reactions can occur. Results of virus isolation or RT-PCR on blood are positive in some antibody-negative cats. False-positive reactions can occur with ELISA; therefore positive ELISA results in healthy or low-risk cats should be confirmed by Western blot immunoassay or RT-PCR. Kittens can have detectable, colostrum-derived antibodies for several months. Kittens younger than 6 months that are FIV seropositive should be tested every 60 days until the result is negative. If antibodies persist at 6 months of age, the kitten is likely infected. Virus isolation or PCR on blood can also be performed to confirm infection. The biggest problem with FIV RT-PCR assays to date is lack of standardization among laboratories and the potential for both false-positive and false-negative results (Crawford et al., 2005).

Detection of antibodies against FIV in the serum of cats that have not been vaccinated against FIV documents exposure and correlates well with persistent infection but does not correlate with disease induced by the virus. Because many clinical syndromes associated with FIV can be caused by opportunistic infections, further diagnostic procedures may determine treatable etiologies (see Table 96.2). For example, some FIV-seropositive cats with uveitis are coinfected by *T. gondii* and often respond to the administration of anti-*Toxoplasma* drugs (see Chapter 98).

Treatment

Because FIV-seropositive cats are not necessarily immunosuppressed or diseased from FIV, the cat should be evaluated and treated for other potential causes of the clinical syndrome (Tasker et al., 2006a). Some FIV-seropositive cats are immunodeficient; if infectious diseases are identified, bacteriocidal drugs administered at the upper end of the dosage should be chosen. Long-term antibiotic therapy or multiple

treatment periods may be required. The only way to determine if an FIV-seropositive cat with a concurrent infection has a poor prognosis is to treat the concurrent infection.

A number of antilentiviral drugs may be effective for the treatment of FIV-infected cats, but controlled studies are largely lacking (Hartmann et al., 2015; Mohammad and Bienzle, 2012). Administration of interferons has shown clinical benefit in some studies. Oral administration of 10 IU/kg of human interferon-α led to improved clinical signs and prolonged survival compared with a placebo-treated control group in one study (Pedretti et al., 2006). In another study, feline recombinant interferon was administered at 10^6 U/kg/day subcutaneously (SC) for 5 days in three series (starting on days 0, 14, and 60) and was shown to improve clinical signs early in the study and prolong survival in treated cats (de Mari et al., 2004). In another study with recombinant feline interferon omega, neither a subcutaneous protocol nor an oral protocol lessened FIV viremia, but IL-6 was decreased (Leal et al., 2015). The use of feline interferon and potential immunomodulatory effects on FIV infection have been reviewed (Leal and Gil, 2016). Administration of bovine lactoferrin by mouth was beneficial in the treatment of intractable stomatitis in FIV-seropositive cats (Sato et al., 1996). Removal of all premolar and molar teeth has also been effective for treatment of intractable stomatitis in some FIV-seropositive cats.

Other substances like the reverse transcriptase inhibitor azidothymidine (AZT), melittin, and phosphonate 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine, 9-(2-phosphonylmethoxyethyl) adenine, or plerixafor have had mixed success in the treatment of FIV and are generally not used clinically in the United States for management of FIV cats. Human recombinant erythropoietin administration increased red blood cell and white blood cell counts, did not increase viral load, and had no measurable adverse clinical effects in FIV-infected cats compared with placebo (Arai et al., 2000) and could be considered for management of anemia in FIV-infected cats. In contrast, although administration of human recombinant granulocyte-monocyte colony-stimulating factor (GM-CSF) to FIV-infected cats increased white blood cell counts in some treated cats, it also induced fever, anti–GM-CSF antibodies, and increased viral load; GM-CSF therefore appears to be contraindicated for this syndrome. Cats with FIV and hospitalized cats had lower serum 25-hydroxyvitamin D [25(OH)D] concentrations than healthy cats in one study (Titmarsh et al., 2015). Whether supplementation will have clinical benefit in the management if FIV infections remains to be proven.

Prevention and Zoonotic Aspects

Housing cats indoors to avoid fighting and testing new cats before introduction to an FIV-seronegative, multiple-cat household will prevent most cases of FIV. Transmission by fomites is unusual because the virus is not easily transmitted by casual contact, is susceptible to most routine disinfectants, and dies when out of the host after minutes to hours, especially when dried. Cleaning litter boxes and dishes shared by cats with scalding water and detergent inactivates the virus. Cats with potential exposure from fighting should be retested 60 days after the exposure (Goldkamp et al., 2008). Cats that are FIV-infected should be housed indoors at all times to avoid exposing FIV-naïve cats in the environment to the virus and to lessen the affected animal's chance of acquiring opportunistic infections. Kittens queened by FIV-infected cats should not be allowed to nurse to avoid transmission by ingestion of milk; they should be shown to be serologically negative at 6 months of age to document failure of lactogenic or transplacental transmission before being sold or adopted. In one study, FIV-positive cats housed in groups of ≤ 2 cats had better long-term outcomes than FIV-positive cats housed in large groups (Beczkowski et al., 2015). A killed vaccine containing immunogens from two FIV isolates is licensed for use in some countries. However, the efficacy of the vaccine is in question (Westman et al., 2016b).

HIV and FIV are morphologically similar but antigenically distinct. Antibodies against FIV have not been documented in the serum of human beings, even after accidental exposure to virus-containing material (Butera et al., 2000; Dickerson et al., 2012). Cats with FIV infection resulting in immunodeficiency may be more likely to spread other zoonotic agents into the human environment; clinically ill, FIV-seropositive cats should therefore undergo a thorough diagnostic evaluation (see Chapter 99).

FELINE LEUKEMIA VIRUS

Etiology and Epidemiology

FeLV is a single-strand RNA virus in the family Retroviridae, subfamily Oncovirinae. The virus produces reverse transcriptase, which catalyzes the reaction, resulting in the formation of a DNA copy (provirus) of FeLV viral RNA in the cytoplasm of infected cells; the provirus is inserted into the host cell genome. On subsequent host cell divisions the provirus serves as a template for new virus particles formed in the cytoplasm and is released across the cell membrane by budding. FeLV is composed of several core and envelope proteins. Envelope protein p15e induces immunosuppression. Core protein p27 is present in the cytoplasm of infected cells, peripheral blood, saliva, and tears of infected cats; detection of p27 is the basis of most FeLV antigen tests. The envelope glycoprotein 70 (gp70) contains the subgroup antigens A, B, or C, which are associated with the infectivity, virulence, and disease caused by individual strains of the virus. Neutralizing antibodies are produced by some cats after exposure to gp70. Antibodies against feline oncornavirus-associated cell membrane antigen (FOCMA) are formed by some cats but are generally not used clinically.

The principal route of infection by FeLV is prolonged contact with infected cat saliva and nasal secretions; grooming or sharing common water or food sources effectively results in infection. Because the organism does not survive in the environment, feces, urine, fomite, and aerosol

transmission is unlikely. Transplacental, lactational, and venereal transmission are less important than casual contact. FeLV infection has worldwide distribution; the seroprevalence of infection varies geographically and by the population of cats tested. Infection is most common in outdoor male cats between ages 1 and 6 years. The prevalence of FeLV antigen in North America and Canada was 3.1% in a 2017 study (Burling et al., 2017), which is higher than the 2.3% in a study reported in 2006 (Levy et al., 2006). FeLV can be detected in feces of infected fleas for 2 weeks (Vobis et al., 2005). However, the prevalence rates for FeLV vary little across regions of the United States with high and low prevalence rates of fleas, so this is an unlikely route of infection.

The virus replicates first in the oropharynx, followed by dissemination through the body to the bone marrow (Table 96.3). If persistent bone marrow infection occurs, infected white blood cells and platelets leave the bone marrow with ultimate infection of epithelial structures, including salivary and lacrimal glands. Whether infection occurs after natural exposure to FeLV is determined by the virus subtype or strain, the virus dose, the age of the cat when exposed, and the cat's immune responses. Using real-time PCR and antigen ELISA results, four classes of FeLV infection (Torres et al., 2005; Levy et al., 2008) were defined (see Table 96.3). Some FeLV-exposed cats can eliminate the infection (abortive), whereas others progress to clinical illness and persistent viremia (progressive). Other FeLV-exposed cats will develop regressive infection characterized by antigen-negative results and lower transiently positive real-time PCR results. Focal infections are transiently antigen-positive but have persistently positive real-time PCR results. Focal and regressive infections can be potentially activated by the administration of glucocorticoids or other immunosuppressive drugs. Blood from cats with regressive infection (provirus-positive) can infect previously naïve cats (Nesina et al., 2015).

The pathogenesis of various syndromes induced by FeLV is complex but includes induction of lymphoma from activation of oncogenes by the virus or insertion of a provirus into the genome of lymphoid precursors; subgroup C induction of aplastic anemia from increased secretion of tumor necrosis factor-α; immunodeficiency attributable to T-lymphocyte depletion (both $CD4^+$ and $CD8^+$ lymphocytes) or dysfunction; neutropenia; neutrophil function disorders; malignant transformation; viral induction of bone marrow growth-promoting substances leading to myeloproliferative diseases; and potentially co-infections with other retroviruses like FIV and feline foamy virus (FFV). Cats with FeLV infection or FeLV and FIV infections had significantly shorter life spans than cats infected with FIV alone (Spada et al., 2018). In one study, differences in viral RNA and provirus tissue loads influenced the different infection outcomes like lymphoma, leukemia, and nonregenerative anemia (Helfer-Hungerbuehler AK, et al., 2015). In that study, FeLV viral RNA and provirus DNA were detected in cats with regressive infection for up to 12 years. A closed colony of research cats was used to evaluate for associations amongst FeLV, FFV, feline gammaherpesvirus, and feline coronavirus. In that study, progressive FeLV infection and FeLV-B presence were associated with higher FeLV proviral and plasma viral loads. Female cats were more likely to have progressive infections, and males were more likely to have abortive infections. Higher proviral loads of FFV associated with higher FeLV proviral and plasma viral loads, FeLV-B, and feline coronavirus. FcaGHV-1 co-infections were more likely to occur in male cats (Powers et al., 2018). Future FeLV field studies should also include comparison with FFV and feline gammaherpesvirus test results.

Clinical Features

Owners generally present FeLV-infected cats for evaluation of nonspecific signs such as anorexia, weight loss, and depression, or abnormalities associated with specific organ systems. Of the FeLV-infected cats evaluated at necropsy, 23% had evidence of neoplasia (96% lymphoma/leukemia); the remainder died from nonneoplastic diseases (Reinacher, 1989). Specific clinical syndromes can result from specific effects of the virus or from opportunistic infections caused

TABLE 96.3

Outcomes of FeLV Infection

OUTCOME OF FELV EXPOSURE	FELV P27 ANTIGEN IN BLOOD	VIRAL BLOOD CULTURE	VIRAL TISSUE CULTURE	VIRAL RNA IN BLOOD	PROVIRAL DNA IN BLOOD	VIRAL SHEDDING	FELV-ASSODATED DISEASE
Progressive infection	Positive	Positive	Positive	Positive	Positive	Positive	Likely
Regressive infection	Negative or transiently positive	Negative or transiently positive	Negative or transiently positive	Transiently or persistently positive	Positive	Negative	Unlikely
Abortive exposure	Negative	Negative	Negative	Not tested	Negative	Negative	Unlikely
Focal infection	Negative	Negative	Positive	Not tested	Not tested	Variable	Unlikely

Reprinted with permission from Levy et al., 2008.

by immunosuppression. A positive FeLV test result does not prove disease induced by FeLV. When a clinical syndrome is diagnosed in a FeLV-seropositive cat, the workup should include diagnostic tests for other potential causes. The opportunistic agents discussed for FIV are also common in FeLV-infected cats (see Table 96.2).

Bacterial or calicivirus-induced stomatitis occurs in some FeLV-infected cats as a result of immunosuppression. FeLV infection can result in vomiting or diarrhea from a form of enteritis clinically and histopathologically resembling panleukopenia, from alimentary lymphoma, or from secondary infections attributable to immunosuppression. Icterus in FeLV-infected cats can be prehepatic from immune-mediated destruction of red blood cells induced by FeLV or secondary infection by *M. haemofelis* or *"Candidatus Mycoplasma haemominutum";* hepatic from hepatic lymphoma, hepatic lipidosis, or focal liver necrosis; or posthepatic from alimentary lymphoma. Some FeLV-infected cats with icterus may be concurrently infected by FIP virus or *T. gondii.*

Clinical signs of rhinitis or pneumonia occur in some FeLV-infected cats as a result of secondary infections. Dyspnea or dysphagia from mediastinal lymphoma occurs in some cats. These cats are generally younger than 3 years and may have decreased cranial chest compliance on palpation, as well as muffled heart and lung sounds if pleural effusion is present.

Mediastinal, multicentric, and alimentary lymphomas are the most common neoplasms associated with FeLV; lymphoid hyperplasia also occurs. Alimentary lymphoma most commonly involves the small intestine, mesenteric lymph nodes, kidneys, and liver of older cats; however, most cats with alimentary lymphoma are FeLV-negative. Renal lymphoma can involve one or both kidneys, which are usually enlarged and irregularly marginated on physical examination. For additional discussion, please see Chapter 79. Fibrosarcomas occasionally develop in young cats co-infected with FeLV and feline sarcoma virus (see Chapter 81). Lymphocytic, myelogenous, erythroid, and megakaryocytic leukemia all are reported with FeLV infection; erythroleukemia and acute myelomonocytic leukemia are the most common (see Chapter 80). The history and physical examination findings are nonspecific.

Renal failure occurs in some FeLV-infected cats from renal lymphoma or glomerulonephritis. Affected cats are presented for evaluation of polyuria, polydipsia, weight loss, and inappetence during the last stages of disease. Urinary incontinence from sphincter incompetence or detrusor hyperactivity occurs in some cats; small-bladder nocturnal incontinence is reported most frequently.

Some FeLV-infected cats are presented for miosis, blepharospasm, or cloudy eyes from ocular lymphoma. Aqueous flare, mass lesions, keratic precipitates, lens luxations, and glaucoma are often found on ocular examination. FeLV does not likely induce uveitis without lymphoma. Neurologic abnormalities associated with FeLV infection include anisocoria, ataxia, weakness, tetraparesis, paraparesis, behavioral changes, and urinary incontinence. Nervous system disease is likely to develop as a result of polyneuropathy or lymphoma. Intraocular and nervous system disease in FeLV-infected cats can occur from infection with other agents, including FIPV, *Cryptococcus neoformans,* or *T. gondii.*

Abortion, stillbirth, or infertility occurs in some FeLV-infected queens. Kittens infected in utero that survive to birth generally develop accelerated FeLV syndromes or die as part of the kitten mortality complex.

Some FeLV-seropositive cats present for lameness or weakness from suppurative nonseptic polyarthritis attributed to immune complex deposition. Multiple cartilaginous exostoses occur in some cats and may be FeLV related.

Diagnosis

A variety of nonspecific hematologic, biochemical, urinalysis, and radiographic abnormalities occur in FeLV-infected cats. Nonregenerative anemia alone or in combination with decreases in lymphocyte, neutrophil, and platelet counts is common. The presence of increased numbers of circulating nucleated red blood cells or macrocytosis in association with severe nonregenerative anemia occurs frequently; examination of bone marrow often documents a maturation arrest in the erythroid line (erythrodysplasia). Immune-mediated destruction of erythrocytes can be induced by FeLV and occurs in cats co-infected with hemoplasmas; regenerative anemia, microagglutination or macroagglutination of erythrocytes, and a positive result on the direct Coombs test are common in these cats. Neutropenia and thrombocytopenia occur from bone marrow suppression or immune-mediated destruction. In one study, 37 cats with nonregenerative cytopenias were evaluated for focal FeLV in the bone marrow by RT-PCR assay and 2 cats were positive (Stützer et al., 2010). FeLV-infected cats with the panleukopenia-like syndrome have gastrointestinal tract signs and neutropenia and are difficult to differentiate from cats with panleukopenia virus infection or salmonellosis. However, cats with FeLV-induced panleukopenia-like syndrome usually have anemia and thrombocytopenia, abnormalities rarely associated with panleukopenia virus infection. In one study, FeLV-positive cats with anemia at the time of initial diagnosis had shorter life span than FeLV-positive cats with normal red blood cells (Spada et al., 2018).

Azotemia, hyperbilirubinemia, bilirubinuria, and increased activity of liver enzymes are common biochemical abnormalities. Proteinuria occurs in some FeLV-infected cats with glomerulonephritis. Cats with lymphoma have mass lesions radiographically depending on the organ system affected. Mediastinal lymphoma can result in pleural effusion; alimentary lymphoma can cause obstructive intestinal patterns.

Lymphoma can be diagnosed by cytologic or histopathologic evaluation of affected tissues (see Chapters 74 and 79). Because lymphoma can be diagnosed cytologically and treated with chemotherapy, cats with mediastinal masses, lymphadenopathy, renomegaly, hepatomegaly, splenomegaly, or intestinal masses should be evaluated cytologically before surgical intervention. Malignant lymphocytes are also

occasionally identified in peripheral blood smears, effusions, and CSF.

Most cats with suspected FeLV infection are screened for FeLV antigens in neutrophils and platelets by immunofluorescent antibody (IFA) testing or in whole blood, plasma, serum, saliva, or tears by ELISA. Blood or plasma may be the most accurate fluids to assess in ELISA tests. There are multiple point of care tests around the world, and results can vary between tests and between the same test in two different studies (Hartmann et al., 2007; Westman et al., 2017; Levy et al., 2017; Liu et al., 2016; Krecic et al., 2018). IFA results are not positive until the bone marrow has been infected. Generally, the results of IFA testing are accurate more than 95% of the time. False-negative reactions may occur when leukopenia or thrombocytopenia prevents evaluation of an adequate number of cells. False-positive reactions can occur if the blood smears submitted for evaluation are too thick. A positive IFA result indicates that the cat is viremic and contagious; approximately 90% of cats with positive IFA results are viremic for life. The rare combination of IFA-positive and ELISA-negative results suggests technique-related artifact.

The virus can be detected in serum by ELISA before infection of bone marrow and can therefore be positive in some cats during early progressive stages of infection or during early latent infection, even though IFA results are negative. Other possibilities for discordant results (ELISA-positive, IFA-negative) are false-positive ELISA results or false-negative IFA results. Cats with positive ELISA results and negative IFA results should be isolated until retested 4 to 6 weeks later because progression to persistent viremia and epithelial cell infection may be occurring.

ELISA-positive cats that revert to negative have developed focal (latent) infections or regressive infection. Virus isolation, IFA performed on bone marrow cells, immunohistochemical staining of tissues for FeLV antigen, and PCR can be used to confirm focal or regressive infection in some cats. Cats with focal or regressive infection are not likely contagious to other cats by direct contact, but infected queens may pass the virus to kittens during gestation or parturition, or by milk. Cats with regressive or focal infection can be immunodeficient and may become viremic (IFA- and ELISA-positive) after administration of glucocorticoids, or after extreme stress.

A delay of 1 to 2 weeks generally occurs after the onset of viremia before ELISA tear and saliva test results become positive; therefore these test results can be negative even when results with serum are positive and so are not generally not recommended for use unless blood cannot be collected. Antibody titers to FeLV envelope antigens (neutralizing antibody) and against virus-transformed tumor cells have been detected in research studies, but the diagnostic and prognostic significance of results from these tests is unknown. Real-time PCR assays are more sensitive than conventional PCR for FeLV infections, but testing is not standardized amongst most laboratories in the United States (Torres et al., 2005).

FeLV has been transmitted by blood from some cats that are FeLV provirus-positive, p27 antigen-negative (Nesina et al., 2015). Thus results support the recommendation to optimally use FeLV antigen-negative and provirus DNA-negative cats as blood donors (Wardrop et al., 2016)

Treatment

Antiretroviral drugs that could be potentially used for the management of cats with clinical disease related to FeLV have been reviewed (Hartmann et al., 2015). Several antiviral agents have been proposed for the treatment of FeLV; the reverse transcriptase inhibitor AZT has been studied the most. Unfortunately, administration of AZT to persistently viremic cats does not appear to clear viremia in most, and it had minimal benefits for clinically ill cats in a study (Hartmann et al., 2002). Interferons have an effect against FeLV in vivo and in vitro (Collado et al., 2007; de Mari et al., 2004) and lessen clinical disease in FeLV-infected cats by immune modulation as described for FIV (Domenech et al., 2011; Leal and Gil, 2016; Pedretti et al., 2006). Immunotherapy with drugs compounds such as *Staphylococcus* protein A, *Propionibacterium acnes,* or acemannan have been purported to improve clinical signs in some cats, but controlled studies are lacking.

Chemotherapy should be administered to cats with FeLV-associated neoplasia (see Chapters 76 and 79). Opportunistic agents should be managed as indicated; the upper dose range and duration of antibiotic therapy are generally required. Supportive therapies such as hematinic agents, vitamin B_{12}, folic acid, anabolic steroids, and erythropoietin generally have been unsuccessful in the management of nonregenerative anemia. Blood transfusion is required in many cases. Cats with immune-mediated hemolytic anemia require immunosuppressive therapy, but this may activate virus replication. The prognosis for persistently viremic cats is guarded; the majority die within 2 to 3 years.

Prevention and Zoonotic Aspects

Avoiding contact with FeLV by housing cats indoors is the best form of prevention. Potential fomites such as water bowls and litter pans should not be shared by seropositive and seronegative cats. Testing and removal of seropositive cats can result in virus-free catteries and multiple-cat households.

Because of variations in challenge study methods and the difficulty of assessing the preventable fraction of a disease with a relatively low infection rate, long subclinical phase, and multiple field strains, the efficacy of individual vaccines continues to be in question (see Chapter 93). In one recent study, all three FeLV vaccines studied gave similar efficacies (Grosenbaugh et al., 2017). Vaccination of cats not previously exposed to FeLV should be considered in cats at high risk (i.e., contact with other cats), but owners should be warned of the potential efficacy of less than 100%. Cats with persistent FeLV viremia do not benefit from vaccination. Vaccination is related to the development of fibrosarcoma in some cats (see Chapter 93). Cats developing these tumors may be genetically predisposed.

FeLV-infected cats should be housed indoors to avoid infecting other cats and avoid exposure to opportunistic agents. Flea control should be maintained to avoid exposure to hemoplasmas, and *Bartonella* spp. FeLV-infected cats should not be allowed to hunt or be fed undercooked meats to avoid infection by *T. gondii, Cryptosporidium parvum, Giardia* spp., and other infectious agents carried by transport hosts.

Antigens of FeLV have never been documented in the serum of human beings, suggesting that the zoonotic risk is minimal. However, FeLV-infected cats may be more likely than FeLV-naïve cats to pass other zoonotic agents, such as *C. parvum* and *Salmonella* spp., into the human environment.

Suggested Readings

Canine Distemper Virus

Amude AM, et al. Clinicopathological findings in dogs with distemper encephalomyelitis presented without characteristic signs of the disease. *Res Vet Sci*. 2007;82:416.

Anis E, et al. Antigenic analysis of genetic variants of Canine distemper virus. *Vet Microbiol*. 2018;219:154.

Athanasiou LV, et al. Evaluation of a direct immunofluorescent assay and/or conjunctival cytology for detection of canine distemper virus antigen. *Viral Immunol*. 2018;31:272.

Burton JH, et al. Detection of canine distemper virus RNA from blood and conjunctival swabs collected from healthy puppies after administration of a modified live vaccine, ACVIM San Antonio, TX, June 4-7, 2008 (oral).

Carvalho OV, et al. In-vitro antiviral efficacy of ribavirin and interferon-alpha against canine distemper virus. *Can J Vet Res*. 2014;78:283.

Gray LK, et al. Comparison of two assays for detection of antibodies against canine parvovirus and canine distemper virus in dogs admitted to a Florida animal shelter. *J Am Vet Med Assoc*. 2012;240:1084.

Jensen WA, et al. Use of serologic tests to predict resistance to Canine distemper virus-induced disease in vaccinated dogs. *J Vet Diagn Invest*. 2015;27:576.

Kapil S, et al. Canine distemper virus strains circulating among North American dogs. *Clin Vaccine Immunol*. 2008;15:707.

Killey R, et al. Long-lived immunity to canine core vaccine antigens in UK dogs as assessed by an in-practice test kit. *J Small Anim Pract*. 2018;59:27.

Litster A, et al. Prevalence of positive antibody test results for canine parvovirus (CPV) and canine distemper virus (CDV) and response to modified live vaccination against CPV and CDV in dogs entering animal shelters. *Vet Microbiol*. 2012a;157:86.

Litster AL, et al. Accuracy of a point-of-care ELISA test kit for predicting the presence of protective canine parvovirus and canine distemper virus antibody concentrations in dogs. *Vet J*. 2012b;[Epub ahead of print].

Mahon JL, et al. Prevalence of serum antibody titers against canine distemper virus and canine parvovirus in dogs hospitalized in an intensive care unit. *J Am Vet Med Assoc*. 2017;250:1413.

Saito TB, et al. Detection of canine distemper virus by reverse transcriptase-polymerase chain reaction in the urine of dogs with clinical signs of distemper encephalitis. *Res Vet Sci*. 2006;80:116.

Spindel ME, et al. Evaluation of a community's risk for canine parvovirus and distemper using antibody testing and GIS mapping of animal shelter intakes. *J Appl Anim Welf Sci*. 2018;20:1.

Wostenberg DJ, et al. Evidence of two co-circulating canine distemper virus strains in mesocarnivores from northern Colorado, USA. *J Wildl Dis*. 2018;54:534.

Yi L, et al. Development of a combined canine distemper virus specific RT-PCR protocol for the differentiation of infected and vaccinated animals (DIVA) and genetic characterization of the hemagglutinin gene of seven Chinese strains demonstrated in dogs. *J Virol Methods*. 2012;179:281.

Feline Infectious Peritonitis Virus

Addie D, et al. Feline infectious peritonitis. ABCD guidelines on prevention and management. *J Feline Med Surg*. 2009;11:594.

Addie DD, et al. Use of a reverse-transcriptase polymerase chain reaction for monitoring the shedding of feline coronavirus by healthy cats. *Vet Rec*. 2001;148:649.

Addie DD, et al. Utility of feline coronavirus antibody tests. *J Feline Med Surg*. 2015;17:152.

Bank-Wolf BR, et al. Mutations of 3c and spike protein genes correlate with the occurrence of feline infectious peritonitis. *Vet Microbiol*. 2014;173:177.

Barker EN, et al. Limitations of using feline coronavirus spike protein gene mutations to diagnose feline infectious peritonitis. *Vet Res*. 2017;48:60.

Boettcher IC, et al. Use of anti-coronavirus antibody testing of cerebrospinal fluid for diagnosis of feline infectious peritonitis involving the central nervous system in cats. *J Am Vet Med Assoc*. 2007;230:199.

Can-S Ahna K, et al. The detection of feline coronaviruses in blood samples from cats by mRNA RT-PCR. *J Feline Med Surg*. 2007;9:369.

Crawford AH, et al. Clinicopathologic features and magnetic resonance imaging findings in 24 cats with histopathologically confirmed neurologic feline infectious peritonitis. *J Vet Intern Med*. 2017;31:1477.

Doenges SJ, et al. Comparison of real-time reverse transcriptase polymerase chain reaction of peripheral blood mononuclear cells, serum and cell-free body cavity effusion for the diagnosis of feline infectious peritonitis. *J Feline Med Surg*. 2017;19:344.

Doenges SJ, et al. Detection of feline coronavirus in cerebrospinal fluid for diagnosis of feline infectious peritonitis in cats with and without neurological signs. *J Feline Med Surg*. 2016;18:104.

Doki T, et al. Therapeutic effect of anti-feline TNF-alpha monoclonal antibody for feline infectious peritonitis. *Res Vet Sci*. 2016;104:17.

Felten S, et al. Utility of an immunocytochemical assay using aqueous humor in the diagnosis of feline infectious peritonitis. *Vet Ophthalmol*. 2018;21:27.

Felten S, et al. Investigation into the utility of an immunocytochemical assay in body cavity effusions for diagnosis of feline infectious peritonitis. *J Feline Med Surg*. 2017;19:410.

Fish EJ, et al. Cross-sectional quantitative RT-PCR study of feline coronavirus viremia and replication in peripheral blood of healthy shelter cats in Southern California. *J Feline Med Surg*. 2018;20:295.

Fischer Y, et al. Randomized, placebo controlled study of the effect of propentofylline on survival time and quality of life of cats with feline infectious peritonitis. *J Vet Intern Med*. 2011;25:1270.

Giori L. Performances of different diagnostic tests for feline infectious peritonitis in challenging clinical cases. *J Small Anim Pract*. 2011;52:152.

Gruendl S, et al. Diagnostic utility of cerebrospinal fluid immunocytochemistry for diagnosis of feline infectious peritonitis

manifesting in the central nervous system. *J Feline Med Surg*. 2017;19:576.
Gunn-Moore DA, et al. Detection of feline coronaviruses by culture and reverse transcriptase-polymerase chain reaction of blood samples from healthy cats and cats with clinical feline infectious peritonitis. *Vet Microbiol*. 1998;62:193.
Harvey CJ, et al. An uncommon intestinal manifestation of feline infectious peritonitis: 26 cases (1986-1993). *J Am Vet Med Assoc*. 1996;209:1117.
Hartmann K, Ritz S. Treatment of cats with feline infectious peritonitis. *Vet Immunol Immunopathol*. 2008;123:172.
Hazuchova K, et al. Usefulness of acute phase proteins in differentiating between feline infectious peritonitis and other diseases in cats with body cavity effusions. *J Feline Med Surg*. 2017;19:809.
Ishida T, et al. Use of recombinant feline interferon and glucocorticoid in the treatment of feline infectious peritonitis. *J Feline Med Surg*. 2004;6:107.
Kim Y, et al. Broad-spectrum inhibitors against 3C-like proteases of feline coronaviruses and feline caliciviruses. *J Virol*. 2015;89:4942.
Legendre AM, Bartges JW. Effect of polyprenyl immunostimulant on the survival times of three cats with the dry form of feline infectious peritonitis. *J Feline Med Surg*. 2009;11:624.
Legendre AM, et al. Polyprenyl immunostimulant treatment of cats with presumptive non-effusive feline infectious peritonitis in a field study. *Front Vet Sci*. 2017;4:7.
Lewis CS, et al. Genotyping coronaviruses associated with feline infectious peritonitis. *J Gen Virol*. 2015;96:1358.
Lewis KM, O'Brien RT. Abdominal ultrasonographic findings associated with feline infectious peritonitis: a retrospective review of 16 cases. *J Am Anim Hosp Assoc*. 2010;46:152.
Longstaff L, et al. Feline coronavirus quantitative reverse transcriptase polymerase chain reaction on effusion samples in cats with and without feline infectious peritonitis. *J Feline Med Surg*. 2017;19:240.
McDonagh P, et al. In vitro inhibition of feline coronavirus replication by small interfering RNAs. *Vet Microbiol*. 2011;150:220.
Pedersen NC. An update on feline infectious peritonitis: virology and immunopathogenesis. *Vet J*. 2014a;201:123.
Pedersen NC. An update on feline infectious peritonitis: diagnostics and therapeutics. *Vet J*. 2014b;201:133.
Pedersen NC, et al. The influence of age and genetics on natural resistance to experimentally induced feline infectious peritonitis. *Vet Immunol Immunopathol*. 2014c;162:33.
Pedersen NC, et al. Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis. *J Feline Med Surg*. 2017;20:378.
Pedersen NC, et al. Levels of feline infectious peritonitis virus in blood, effusions, and various tissues and the role of lymphopenia in disease outcome following experimental infection. *Vet Microbiol*. 2015;175:157.
Pesteanu-Somogyi LD, et al. Prevalence of feline infectious peritonitis in specific cat breeds. *J Feline Med Surg*. 2006;8:1.
Riemer F, et al. Clinical and laboratory features of cats with feline infectious peritonitis–a retrospective study of 231 confirmed cases (2000-2010). *J Feline Med Surg*. 2016;18:348.
Rissi DR. A retrospective study of the neuropathology and diagnosis of naturally occurring feline infectious peritonitis. *J Vet Diagn Invest*. 2018;30:392.
Ritz S, et al. Effect of feline interferon-omega on the survival time and quality of life of cats with feline infectious peritonitis. *J Vet Intern Med*. 2007;21:1193.
Rottier PJ, et al. Acquisition of macrophage tropism during the pathogenesis of feline infectious peritonitis is determined by mutations in the feline coronavirus spike protein. *J Virol*. 2005;79:14122.
Simons FA, et al. A mRNA PCR for the diagnosis of feline infectious peritonitis. *J Virol Methods*. 2005;124:111.
Stranieri A, et al. Comparison of the performance of laboratory tests in the diagnosis of feline infectious peritonitis. *J Vet Diagn Invest*. 2018;30:459.
Tanaka Y, et al. Suppression of feline coronavirus replication in vitro by cyclosporin A. *Vet Res*. 2012;43:41.
Tasker S. Diagnosis of feline infectious peritonitis: update on evidence supporting available tests. *J Feline Med Surg*. 2018;20:228.
Tekes G, et al. Feline coronaviruses: pathogenesis of feline infectious peritonitis. *Adv Virus Res*. 2016;96:193.
Timmann D, et al. Retrospective analysis of seizures associated with feline infectious peritonitis in cats. *J Feline Med Surg*. 2008;10:9.
Worthing KA, et al. Risk factors for feline infectious peritonitis in Australian cats. *J Feline Med Surg*. 2012;14:405.
Ziółkowska N, et al. Feline Infectious Peritonitis: immunohistochemical features of ocular inflammation and the distribution of viral antigens in structures of the eye. *Vet Pathol*. 2017;54:933.

Feline Immunodeficiency Virus

Arai M, et al. The use of human hematopoietic growth factors (rhGM-CSF and rhEPO) as a supportive therapy for FIV-infected cats. *Vet Immunol Immunopathol*. 2000;77:71.
Baxter KJ, et al. Renal disease in cats infected with feline immunodeficiency virus. *J Vet Intern Med*. 2012;26:238.
Bęczkowski PM, et al. Contrasting clinical outcomes in two cohorts of cats naturally infected with feline immunodeficiency virus (FIV). *Vet Microbiol*. 2015;176:50.
Burling AN, et al. Seroprevalences of feline leukemia virus and feline immunodeficiency virus infection in cats in the United States and Canada and risk factors for seropositivity. *J Am Vet Med Assoc*. 2017;251:187.
Butera ST, et al. Survey of veterinary conference attendees for evidence of zoonotic infection by feline retroviruses. *J Am Vet Med Assoc*. 2000;217:1475.
Chhetri BK, et al. Comparison of the geographical distribution of feline immunodeficiency virus and feline leukemia virus infections in the United States of America (2000-2011). *BMC Vet Res*. 2013;9:2.
Crawford PC, et al. Accuracy of polymerase chain reaction assays for diagnosis of feline immunodeficiency virus infection in cats. *J Am Vet Med Assoc*. 2005;226:1503.
de Mari K, et al. Therapeutic effects of recombinant feline interferon-omega on feline leukemia virus (FeLV)-infected and FeLV/feline immunodeficiency virus (FIV)-coinfected symptomatic cats. *J Vet Intern Med*. 2004;18:477.
Dickerson F, et al. Antibodies to retroviruses in recent onset psychosis and multi-episode schizophrenia. *Schizophr Res*. 2012;138:198.
Doménech A, et al. Use of recombinant interferon omega in feline retrovirosis: from theory to practice. *Vet Immunol Immunopathol*. 2011;143:301.
Hartmann AD, et al. Clinical efficacy of melittin in the treatment of cats infected with the feline immunodeficiency virus. *Tierarztl Prax Ausg K Kleintiere Heimtiere*. 2016;44:417.
Hartmann AD, et al. Clinical efficacy of the acyclic nucleoside phosphonate 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine

(PMPDAP) in the treatment of feline immunodeficiency virus-infected cats. *J Feline Med Surg*. 2012;14:107.
Hartmann K, et al. AZT in the treatment of feline immunodeficiency virus infection I. *Fel Pract*. 1995a;23:16.
Hartmann K, et al. AZT in the treatment of feline immunodeficiency virus infection II. *Fel Pract*. 1995b;23:16.
Hartmann K. Clinical aspects of feline immunodeficiency and feline leukemia virus infection. *Vet Immunol Immunopathol*. 2011;143:190.
Hartmann K, et al. Efficacy and adverse effects of the antiviral compound plerixafor in feline immunodeficiency virus-infected cats. *J Vet Intern Med*. 2012;26:483.
Hartmann K, et al. Efficacy of antiviral drugs against feline immunodeficiency virus. *Vet Sci*. 2015;2:456.
Kann RK, et al. Association between feline immunodeficiency virus (FIV) plasma viral RNA load, concentration of acute phase proteins and disease severity. *Vet J*. 2014;201:181.
Kornya MR, et al. Association between oral health status and retrovirus test results in cats. *J Am Vet Med Assoc*. 2014;245: 916.
Lappin MR, et al. Primary and secondary Toxoplasma gondii infection in normal and feline immunodeficiency virus-infected cats. *J Parasitol*. 1996;82:733.
Leal RO, et al. Evaluation of viremia, proviral load and cytokine profile in naturally feline immunodeficiency virus infected cats treated with two different protocols of recombinant feline interferon omega. *Res Vet Sci*. 2015;99:87.
Leal RO, Gil S. The use of recombinant feline interferon omega therapy as an immune-modulator in cats naturally infected with feline immunodeficiency virus: new perspectives. *Vet Sci*. 2016;3:E32. doi:10.3390/vetsci3040032.
Levy J, et al. 2008 American Association of Feline Practitioners' feline retrovirus management guidelines. *J Fel Med Surg*. 2008;10:300.
Levy JK, et al. Effect of vaccination against feline immunodeficiency virus on results of serologic testing in cats. *J Am Vet Med Assoc*. 2004;225:1558.
Levy JK, et al. Seroprevalence of feline leukemia virus and feline immunodeficiency virus infection among cats in North America and risk factors for seropositivity. *J Am Vet Med Assoc*. 2006;228:371.
Levy JK, et al. Performance of 4 point-of-care screening tests for feline leukemia virus and feline immunodeficiency virus. *J Vet Intern Med*. 2017;31:521.
Liem BP, et al. Clinical findings and survival in cats naturally infected with feline immunodeficiency virus. *J Vet Intern Med*. 2013;27:798.
Litster AL. Transmission of feline immunodeficiency virus (FIV) among cohabiting cats in two cat rescue shelters. *Vet J*. 2014;201:184.
Magden E, et al. FIV associated neoplasms—a mini-review. *Vet Immunol Immunopathol*. 2011;143:227.
McLuckie AJ, et al. *Felis catus* gammaherpesvirus 1 DNAemia in whole blood from therapeutically immunosuppressed or retrovirus-infected cats. *Vet Sci*. 2017;14:4.
Miller C, et al. Pathogenesis of oral FIV infection. *PLoS ONE*. 2017;12:e0185138.
Mohammadi H, Bienzle D. Pharmacological inhibition of feline immunodeficiency virus (FIV). *Viruses*. 2012;4:708.
Murphy BG, et al. Multiple, independent T cell lymphomas arising in an experimentally FIV-infected cat during the terminal stage of infection. *Viruses*. 2018;24:10.
Nichols J, et al. Commercially available enzyme-linked immunosorbent assay and polymerase chain reaction tests for detection of feline immunodeficiency virus infection. *J Vet Intern Med*. 2017;3:55.
Pedersen NC, et al. Isolation of a T-lymphotrophic virus from domestic cats with an immunodeficiency-like syndrome. *Science*. 1987;235:790.
Pedretti E, et al. Low-dose interferon-alpha treatment for feline immunodeficiency virus infection. *Vet Immunol Immunopathol*. 2006;109:245.
Power C. Neurologic disease in feline immunodeficiency virus infection: disease mechanisms and therapeutic interventions for NeuroAIDS. *J Neurovirol*. 2018;24:220.
Rolim VM, et al. Myocarditis caused by feline immunodeficiency virus in five cats with hypertrophic cardiomyopathy. *J Comp Pathol*. 2016;154:3.
Sarvani E, et al. Prevalence and risk factor analysis for feline haemoplasmas in cats from Northern Serbia, with molecular subtyping of feline immunodeficiency virus. *JFMS Open Rep*. 2018;4:2055116918770037.
Sato R, et al. Oral administration of bovine lactoferrin for treatment of intractable stomatitis in feline immunodeficiency virus (FIV)-positive and FIV-negative cats. *Am J Vet Res*. 1996;57:1443.
Spada E, et al. Survival time and effect of selected predictor variables on survival in owned pet cats seropositive for feline immunodeficiency and leukemia virus attending a referral clinic in northern Italy. *Prev Vet Med*. 2018;150:38.
Taffin ER, et al. Systolic blood pressure, routine kidney variables and renal ultrasonographic findings in cats naturally infected with feline immunodeficiency virus. *J Feline Med Surg*. 2017;19:672.
Tasker S, et al. Effect of chronic FIV infection, and efficacy of marbofloxacin treatment, on Mycoplasma haemofelis infection. *Vet Microbiol*. 2006a;117:169.
Tasker S, et al. Effect of chronic feline immunodeficiency infection, and efficacy of marbofloxacin treatment, on "Candidatus Mycoplasma haemominutum" infection. *Microbes Infect*. 2006b;8: 653.
Titmarsh HF, et al. Vitamin D status in cats with feline immunodeficiency virus. *Vet Med Sci*. 2015;1:72.
Weese JS, et al. The rectal microbiota of cats infected with feline immunodeficiency virus infection and uninfected controls. *Vet Microbiol*. 2015a;180:96.
Weese SJ, et al. The oral and conjunctival microbiotas in cats with and without feline immunodeficiency virus infection. *Vet Res*. 2015b;46:21.
Westman ME, et al. Duration of antibody response following vaccination against feline immunodeficiency virus. *J Feline Med Surg*. 2017;19:1055.
Westman ME, et al. Diagnosing feline immunodeficiency virus (FIV) infection in FIV-vaccinated and FIV-unvaccinated cats using saliva. *Comp Immunol Microbiol Infect Dis*. 2016a;46:66.
Westman ME, et al. The protective rate of the feline immunodeficiency virus vaccine: an Australian field study. *Vaccine*. 2016b;34:4752.

Feline Leukemia Virus

Addie DD, et al. Long-term impact on a closed household of pet cats of natural infection with feline coronavirus, feline leukaemia virus and feline immunodeficiency virus. *Vet Rec*. 2000;146:419.
Cattori V, et al. The kinetics of feline leukaemia virus shedding in experimentally infected cats are associated with infection outcome. *Vet Microbiol*. 2009;133:292.

Collado VM, et al. Effect of type I interferons on the expression of feline leukaemia virus. *Vet Microbiol*. 2007;123:180.

Goldkamp CE, et al. Seroprevalences of feline leukemia virus and feline immunodeficiency virus in cats with abscesses or bite wounds and rate of veterinarian compliance with current guidelines for retrovirus testing. *J Am Vet Med Assoc*. 2008;232:1152.

Grosenbaugh DA, et al. Efficacy of a nonadjuvanted recombinant FeLV vaccine and two inactivated FeLV vaccines when subject to consistent virulent FeLV challenge conditions. *Biologicals*. 2017;49:76.

Hartmann K. Efficacy of antiviral chemotherapy for retrovirus-infected cats: what does the current literature tell us? *J Feline Med Surg*. 2015;17:925.

Hartmann K, et al. Quality of different in-clinic test systems for feline immunodeficiency virus and feline leukaemia virus infection. *J Feline Med Surg*. 2007;Jun 30, [Epub ahead of print].

Hartmann K, et al. Treatment of feline leukemia virus-infected cats with paramunity inducer. *Vet Immunol Immunopathol*. 1998;65:267.

Hartmann K, et al. Treatment of feline leukemia virus infection with 3'-azido-2,3-dideoxythymidine and human alpha-interferon. *J Vet Intern Med*. 2002;16:345.

Helfer-Hungerbuehler AK, et al. Long-term follow up of feline leukemia virus infection and characterization of viral RNA loads using molecular methods in tissues of cats with different infection outcomes. *Virus Res*. 2015;197:137.

Herring ES, et al. Detection of feline leukaemia virus in blood and bone marrow of cats with varying suspicion of latent infection. *J Fel Med Surg*. 2001;3:133.

Hofmann-Lehmann R, et al. Vaccination against the feline leukaemia virus: outcome and response categories and long-term follow-up. *Vaccine*. 2007;25:5531.

Jirjis F, et al. Protection against feline leukemia virus challenge for at least 2 years after vaccination with an inactivated feline leukemia virus vaccine. *Vet Ther*. 2010;11:E1.

Krecic MR, et al. Diagnostic performances of two rapid tests for detection of feline leukemia virus antigen in sera of experimentally feline leukemia virus-infected cats. *JFMS Open Rep*. 2018;4:2055116917748117.

Liu J, et al. Evaluation of rapid diagnostic test kits for feline leukemia virus infection using samples from naturally infected cats. *JFMS Open Rep*. 2016;2:2055116916667757.

Lutz H, et al. Feline leukaemia. ABCD guidelines on prevention and management. *J Feline Med Surg*. 2009;11:565.

Nesina S, et al. Retroviral DNA–the silent winner: blood transfusion containing latent feline leukemia provirus causes infection and disease in naïve recipient cats. *Retrovirology*. 2015;12:105.

Powers JA, et al. Feline leukemia virus disease outcomes in a domestic cat breeding colony: relationship to endogenous FeLV and other chronic viral infections. *J Virol*. 2018;doi:10.1128/JVI.00649-18. pii: JVI.00649-18.

Reinacher M. Diseases associated with spontaneous feline leukemia virus (FeLV) infection in cats. *Vet Immunol Immunopathol*. 1989;21:85.

Stützer B, et al. Role of latent feline leukemia virus infection in nonregenerative cytopenias of cats. *J Vet Intern Med*. 2010;24:192.

Torres AN, et al. Development and application of a quantitative real-time PCR assay to detect feline leukemia virus RNA. *Vet Immunol Immunopathol*. 2008;123:81.

Torres AN, et al. Re-examination of feline leukemia virus: host relationships using realtime PCR. *Virology*. 2005;332:272.

Vobis M, et al. Experimental quantification of the feline leukaemia virus in the cat flea (Ctenocephalides felis) and its faeces. *Parasitol Res*. 2005;1:S102.

Wardrop KJ, et al. Update on canine and feline blood donor screening for blood-borne pathogens. *J Vet Intern Med*. 2016;30:15.

Westman ME, et al. Comparison of three feline leukaemia virus (FeLV) point-of-care antigen test kits using blood and saliva. *Comp Immunol Microbiol Infect Dis*. 2017;50:88.

CHAPTER 97

Polysystemic Mycotic Infections



BLASTOMYCOSIS

Etiology and Epidemiology

Blastomyces dermatitidis is a saprophytic yeast found primarily in the Mississippi, Missouri, and Ohio River valleys; the mid-Atlantic states; and southern Canada. An extracellular yeast form (5-20 µm in diameter) with broad-based budding develops in the vertebrate host (Table 97.1). The infectious mycelial phase occurs in the soil and in culture.

Blastomycosis develops most frequently in areas exposed to high humidity, fog, excavation sites, and sandy, acidic soils near bodies of water. Potential for disease may vary with the virulence of the field strain, the inoculum dose, and the immune status of the host. Most clinical cases occur from point source exposure; multiple cases are diagnosed in an area, and clusters of infection in people and dogs have been reported. Seasonal, weather, and environmental variables influence prevalence rates. Transmission is from inhalation or contamination of open wounds with spores from the environment. Nasal culture failed to identify the fungus on samples collected from 110 clinically normal dogs living in an endemic area, suggesting colonization of this site is not common (Varani et al., 2009). After inhalation, the organism probably replicates in the lungs initially and then spreads hematogenously to other tissues, including the skin and subcutaneous tissues, eyes, bones, lymph nodes, external nares, brain, testes, nasal passages, prostate, liver, mammary glands, vulva, and heart. However, central nervous system (CNS) disease may result from extension from the nasal cavity. The organism can be swallowed and passed in feces. Incomplete clearance of the organism by individuals with poor cell-mediated immune responses results in pyogranulomatous inflammation in affected organs, which can cause clinical signs of disease. Subclinical infection is believed to be uncommon in dogs and cats.

Clinical Features

Large-breed, young, male, sporting dogs are infected most commonly by *B. dermatitidis* most likely because of an increased chance for exposure to the organism. Anorexia, cough, dyspnea, exercise intolerance, weight loss, ocular disease, skin disease, depression, lameness, and syncope are the most common presenting complaints.

Fever occurs in approximately 40% of affected dogs. Interstitial lung disease and hilar lymphadenopathy result in cough, dry and harsh lung sounds, and dyspnea; hypertrophic osteopathy occurs in some dogs. Infection of the nasal cavity, the nasopharynx, and the retrobulbar area occurs rarely and can extend intracranially. Dyspnea from chylothorax caused by cranial vena cava syndrome has been described. Valvular endocarditis occurs as well, and conduction disturbances from myocarditis are detected in some dogs with cardiac blastomycosis. Lymphadenopathy and cutaneous or subcutaneous nodules, abscesses, plaques, or ulcers occur in 20% to 40% of infected dogs. Splenomegaly is common. Lameness from fungal osteomyelitis of the spine or appendicular skeleton occurs in approximately 30% of dogs with blastomycosis. Infection of the testes, prostate, urinary bladder, mammary glands, and kidneys occurs rarely.

Ocular manifestations are recognized in approximately 30% of dogs with blastomycosis; anterior uveitis, endophthalmitis, posterior segment disease, and optic neuritis occur. Cataracts can result from chronic inflammation or rupture of the lens capsule. Fungal infections of the CNS were recently reviewed (Bentley et al., 2018). Blastomycosis of the CNS often is an intracranial mass or a cause of ventriculitis. Depression and seizures from diffuse or multifocal CNS involvement occur in some dogs.

Blastomycosis can occur in any cat but is most common in young males. Both cats housed indoors and cats allowed outdoors can develop disease. Infected cats develop respiratory tract disease, CNS disease, regional lymphadenopathy, dermatologic disease, ocular disease, gastrointestinal tract disease, and urinary tract disease. Pleural or peritoneal effusion resulting in dyspnea or abdominal distension occurs in some cats. Ocular disease usually involves the posterior segment.

Diagnosis

Hematologic abnormalities commonly identified in dogs or cats with blastomycosis are normocytic normochromic

TABLE 97.1

Morphologic Appearance of Systemic Canine and Feline Fungal Agents

AGENT	CYTOLOGIC APPEARANCE
Blastomyces dermatitidis	Extracellular yeast, 5-20 µm in diameter; thick, refractile, double-contoured wall; broad-based bud; routine stains are adequate
Cryptococcus spp.	Extracellular yeast, 3.5-7.0 µm in diameter; thick, unstained capsule; thin-based bud; violet color with light-red capsule with Gram stain; unstained capsule with India ink
Coccidiodes spp.	Extracellular spherules (20-200 µm in diameter) containing endospores; deep red to purple double outer wall with bright red endospores with PAS stain
Histoplasma capsulatum	Intracellular yeast in mononuclear phagocytes, 2-4 µm in diameter, basophilic center with lighter body with Wright stain
Sporothrix schenckii	Intracellular yeast in mononuclear phagocytes, 2-3 µm × 3-6 µm in diameter; round, oval, or cigar-shaped

PAS, Periodic acid–Schiff.

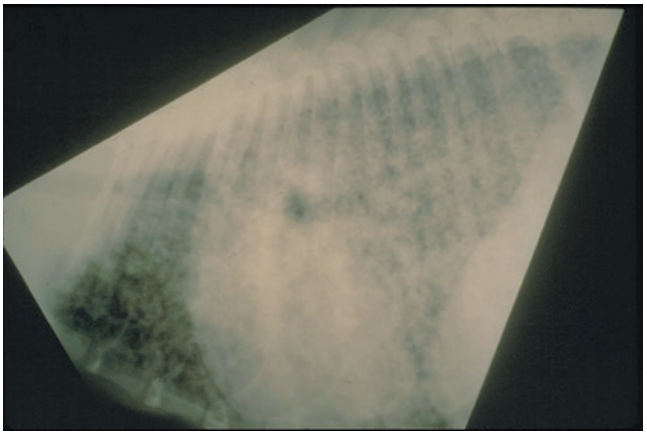


FIG 97.1
Miliary interstitial lung pattern consistent with blastomycosis in a dog. (Courtesy Dr. Lynelle Johnson, College of Veterinary Medicine, University of California, Davis.)

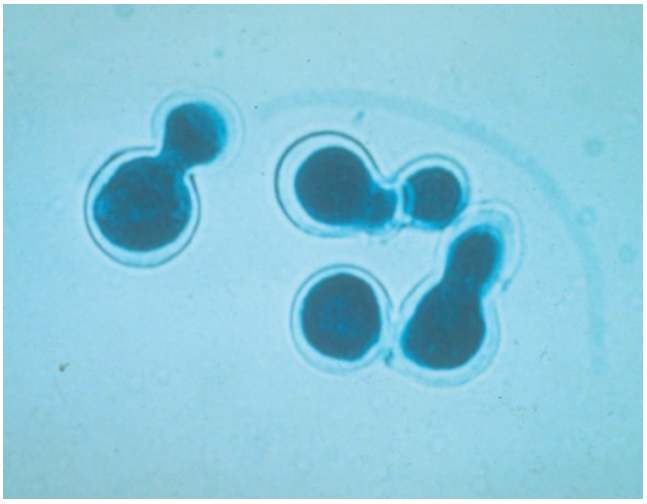


FIG 97.2
Cytologic appearance of the budding yeast, *Blastomyces dermatitidis*. The organism is 5 to 20 µm in diameter with a thick, refractile, double-contoured wall. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

nonregenerative anemia, lymphopenia, neutrophilic leukocytosis with or without a left shift, and monocytosis. Hypoalbuminemia and hyperglobulinemia (i.e., polyclonal gammopathy) caused by chronic inflammation are common serum biochemical abnormalities; hypercalcemia occurs rarely in dogs. Most infected dogs and cats with respiratory disease have diffuse, miliary, or nodular interstitial lung patterns and intrathoracic lymphadenopathy on thoracic radiographs (Fig. 97.1); single masses and pleural effusion from chylothorax sometimes occur. Alveolar lung disease occurs in some cats. Bone lesions induced by blastomycosis are lytic with a secondary periosteal reaction and soft tissue swelling. Intracranial blastomycosis generally reveals evidence of extension from the nasal cavity on diagnostic imaging but solitary CNS granulomas do occur (Bentley et al., 2018).

Serum antibodies develop in some infected animals; agar gel immunodiffusion (AGID) or a commercially available canine assay (www.miravistalabs.com) is frequently used. Because blastomycosis rarely causes subclinical infection, positive serum antibody assay results combined with appropriate clinical signs and radiographic abnormalities allow presumptive diagnosis if the organism cannot be demonstrated. Antibody titers do not always revert to negative after successful treatment. False-negative results can occur in animals with peracute infection, immunosuppression, or advanced infection that overwhelms the immune system; many cats with blastomycosis are seronegative.

Detection of the organism in a clinically ill animal with the appropriate presentation can give a definitive diagnosis of blastomycosis. The organism can be demonstrated by cytology, histopathology, culture, antigen test, or amplification of specific DNA by polymerase chain reaction (PCR) assay. Impression smears from skin lesions and aspirates from enlarged lymph nodes and focal lung lesions usually reveal pyogranulomatous inflammation and organisms that can usually be seen at low power (Fig. 97.2). Recovery of organisms from urine is less consistent. Bronchoalveolar

lavage is more sensitive than transtracheal aspiration for organism demonstration; organisms can also be found in samples obtained by percutaneous lung aspirates. However, in one study, *B. dermatitidis* was identified in 13 of 17 dogs after transtracheal aspiration (McMillan and Taylor, 2008). Growth in culture requires 10 to 14 days and is of lower yield than cytology or biopsy.

A *Blastomyces* antigen assay is available for human samples and has been evaluated in small numbers of dogs (MVista *Blastomyces* Antigen EIA; www.miravistalabs.com). The assay is sensitive but not specific for *B. dermatitidis*. In a study of 46 dogs with confirmed blastomycosis, the sensitivities of the antigen test using urine or serum were 93.5% and 87.0%, respectively (Spector et al., 2008). In contrast, the sensitivity of serum antibody results by AGID was 17.4%. In another study, *Blastomyces* antigen was detected in urine of all 21 dogs tested as well as in 18 of 20 sera (Foy et al., 2014). In that study, 71% of the dogs with clinical relapse were positive for *Blastomyces* antigen in urine. *Blastomyces dermatitidis* DNA can also be amplified from cerebrospinal fluid (CSF) of dogs with neurologic disease (Han et al., 2015).

Treatment

Amphotericin B, ketoconazole, both amphotericin B and ketoconazole, and itraconazole alone are used most frequently for the treatment of blastomycosis in dogs (Table 97.2). Amphotericin B is generally used in animals with life-threatening disease; the lipid or liposomal encapsulated product is less likely to cause toxicity. If regular amphotericin B is used, the animal should be well hydrated with 0.9% sodium chloride before treatment, and treatment should be discontinued if the patient becomes azotemic. Because itraconazole is as effective as amphotericin B and ketoconazole alone or in combination and has fewer adverse effects, it has

TABLE 97.2

Antifungal Drugs Used in the Management of the Systemic Canine and Feline Fungal Diseases

DRUG	SPECIES	DOSAGE	ORGANISM
Amphotericin B deoxycholate	D	1 mg/kg, IV, up to 3 times weekly[a] to a cumulative dose of 4-8 mg/kg. 0.5-0.8 mg/kg SC 2-3 times weekly to a cumulative dose of 4-8 mg/kg.[b]	Bl, H, Cr, Co
	C	0.25 mg/kg IV up to 3 times weekly,[c] to a cumulative dose of 4-6 mg/kg 0.5-0.8 mg/kg SC 2-3 times weekly[b] to a cumulative dose of 4-6 mg/kg	Bl, H, Cr, Co
Amphotericin B (lipid complex)	D	2-3 mg/kg, IV, 3 times weekly[d] to a cumulative dose of 12-27 mg/kg	Bl, H, Cr, Co
	C	1 mg/kg IV infusion 3 times weekly to a cumulative dose of 12 mg/kg	
Fluconazole	D	5-10 mg/kg PO or IV q12-24h	Bl, H, Cr, Co
	C	25 or 50 mg/cat PO q12-24h	Cr, Bl, H, Co
Flucytosine[e]	C	50 mg/kg PO q6-8h	Cr
Ketoconazole	D	10 mg/kg PO q12-24h	Bl, H, Cr, Co, Sp
	C	5-10 mg/kg, PO, q24h	Bl, H, Cr, Co, Sp
Itraconazole	D	5-10 mg/kg, PO, q12-24h	Bl, Cr, H, Co, Sp
	C	50-100 mg/cat/day PO	Bl, Cr, H, Co, Sp
Posaconazole	C	30 mg/kg, PO loading dose followed by 15 mg/kg, PO, q48h	Bl, Cr, H, Co, Sp
Terbinafine	D	30-35 mg/kg, PO, q24h	Cr, Bl, H, Co
Voriconazole[f]	D	4 mg/kg, PO, q12h	Bl, Cr, H, Co

[a]In dogs with normal renal function, dilute in 60-120 mL 5% dextrose and administer IV over 15 minutes; in dogs with renal insufficiency but with a blood urea nitrogen level <50 mg/dL, dilute in 500 mL to 1 L 5% dextrose and administer IV over 3-6 hours.
[b]Mix in 400 mL (cats) or 500 mL (dogs) of 0.45% saline and 2.5% dextrose solution, and administer SQ.
[c]In cats with normal renal function, dilute in 50-100 mL 5% dextrose and administer IV over 3-6 hours.
[d]Dilute the contents of a vial with 5% dextrose to a final concentration of 1 mg/mL and shake for 30 seconds. Draw up needed volume and filter through an 18-gauge Monoject filter needle into 100 mL of 5% dextrose. Infuse intravenously over 15 minutes.
[e]Should be used in combination with amphotericin B.
[f]Has been used in cats as well, but is associated with neurotoxicity (Quimby et al., 2010).
B, Dog and cat; *Bl, Blastomyces; C,* cat; *Co, Coccidioides; Cr, Cryptococcus; D,* dog; *H, Histoplasma; IV,* intravenous; *PO,* oral; *SC,* subcutaneously; *Sp, Sporothrix.*

been the drug of choice for the treatment of blastomycosis (see Table 97.2). Dogs should be treated with 5 mg/kg/day twice daily for the first 5 days and then 5 mg/kg once daily. Treatment should be continued for 60 to 90 days or for 4 weeks beyond resolution of measurable disease (i.e., thoracic radiographic abnormalities or skin lesions). A bioequivalence study showed that generic intraconazole was not bioequivalent to the approved product but was close enough to be used clinically (Mawby et al., 2014). In contrast, one source of compounded itraconazole was not suitable for use. Fluconazole can also be used and may be effective for CNS, ocular, and urinary system blastomycosis. In one retrospective study, overall responses to fluconazole or itraconazole in dogs with blastomycosis were similar. However, dogs treated with fluconazole had a higher mortality rate in the first 2 weeks of therapy, suggesting differences between the drugs in early efficacy (Mazepa et al., 2011).

Relapses occur in 20% to 25% of treated dogs. When they occur, a complete course of therapy should be reinstituted. Posterior segment ocular disease responds well to itraconazole, but anterior uveitis and endophthalmitis often require enucleation of the affected eye. In dogs with ocular blastomycosis resulting in euthanasia or enucleation of the affected eye, differences in the presence of the organism was not noted between treated and untreated dogs (Hendrix et al., 2004). In one study of 23 cats with blastomycosis, successful results were reported for two cats treated with amphotericin B and ketoconazole, one cat treated with amputation, and one cat treated with potassium iodide. In a more recent study of eight cats, two cats treated with itraconazole and one cat treated with fluconazole had clinical resolution of their disease (Gilor et al., 2006).

After treatment, decreases in *B. dermatitidis* serum antibody levels are variable. In contrast, in one study of 46 treated dogs, urine antigen concentrations decreased with treatment and so may be of benefit for monitoring therapy with clinical and radiographic parameters (Spector et al., 2008).

Zoonotic Aspects and Prevention

Genetic analyses have confirmed three haplotypes of *B. dermatitidis* that are common to both dogs and humans (Anderson et al., 2013). Direct zoonotic transmission from infected animals is unlikely because the yeast phase is not as infectious as the mycelial phase. One veterinarian was infected after material from a pulmonary aspirate from an infected dog was injected intramuscularly, and another developed disease after being bitten by an infected dog. The mycelial phase develops at temperatures lower than body temperature; positive cultures and contaminated bandages are infectious. Multiple reports have been made of canine and human blastomycosis that developed from the same environmental exposure. Decreasing potential for exposure by avoiding lakes and creeks in endemic areas is the only way to prevent the disease. A vaccine made of a genetically engineered live-attenuated strain of *B. dermatitidis* shows promise for use in dogs (Wüthrich M et al., 2011).

COCCIDIOIDOMYCOSIS

Etiology and Epidemiology

Coccidioides immitis is a dimorphic fungus found deep in sandy alkaline soils in regions with low elevation, low rainfall, and high environmental temperatures, including the southwestern United States, California, Mexico, Central America, and South America. In the United States coccidioidomycosis is diagnosed most frequently in California, Arizona, New Mexico, Utah, Nevada, and southwest Texas. *Coccidioides posadasii* has also been proven in some regions that are endemic for *C. immitis* (Brown et al., 2013; Luna-Isaac et al., 2014). The environmental mycelial phase produces arthrospores (2-4 µm wide, 3-10 µm long) that enter the vertebrate host by inhalation or wound contamination. Large numbers of arthrospores return to the surface after periods of rainfall and are dispersed by the wind; the prevalence of coccidioidomycosis increases in the years after a high rainfall. Most cases of feline coccidioidomycosis are diagnosed between December and May. In one study of dogs residing in an endemic area (Arizona), the cumulative probability of infection (evidenced by seroconversion) by 2 years of age was 28%, and the cumulative probability of clinical infection by 2 years of age was 6% (Shubitz et al., 2005). In another recent study that included 41 dogs with coccidioidomycosis and 79 control dogs, younger age, digging behavior, and travel to Arizona or the California central valley were associated with infection (Gayzel et al., 2017).

Inhaled arthrospores induce neutrophilic inflammation followed by infiltrates of histiocytes, lymphocytes, and plasma cells. The lymphocytic infiltrates associated with infection sites are predominantly T cells. Infection is cleared if cell-mediated immune responses are normal; most people, dogs, and cats exposed to the organism are subclinically affected. The organism disseminates to mediastinal and tracheobronchial lymph nodes, bones and joints, visceral organs (liver, spleen, kidneys), heart and pericardium, testicles, eyes, brain, and spinal cord of some individuals. Spherules (20-200 µm in diameter) containing endospores (see Table 97.1) form in tissues of infected hosts. Endospores are released by cleavage and produce new spherules. Respiratory signs and signs of disseminated disease occur 1 to 3 weeks and 4 months after exposure, respectively.

Clinical Features

Clinical disease in dogs is most common in young, male, large-breed dogs. Dogs that are allowed to roam or walk in the desert in endemic areas, particularly if they also exhibit digging behavior are most likely to be exposed. Approximately 90% of clinically affected dogs have lameness with swollen, painful bones or joints. Cough, dyspnea, anorexia, weakness, weight loss, lymphadenopathy, clinical signs of ocular inflammation, and diarrhea are other presenting complaints. Crackles, wheezes, or muffled lung sounds from pleural effusion are common. Restrictive pericarditis presenting with evidence of right heart failure, such as hepatomegaly, pleural effusion, and ascites, can also occur.

Heart base masses developed in two dogs in a recent report (Ajithdoss et al., 2011). Dermatologic findings in both dogs and cats are most commonly subcutaneous nodules (Simoes et al., 2016). If subcutaneous abscesses, nodules, ulcers, and draining tracts occur, they are usually associated with infected bones. Over 50% of the cats with skin lesions and over 75% of the dogs with cutaneous manifestations also have systemic illness (Simoes et al., 2016). In some dogs, coccidioidomycosis has been initially misdiagnosed as a malignancy (Ramirez-Romero et al., 2016). Of the three cases described in this report, one was infected by *C. posadasii*. Myocarditis, icterus, renomegaly, splenomegaly, hepatomegaly, orchitis, epididymitis, keratitis, iritis, granulomatous uveitis, and glaucoma are detected in some dogs. Depression, seizures, ataxia, central vestibular disease, cranial nerve deficits, and behavioral changes are the most common signs of CNS infection. Solitary CNS granulomas can occur (Bentley et al., 2015).

In one review, the median age of cats with coccidioidomycosis was 5 years; no obvious sex or breed predilection existed (Greene et al., 1995). The most common clinical manifestations include skin disease (56%), respiratory disease (25%), musculoskeletal disease (19%), and either ophthalmic or neurologic disease (19%). If ocular disease occurs, granulomatous chorioretinitis and anterior uveitis occur in most infected cats.

Diagnosis

Normocytic, normochromic nonregenerative anemia; leukocytosis; leukopenia; and monocytosis are the most common hematologic abnormalities. Hyperglobulinemia (i.e., polyclonal gammopathy), hypoalbuminemia, renal azotemia, and proteinuria occur in some infected animals. In one study of 87 dogs with coccidioidomycosis, azotemia (13%) and proteinuria (63%) were common (Mehrkens et al., 2016). Of the 24 dogs with renal histopathology performed, 13 dogs had lesions suggestive of immune complex glomerulonephritis. Thus dogs with proteinuria that have visited endemic areas like Arizona and California should be evaluated for infection.

Diffuse interstitial lung patterns are more common than bronchial, miliary interstitial, nodular interstitial, or alveolar patterns radiographically in dogs and cats with respiratory coccidioidomycosis. Pleural effusion from pleuritis, right-sided heart failure, or constrictive pericarditis can occur. Hilar lymphadenopathy is common in dogs and cats; however, sternal lymphadenopathy or calcification of lymph nodes is not. Bone lesions usually involve the distal diaphysis, epiphysis, and metaphysis of one or more long bones, and they are more proliferative than lytic. It can be difficult to differentiate neoplasia from *Coccidioides* spp. granulomas based on MRI findings (Bentley et al., 2015).

There are currently several methods for detection of serum antibodies against *C. immitis*, including AGID, complement fixation, and enzyme linked immunoassays, and tube precipitin (TP) tests. False-negative results can occur in dogs and cats with early *C. immitis* infections (<2 weeks), chronic infection, rapidly progressive acute infection, and primary cutaneous coccidioidomycosis. The assays can cross-react with antibodies against *Histoplasma capsulatum* and *B. dermatitidis*.

Serum antibodies develop in dogs with and without clinical signs of disease, and titer magnitude failed to correlate with the presence of illness in one study (Shubitz et al., 2005). Thus results of antibody test results alone should not be used to make a definitive diagnosis. The combination of positive serologic test results and radiographic signs of interstitial lung disease, dermatologic disease, or osteomyelitis in animals from endemic areas can be used to make a presumptive diagnosis if the organism cannot be demonstrated. In one study of 131 dogs, hilar lymphadenopathy was assessed as a predictor of a positive serum antibody titer and was shown to have a sensitivity, specificity, positive predictive value, and negative predictive value of 28%, 91.5%, 43.8%, and 84.4%, respectively (Crabtree et al., 2008). The authors concluded that, in endemic areas, the presence of hilar lymphadenopathy in dogs in endemic areas suggested treatment was indicated while waiting for serum antibody test. Titers may persist for months to years after resolution of clinical disease.

Definitive diagnosis requires demonstration of the organism by cytology, biopsy, antigen assay, culture, or amplification of specific DNA. The organism is often difficult to demonstrate by cytology; transtracheal aspiration or bronchoalveolar lavage is commonly negative. Extracellular spherules (Fig. 97.3) are most commonly found in lymph node aspirates, draining masses, and pericardial fluid; wet mount examination of unstained smears or periodic acid–Schiff-stained smears are more suitable than dry mounts.

For *B. dermatitidis* and *H. capsulatum,* detection of antigens of the fungi in serum or urine has shown some clinical utility (see appropriate sections of this chapter). In humans, detection of *C. immitis* antigen in serum or urine shows promise as a diagnostic procedure. However, when *C. immitis*

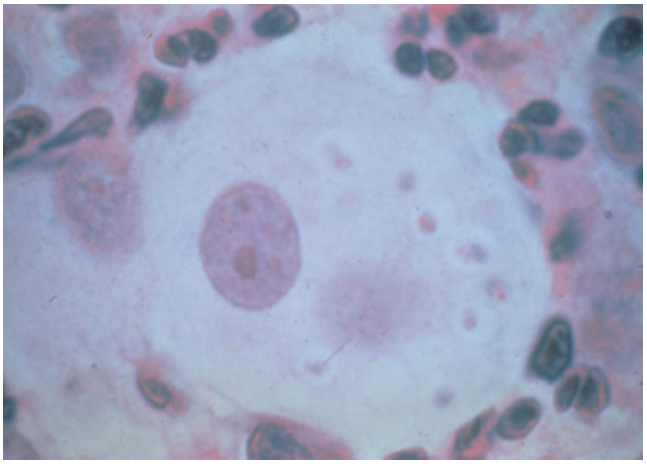


FIG 97.3
Coccidiodes immitis spherule (20-200 µm in diameter) in muscle tissue.

antigen was measured in samples from 60 dogs with antibody titers 1:16 or greater, the sensitivity was low for both serum (19%) and urine (3.5%), suggesting this assay should not be used in dogs (Kirsch et al., 2012).

Treatment

Ketoconazole is inexpensive and a drug of choice for treatment of coccidioidomycosis in dogs (see Table 97.1). However, this drug commonly leads to inappetence, vomiting, diarrhea, weight loss, and increases in liver enzyme activities in some dogs and cats. In dogs, long-term use of ketoconazole can suppress testosterone and cortisol production and has been associated with cataracts. Amphotericin B should be used if life-threatening disease is present or if response to ketoconazole is poor. Itraconazole can be used in animals with toxicity from ketoconazole. Fluconazole should be considered for animals with meningoencephalitis. Posaconazole has fungistatic activity against *Coccidioides* spp. and has been used successfully in management of human cases with refractory respiratory disease. Pharmacokinetic information is now available for this drug in cats (Mawby et al., 2016).

Cats and dogs should be treated for 60 to 90 days or until clinical illness has been resolved for at least 1 month. Bone infections are often incurable; therefore repeated treatments are often required. When treated with ketoconazole, itraconazole, or fluconazole, 32 of 44 cats with coccidioidomycosis were asymptomatic during or after treatment; relapse occurred in 11 cats during or after treatment (Greene et al., 1995). Voriconazole is a newer fluconazole derivative that achieves high concentrations in the CNS and so could be considered for dogs with CNS involvement. Neurologic adverse effects appear to be common in cats but have not been well defined in dogs (Quimby et al., 2010).

Daily administration of lufenuron, a chitin synthesis inhibitor, has been evaluated in a limited number of dogs with coccidioidomycosis. Nikkomycin Z (NikZ) is another chitin synthase inhibitor that was used to treat 12 dogs with *Coccidioides* spp.-associated respiratory disease for an average of 3 months (Shubitz, 2013). Seven of the nine dogs that completed the protocol had clinical and laboratory evidence of improvement. Pharmacologic studies with terbinafine have been completed (Sakai et al., 2011), and it could be considered as another option for the treatment of coccidioidomycosis (30-35 mg/kg, orally [PO], daily).

Zoonotic Aspects and Prevention

One study showed an association between the location of canine and human coccidioidomycosis in California suggesting dogs could be used as sentinels for infection in people (Grayzel et al., 2017). People exposed to *C. immitis* develop asymptomatic infection or mild, transient respiratory signs. The organism is not transmitted from infected animals to people. However, the mycelial phase occurs outside the vertebrate host, so fomites such as bandage material and cultures should be handled carefully. Avoiding endemic areas is the only way to prevent the disease.

CRYPTOCOCCOSIS

Etiology and Epidemiology

Cryptococcus neoformans is a 3.5- to 7.0-µm yeast-like organism with worldwide distribution. It has a thick polysaccharide capsule and reproduces by narrow-based budding (see Table 97.1). *Cryptococcus gattii* is also common in some regions and is associated with disease. Clinical findings with either infection are similar. Many cases have been described in California, British Columbia, and both coasts of Australia. An outbreak of *Cryptococcus* spp. infections recently occurred in people, dogs, cats, ferrets, and a bird in British Columbia (Lester et al., 2004; MacDougall et al., 2007). Most cases were on Vancouver Island and were caused by *C. gattii*. The organisms are acquired from the environment; risk factors significantly associated with infection in animals in the British Columbia outbreak included living near a site of soil disturbance such as logging sites, having an above-average level of activity, hunting, and having owners who hiked or visited a botanic garden (Duncan et al., 2006b). There may be breed predispositions; in one study in California, American Cocker Spaniels were more likely to have cryptococcosis than other breeds (Trivedi et al., 2011a). In the same study, most cats were infected by *C. gattii* and most dogs were infected by *C. neoformans*. Whether disease occurs is dependent on both host and organism factors (Ma and May, 2009).

The route of transmission for *Cryptococcus* spp. is believed to be inhalation. Nasal and pulmonary disease manifestations are common; however, on the basis of culture and serologic studies of healthy animals, an inapparent carrier state also occurs. The organism probably spreads to extrapulmonary sites hematogenously; the CNS may also be infected by direct extension across the cribriform plate from the nasal cavity. Immunity is cell mediated; individuals with incomplete responses do not completely remove the organism, thus resulting in granulomatous lesions. The polysaccharide capsule of the organism inhibits plasma cell function, phagocytosis, leukocyte migration, and opsonization, potentiating infection.

Cryptococcus spp. can be primary pathogens. However, preexisting immunosuppressive conditions are documented in approximately 50% of people with cryptococcosis. Serologic evidence of co-infection with feline immunodeficiency virus or feline leukemia virus occurs in some cats with cryptococcosis. Potentially immunosuppressive conditions such as administration of corticosteroids, ehrlichiosis, heartworm disease, and neoplasia are identified in a small percentage of dogs with cryptococcosis.

Clinical Features

Cryptococcosis is the most common systemic fungal infection of cats and should be considered a differential diagnosis for cats with clinical evidence of upper or lower respiratory tract disease, subcutaneous nodules, lymphadenopathy, intraocular inflammation, fever, or CNS disease. Lower urinary tract disease has also been described. All ages of cats

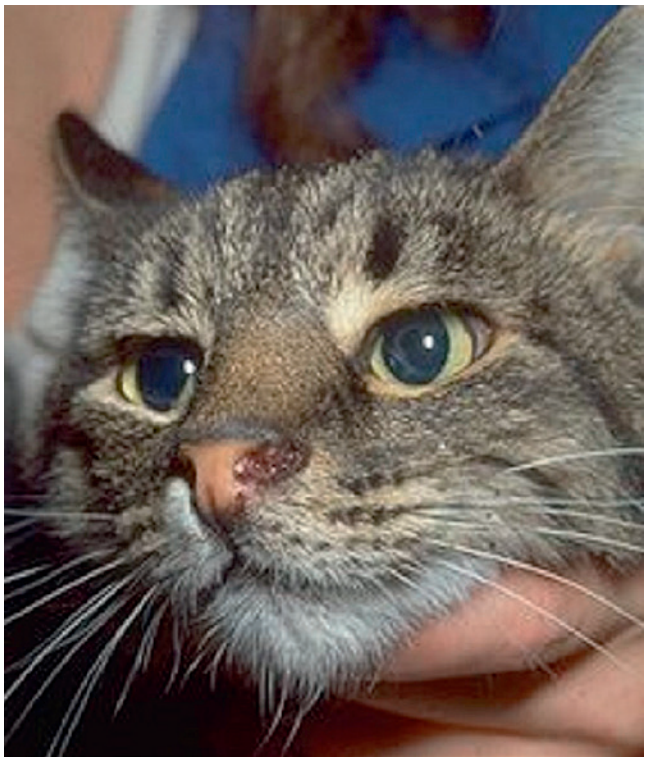


FIG 97.4
Nasal cryptococcosis in a cat in Colorado.

have been infected, but young cats are generally overrepresented. In one study in Australia, Siamese, Himalayan, and Ragdoll breeds were overrepresented (O'Brien et al., 2004). Infection of the nasal cavity, resulting in sneezing and nasal discharge (Fig. 97.4), is reported most frequently. The nasal discharge can be unilateral or bilateral, range from serous to mucopurulent, and often contains blood. Granulomatous lesions extruding from the external nares, facial deformity over the bridge of the nose, and ulcerative lesions on the nasal planum are common; mandibular lymphadenopathy is detected in most cats with rhinitis. These signs are also common in cats with upper airway lymphoma and feline aspergillosis, so every effort should be made to obtain a diagnosis before instituting treatment. The nasopharynx is the primary site of involvement in some infected cats and dogs, resulting in snoring and stertor as the predominant clinical signs. *Cryptococcus gattii* has also been detected in pleural effusion (Barrs et al., 2005).

Single or multiple, small (<1 cm), cutaneous or subcutaneous masses also have been reported commonly in cats infected with *C. neoformans*. The masses can be either firm or fluctuant and have a serous discharge if ulcerated. Anterior uveitis, chorioretinitis, or optic neuritis occurs in association with ocular infection; lens luxations and glaucoma are common sequelae. Chorioretinitis lesions can be punctate or large; suppurative retinal detachment occurs in some infected cats.

CNS signs of disease result from diffuse or focal meningoencephalitis or focal granuloma formation. Manifestations include depression, behavioral changes, seizures, blindness, circling, ataxia, loss of sense of smell, and paresis depending on the location of the lesion; peripheral vestibular disease can also occur. When pain from cryptococcosis occurred in cats, it was generalized or localized to the thoracolumbar spine or pelvic limbs in one study (Sykes et al., 2010). Nonspecific signs of anorexia, weight loss, and fever occur in some infected cats.

Clinical findings in dogs with cryptococcosis depend on the organ systems involved and are similar to those that occur in the cat. Cryptococcosis is diagnosed most commonly in young purebred dogs. Clinical manifestations include signs of upper or lower respiratory tract infection, disseminated disease including intraabdominal masses, CNS disease, disease of the orbit or eye, skin lesions, nasal cavity disease, and lymph node involvement. Seizures, ataxia, central vestibular syndrome, cranial nerve deficits, and clinical signs of cerebellar disease are the common CNS manifestations in dogs (Sykes et al., 2010). Dogs with *Cryptococcus* spp.–associated pyelonephritis (Newman et al., 2003) and gastrointestinal disease (Graves et al., 2005) have been reported. Abdominal cryptococcosis, responsive to fluconazole therapy without surgery, was recently reported in two dogs (Tangeman et al., 2015). One dog had primary alimentary cryptococcosis alone and the other dog pancreatic and disseminated cryptococcosis.

Diagnosis

Nonregenerative anemia and monocytosis are the most common hematologic abnormalities; neutrophil counts and biochemical panels are generally normal. In dogs with CNS involvement, CSF protein concentrations vary from normal to 500 mg/dL and cell counts vary from normal to 4500/μL; neutrophils and mononuclear cells predominate, but eosinophils are present in some cases. Imaging changes consistent with cryptococcosis include increased soft tissue density in the nasal cavity caused by fungal granuloma formation, as well as nasal bone deformity and lysis. Hilar lymphadenopathy and diffuse to miliary pulmonary interstitial patterns are common thoracic radiographic abnormalities.

Because circulating *Cryptococcus* spp. antibodies can be detected in both healthy and diseased animals, their presence does not document clinical disease. In addition, in one study all infected cats were seronegative (Flatland et al., 1996). Cryptococcal antigen can be detected in serum, aqueous humor, or CSF by a number of methods; serum antigen tests are positive in most cats and dogs infected by *C. neoformans*. For example, 51 of 53 cats and 15 of 18 dogs tested were positive for serum antigen in a retrospective study in California (Trivedi et al., 2011a). However, animals with acute disease, chronic low-grade infections, drug-induced remission, localized disease, or infection by *C. gattii* can be latex agglutination (LA) test-negative (Tintelnot et al., 2015). The LA performed on CSF is positive in almost all animals with CNS cryptococcosis. Because of the problems associated with detection of *C. gattii* antigen by some assays, culture or PCR assays should be considered in

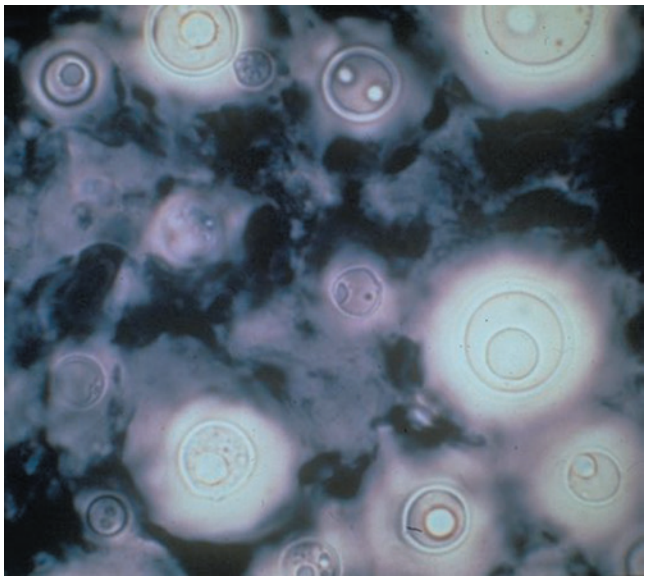


FIG 97.5
Cytologic appearance of *Cryptococcus neoformans*. The organism is 3.5 to 7.0 µm in diameter and has a thick polysaccharide capsule. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

cases with characteristic clinical and laboratory findings but negative antigen test results.

A definitive diagnosis of cryptococcosis is based on positive antigen testing, cytologic, histopathologic, culture, or PCR assay demonstration of the organism (Fig. 97.5) combined with appropriate clinical manifestations of disease. The organism is found during cytologic evaluation of nasal lesions, cutaneous lesions, lymph node aspirates, CSF, and bronchoalveolar lavage fluid in most affected animals; it can also be cultured. The agents can be cultured from the nasal cavity of some asymptomatic animals, so positive culture results do not always correlate to disease. One study evaluating subclinical carriage of *C. gattii* showed some animals eliminated the infection, some remained persistently colonized, and some progressed to clinical illness (Duncan et al., 2005a). If organism numbers are low in tissues and are not detected cytologically or histopathologically, immunohistochemistry, PCR, and fungal culture can be used to confirm infection (Myers et al., 2017).

Treatment

There are molecular types of *C. neoformans* and *C. gattii* that affect antifungal drug susceptibility (Singer et al., 2014). In one study of 42 isolates, it was shown that, when compared with the mean inhibitory concentration (MIC) for *C. neoformans*, *C. gattii* MICs were lower for flucytosine and strain VGIII MICs (all from cats) were lower for flucytosine and itraconazole. In addition, for all drugs except itraconazole, *C. gattii* isolates exhibited a wider range of MICs than *C. neoformans*. In addition, it is now known that resistance to fluconazole can develop in infected animals and the mechanisms confirmed with molecular assays (Sykes et al., 2017). Thus treatment responses in individual animals may be variable.

Dogs and cats with cryptococcosis have been treated with amphotericin B, ketoconazole, itraconazole, fluconazole, posaconazole, voriconazole, or 5-flucytosine alone and in various combinations (see Table 97.2). Amphotericin B is usually not indicated unless life-threatening disseminated disease requiring rapid response to therapy is required. If amphotericin B is deemed necessary, lipid or liposomal encapsulated amphotericin is likely optimal because fewer adverse effects are associated with these formulations compared with regular amphotericin B. However, for owners who cannot afford this therapy, a less expensive subcutaneous protocol for administration of regular amphotericin B has been used successfully for the treatment of cryptococcosis in dogs and cats and may be effective for other systemic fungi susceptible to the drug (Malik et al., 1996; see Table 97.2).

Ketoconazole, itraconazole, or fluconazole are used as a single agent in dogs or cats without life-threatening disease. Ketoconazole is inexpensive but commonly leads to inappetence, vomiting, diarrhea, weight loss, and increases in liver enzyme activities in some dogs and cats. In dogs, long-term use of ketoconazole can suppress testosterone and cortisol production and has been associated with cataracts. Because of these problems, ketoconazole is used less frequently than itraconazole and fluconazole. Fluconazole should be considered for dogs or cats with ocular or CNS infection. If clinical signs of toxicity develop (inappetence; drug eruptions) or increased activity of alanine aminotransferase is detected, drug therapy should be stopped and then reinstituted at 50% of the original dose after signs of toxicity abate. In one study, *C. neoformans* minimum inhibitory concentrations for itraconazole and voriconazole were similar (Okabayashi et al., 2009). Because voriconazole has been associated with CNS toxicity in cats, it should probably not be selected over fluconazole or itraconazole for the treatment of this disease (Quimby et al., 2010).

Flucytosine crosses the blood-brain barrier better than ketoconazole or amphotericin B, so it has been used primarily for the treatment of CNS cryptococcosis. It must be used in combination with other antifungal drugs and has many adverse effects, including vomiting, diarrhea, hepatotoxicity, cutaneous reactions, and bone marrow suppression. One dog with protein-losing enteropathy from intestinal cryptococcosis responded to administration of terbinafine after failing treatment with amphotericin B and fluconazole (Olsen et al., 2012).

Clinical signs of nasal and cutaneous cryptococcosis generally resolve with treatment, but dogs or cats with CNS or ocular disease are less likely to respond. In one study of dogs and cats with CNS cryptococcosis, 32% of the treated animals survived longer than 6 months; presence of decreased mentation was a poor prognostic indicator (Sykes et al., 2010). Administration of glucocorticoids was associated with increased short-term survival in this study and one other (Vorathavorn et al., 2013).

Treatment should continue for at least 1 to 2 months past resolution of clinical disease. Serum and CSF LA antigen titers can diminish with therapy and have been used to monitor response. Antigen titers fail to decrease in some animals without clinical evidence of disease, suggesting persistence of the organism in tissues.

Zoonotic Aspects and Prevention

People and animals can have the same environmental exposure to *Cryptococcus* spp., but zoonotic transfer from contact with infected animals is unlikely. Prevention is achieved by decreasing potential for exposure.

HISTOPLASMOSIS

Etiology and Epidemiology

Histoplasma capsulatum is a saprophytic dimorphic fungus found in the soil in all regions with tropical and subtropical climates; histoplasmosis is diagnosed most frequently in the Mississippi, Missouri, and Ohio River valleys and in the mid-Atlantic states. The organism is considered endemic in 31 of the 48 contiguous United States. The organism has also been associated with disease in dogs in some other countries. The microconidia (2-4 µm) and macroconidia (5-18 µm) of the mycelial phase are found in the environment. In the vertebrate host, the 2- to 4-µm yeast phase is found in the cytoplasm of mononuclear phagocytes (see Fig. 97.6 and Table 97.1).

Histoplasma capsulatum is concentrated most heavily in soil contaminated with bird or bat excrement. Point sources for infection are found in endemic areas; two dogs and 20 people developed pulmonary histoplasmosis after removing a tree that had served as a bird roost (Ward et al., 1979). Subclinical infections are common in dogs. Dogs in endemic areas are commonly exposed, but the prevalence of disease is low. Immunosuppression may predispose to clinical infection in dogs and cats. In one study of 30 cats, 11 cats were housed strictly indoors with potted plants (5 cats) or unfinished basements (6 cats) being the possible sources of infection (Reinhart et al., 2012).

Infection is by ingestion or inhalation of microconidia from the environment. The organism is engulfed by mononuclear phagocytes, transformed to the yeast phase, and transported throughout the body in the blood and lymph. Granulomatous inflammation results in persistently infected organs and clinical signs of disease. Disseminated disease is common in cats.

Clinical Features

Most dogs with histoplasmosis are outdoor sporting breeds younger than 7 years. Subclinical infection, pulmonary infection, and disseminated infection are recognized most frequently. Most affected dogs are presented for evaluation of anorexia, fever, depression, weight loss, cough, dyspnea, or diarrhea. Large-bowel diarrhea is most common, but small-bowel diarrhea, mixed-bowel diarrhea, and protein-losing enteropathy occur in some.

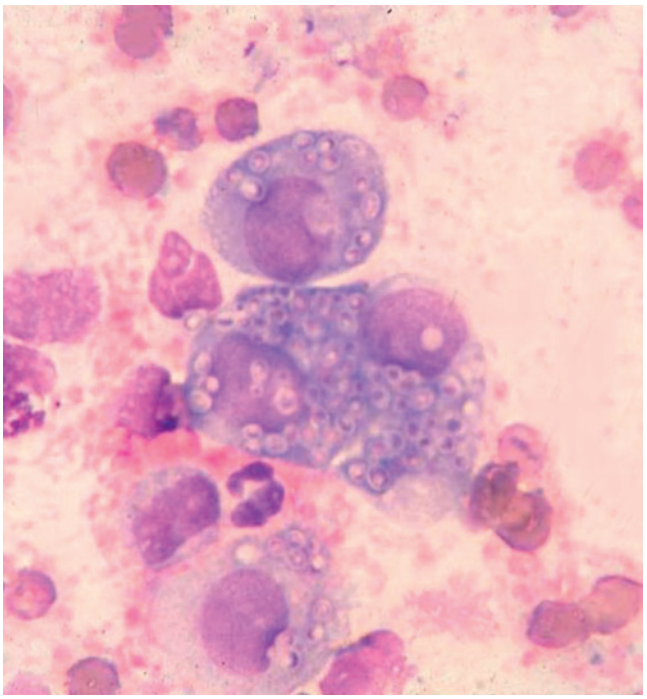


FIG 97.6
Histoplasma capsulatum (2-4 µm in diameter) in mononuclear cells. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

Physical examination abnormalities often include depression, increased bronchovesicular sounds, respiratory wheezes, fever, evidence of diarrhea, pale mucous membranes, hepatomegaly, splenomegaly, icterus, ascites, and intraabdominal lymph node enlargement. Airway obstruction from massive hilar lymphadenopathy occurs in some dogs. Lameness from bone infection or polyarthritis, peripheral lymphadenopathy, chorioretinitis, CNS disease, and skin disease occur occasionally. Subcutaneous nodules rarely drain or ulcerate and are less common than in dogs with cryptococcosis or blastomycosis.

Infected cats are either normal or develop disseminated disease. Most clinically affected cats are younger than 4 years, and some are co-infected with feline leukemia virus. Depression, weight loss, anorexia, lameness, and dyspnea are common presenting complaints. Weight loss can be severe and develop in as little as 2 weeks. Fever, pale mucous membranes, abnormal lung sounds, oral erosions or ulcers, peripheral or visceral lymphadenopathy, icterus, soft tissue swelling around osseous lesions, hepatomegaly, skin nodules, and, rarely, splenomegaly are physical examination abnormalities potentially consistent with histoplasmosis. Disseminated disease has a grave prognosis in cats. Osseous histoplasmosis is most common in bones of the appendicular skeleton distal to the stifle or elbow joints, and one or more limbs can be involved. Feline ocular histoplasmosis manifests with conjunctivitis, chorioretinitis, retinal detachment, or optic

neuritis and may result in glaucoma and blindness. Other than depression, CNS signs are uncommon.

Diagnosis

A variety of nonspecific clinicopathologic and radiographic abnormalities are associated with histoplasmosis. Normocytic, normochromic, nonregenerative anemia is the most common hematologic abnormality in both dogs and cats. Neutrophil counts can be normal, increased, or decreased. Unlike the other systemic fungi, *H. capsulatum* is occasionally seen in circulating cells, particularly on examination of a buffy coat smear; mononuclear cell infection is most common, followed by eosinophils. Thrombocytopenia from disseminated intravascular coagulation or microangiopathic destruction occurs in approximately 50% of dogs and some cats. Some affected cats develop pancytopenia from bone marrow infection. Hypoproteinemia and increased activities of alkaline phosphatase and alanine aminotransferase occur in some infected animals.

Lysis predominates in animals with bone infection; periosteal and endosteal new bone production occurs in some cases. In dogs with pulmonary infection, radiographic abnormalities include diffuse interstitial, miliary-to-nodular interstitial disease; hilar lymphadenopathy; pleural effusion; and calcified pulmonary parenchyma caused by chronic disease. In some dogs, massive hilar lymphadenopathy is the only radiographic finding. Alveolar lung disease, tracheobronchial lymphadenopathy, and calcified lymph nodes are uncommon in cats. Colonoscopic findings in dogs with gastrointestinal infection include increased mucosal granularity, friability, ulceration, and thickness.

Several tests have been evaluated for the detection of circulating antibodies against *H. capsulatum* in the serum of dogs and cats, but the sensitivity and specificity are poor for all. Serologic diagnosis is unreliable and should be used only to establish a presumptive diagnosis when the organism cannot be demonstrated by cytology, histopathology, culture, or PCR assay, and the clinical signs are suggestive of the disease.

Definitive diagnosis requires demonstration of the organism by cytology, antigen assay, biopsy, culture, or amplification of specific DNA by PCR assay (see Fig. 97.6). The organism is found most frequently in rectal scrapings or biopsies from dogs with large-bowel diarrhea, in bone marrow or buffy coat cells from cats with disseminated disease, and in other locations (e.g., lymph nodes, lung, spleen, liver, skin nodules). The organism has also been identified in pleural and peritoneal effusions and in CSF.

In one retrospective study, results of a urine antigen assay were compared with standard diagnostic methods in 18 cats with clinical signs and clinicopathologic findings supportive of histoplasmosis (MVista *Histoplasma* Antigen EIA; www.miravistalabs.com). Antigen was detected in the urine of 17 of 18 cats, suggesting this assay may be useful for diagnosing this disease in cats. However, in cats with ocular histoplasmosis, false negative antigen test results occurred using serum, urine, and subretinal fluid (Smith et al., 2017). In one feline case, H. capsulatum antigen was detected in serum but not urine. In dogs, the urine antigen assay has been evaluated in several studies. In one study of 17 confirmed cases of histoplasmosis and 41 cases with other diseases, there were 2 false-negative antigen assay results but no false-positive results (Cunningham et al., 2015).

Treatment

Because of its effectiveness and minimal toxicity, itraconazole is the initial drug of choice for dogs and cats with histoplasmosis (see Table 97.2). Animals should be treated for 60 to 90 days or until clinical evidence of disease has been resolved for at least 1 month. Amphotericin B can be used in animals with life-threatening disease or in those unable to absorb oral medications because of intestinal disease. Ketoconazole and fluconazole are also effective in some animals. However, ketoconazole has more adverse effects than itraconazole, and some cases that do not respond to fluconazole respond to intraconazole. The overall success rate for the treatment of histoplasmosis in cats was 33% in one study (Clinkenbeard et al., 1989). In another study, all eight cats treated with itraconazole (5 mg/kg PO q12h) were eventually cured (Hodges et al., 1994). Pulmonary disease in dogs has a fair to good prognosis, whereas disseminated disease has a poor prognosis. In one study, clinical outcomes were similar for 17 cats treated with fluconazole and 13 cats treated with itraconazole (Reinhart et al., 2012). *Histoplasma capsulatum* may develop resistance to fluconazole during treatment (Renschler et al., 2017) as documented for *C. gattii* (Sykes et al., 2017). Use of serum and urine antigen testing has been used to monitor response to treatment or recurrence in one series of 15 cats and showed potential clinical utility (Hanzlicek et al., 2016).

Administration of glucocorticoids with or without antifungal drugs lessened clinical signs associated with chronic hilar lymphadenopathy much more quickly than did administration of antifungal drugs alone and did not result in disseminated histoplasmosis (Schulman et al., 1999). However, if the infection is active, administration of glucocorticoids may exacerbate clinical disease.

Zoonotic Aspects and Prevention

Like blastomycosis, direct zoonotic transmission from infected animals is unlikely because the yeast phase is not as infectious as the mycelial phase. Care should be taken when culturing the organism. Prevention includes the avoidance of potentially contaminated soil. Organism numbers in contaminated areas can be decreased by application of 3% formalin.

Suggested Readings

Blastomycosis

Anderson JL, et al. Clinical and molecular epidemiology of veterinary blastomycosis in Wisconsin. *BMC Vet Res*. 2013;9:84.

Baumgardner DJ, et al. Effects of season and weather on blastomycosis in dogs: Northern Wisconsin, USA. *Med Mycol*. 2011; 49:49.

Bentley RT, et al. Fungal infections of the central nervous system in small animals: clinical features, diagnosis, and management. *Vet Clin North Am Small Anim Pract*. 2018;48:63.

Blastomycosis acquired occupationally during prairie dog relocation—Colorado, 1998. *Morb Mortal Wkly Rep*. 1999;48:98.

Blondin N, et al. Blastomycosis in indoor cats: suburban Chicago, Illinois, USA. *Mycopathologia*. 2007;163:59.

Bromel C, Sykes JE. Epidemiology, diagnosis, and treatment of blastomycosis in dogs and cats. *Clin Tech Small Anim Pract*. 2005;20:233.

Clemans JM, et al. Retroperitoneal pyogranulomatous and fibrosing inflammation secondary to fungal infections in two dogs. *J Am Vet Med Assoc*. 2011;238:213.

Crews LJ, et al. Utility of diagnostic tests for and medical treatment of pulmonary blastomycosis in dogs: 125 cases (1989-2006). *J Am Vet Med Assoc*. 2008;232:222.

Ditmyer H, Craig L. Mycotic mastitis in three dogs due to Blastomyces dermatitidis. *J Am Anim Hosp Assoc*. 2011;47:356.

Foy DS, et al. Serum and urine *Blastomyces* antigen concentrations as markers of clinical remission in dogs treated for systemic blastomycosis. *J Vet Intern Med*. 2014;28:305.

Gilor C, et al. Clinical aspects of natural infection with Blastomyces dermatitidis in cats: 8 cases (1991-2005). *J Am Vet Med Assoc*. 2006;229:96.

Han JI, et al. A multiplex quantitative real-time polymerase chain reaction panel for detecting neurologic pathogens in dogs with meningoencephalitis. *J Vet Sci*. 2015;16:341.

Hecht S, et al. Clinical and imaging findings in five dogs with intracranial blastomycosis (Blastomyces dermatiditis). *J Am Anim Hosp Assoc*. 2011;47:241.

Hendrix DV, et al. Comparison of histologic lesions of endophthalmitis induced by Blastomyces dermatitidis in untreated and treated dogs: 36 cases (1986-2001). *J Am Vet Med Assoc*. 2004;224:1317.

Herrmann JA, et al. Temporal and spatial distribution of blastomycosis cases among humans and dogs in Illinois (2001-2007). *J Am Vet Med Assoc*. 2011;239:335.

Legendre AM, et al. Treatment of blastomycosis with itraconazole in 112 dogs. *J Vet Intern Med*. 1996;10:365.

MacDonald PD, et al. Human and canine pulmonary blastomycosis, North Carolina, 2001-2002. *Emerg Infect Dis*. 2006;12:1242.

Mawby DI, et al. Bioequivalence of orally administered generic, compounded, and innovator-formulated itraconazole in healthy dogs. *J Vet Intern Med*. 2014;28:72.

Mazepa AS, et al. Retrospective comparison of the efficacy of fluconazole or itraconazole for the treatment of systemic blastomycosis in dogs. *J Vet Intern Med*. 2011;25:440.

McMillan CJ, Taylor SM. Transtracheal aspiration in the diagnosis of pulmonary blastomycosis (17 cases: 2000-2005). *Can Vet J*. 2008;49:53.

Schmiedt C, et al. Cardiovascular involvement in 8 dogs with Blastomyces dermatitidis infection. *J Vet Intern Med*. 2006;20:1351.

Spector D, et al. Antigen and antibody testing for the diagnosis of blastomycosis in dogs. *J Vet Intern Med*. 2008;22:839.

Totten AK, et al. *Blastomyces dermatitidis* prostatic and testicular infection in eight dogs (1992-2005). *J Am Anim Hosp Assoc*. 2011;47:413.

Wüthrich M, et al. Safety, tolerability, and immunogenicity of a recombinant, genetically engineered, live-attenuated vaccine against canine blastomycosis. *Clin Vaccine Immunol*. 2011;18:783.

Varani N, et al. Attempted isolation of *Blastomyces dermatitidis* from the nares of dogs: Northern Wisconsin, USA. *Med Mycol*. 2009;47:780.

Coccidioidomycosis

Ajithdoss DK, et al. Coccidioidomycosis presenting as a heart base mass in two dogs. *J Comp Pathol*. 2011;145:132.

Bentley RT, et al. Magnetic resonance imaging features and outcome for solitary central nevous system *Coccidioides* granulomas in 11 dogs and cats. *Vet Radiol Ultrasound*. 2015;56:520.

Brown J, et al. Coccidioidomycosis: epidemiology. *Clin Epidemiol*. 2013;5:185.

Butkiewicz CD, et al. Risk factors associated with *Coccidioides* infection in dogs. *J Am Vet Med Assoc*. 2005;226:1851.

Crabtree AC, et al. Relationship between radiographic hilar lymphadenopathy and serologic titers for *Coccidioides* sp. in dogs in an endemic region. *Vet Radiol Ultrasound*. 2008;49:501.

Graupmann-Kuzma A, et al. Coccidioidomycosis in dogs and cats: a review. *J Am Anim Hosp Assoc*. 2008;44:226.

Grayzel SE, et al. Risk factors and spatial distribution of canine coccidioidomycosis in California, 2005-2013. *Transbound Emerg Dis*. 2017;64:1110.

Greene RT, et al. Coccidioidomycosis in 48 cats: a retrospective study (1984-1993). *J Vet Intern Med*. 1995;9:86.

Heinritz CK, et al. Subtotal pericardectomy and epicardial excision for treatment of coccidioidomycosis-induced effusive-constrictive pericarditis in dogs: 17 cases (1999-2003). *J Am Vet Med Assoc*. 2005;227:435.

Johnson LR, et al. Clinical, clinicopathologic, and radiographic findings in dogs with coccidioidomycosis: 24 cases (1995-2000). *J Am Vet Med Assoc*. 2003;222:461.

Kirsch EJ, et al. Evaluation of Coccidioides antigen detection in dogs with coccidioidomycosis. *Clin Vaccine Immunol*. 2012;19:343.

Luna-Isaac JA, et al. Genetic analysis of the endemic fungal pathogens *Coccidioides posadasii* and *Coccidioides immitis* in Mexico. *Med Mycol*. 2014;52:156.

Mawby DI, et al. Posaconazole pharmacokinetics in healthy cats after oral and intravenous administration. *J Vet Intern Med*. 2016;30:1703.

Mehrkens LR, et al. Clinicopathologic and histopathologic renal abnormalities in dogs with coccidioidomycosis. *J Vet Intern Med*. 2016;30:1667.

Ramírez-Romero R, et al. Coccidioidomycosis in biopsies with presumptive diagnosis of malignancy in dogs: report of three cases and comparative discussion of published reports. *Mycopathologia*. 2016;181:151.

Sakai MR, et al. Terbinafine pharmacokinetics after single dose oral administration in the dog. *Vet Dermatol*. 2011;22:528.

Shubitz LE, et al. Incidence of *Coccidioides infection* among dogs residing in a region in which the organism is endemic. *J Am Vet Med Assoc*. 2005;226:1846.

Shubitz LF. Comparative aspects of coccidioidomycosis in animals and humans. *Ann N Y Acad Sci*. 2007;1111:395.

Shubitz LF. Efficacy of Nikkomycin Z for respiratory coccidioidomycosis in naturally infected dogs. *Med Mycol*. 2013;51:747.

Simões DM, et al. Retrospective analysis of cutaneous lesions in 23 canine and 17 feline cases of coccidiodomycosis seen in Arizona, USA (2009-2015). *Vet Dermatol*. 2016;27:346.

Tofflemire K, Betbeze C. Three cases of feline ocular coccidioidomycosis: presentation, clinical features, diagnosis, and treatment. *Vet Ophthalmol*. 2010;13:166.

Cryptococcosis

Barrs VR, et al. Feline pyothorax: a retrospective study of 27 cases in Australia. *J Fel Med Surg*. 2005;7:211.

Bernhardt A, et al. Molecular identification of fungal pathogens in nodular skin lesions of cats. *Med Mycol*. 2015;53:132.

Byrnes EJ 3rd, et al. Cryptococcus gattii with bimorphic colony types in a dog in western Oregon: additional evidence for expansion of the Vancouver Island outbreak. *J Vet Diagn Invest*. 2009;21:133.

Duncan C, et al. Clinical characteristics and predictors of mortality for Cryptococcus gattii infection in dogs and cats of southwestern British Columbia. *Can Vet J*. 2006a;47:993.

Duncan CG, et al. Evaluation of risk factors for Cryptococcus gattii infection in dogs and cats. *J Am Vet Med Assoc*. 2006b;228:377.

Duncan C, et al. Follow-up study of dogs and cats with asymptomatic Cryptococcus gattii infection or nasal colonization. *Med Mycol*. 2005a;43:663.

Duncan C, et al. Sub-clinical infection and asymptomatic carriage of Cryptococcus gattii in dogs and cats during an outbreak of cryptococcosis. *Med Mycol*. 2005b;43:511.

Flatland B, et al. Clinical and serologic evaluation of cats with cryptococcosis. *J Am Vet Med Assoc*. 1996;209:1110.

Graves TK, et al. Diagnosis of systemic cryptococcosis by fecal cytology in a dog. *Vet Clin Pathol*. 2005;34:409.

Lester SJ, et al. Clinicopathologic features of an unusual outbreak of cryptococcosis in dogs, cats, ferrets, and a bird: 38 cases (January to July 2003). *J Am Vet Med Assoc*. 2004;225:1716.

Lester SJ, et al. Cryptococcosis: update and emergence of Cryptococcus gattii. *Vet Clin Pathol*. 2011;40:4.

Ma H, May RC. Virulence in Cryptococcus species. *Adv Appl Microbiol*. 2009;67:131.

MacDougall L, et al. Spread of Cryptococcus gattii in British Columbia, Canada, and detection in the Pacific Northwest, USA. *Emerg Infect Dis*. 2007;13:42.

McGill S, et al. Cryptococcosis in domestic animals in Western Australia: a retrospective study from 1995-2006. *Med Mycol*. 2009;47:625.

Malik R, et al. Combination chemotherapy of canine and feline cryptococcosis using subcutaneously administered amphotericin B. *Aust Vet J*. 1996;73:124.

Malk R, et al. Asymptomatic carriage of Cryptococcus neoformans in the nasal cavity of dogs and cats. *J Med Vet Mycol*. 1997; 35:27.

Myers A, et al. Atypical cutaneous cryptococcosis in four cats in the USA. *Vet Dermatol*. 2017;28:405.

Newman SJ, et al. Cryptococcal pyelonephritis in a dog. *J Am Vet Med Assoc*. 2003;222:180.

O'Brien CR, et al. Retrospective study of feline and canine cryptococcosis in Australia from 1981 to 2001: 195 cases. *Med Mycol*. 2004;42:449.

Okabayashi K, et al. Antifungal activity of itraconazole and voriconazole against clinical isolates obtained from animals with mycoses. *Nippon Ishinkin Gakkai Zasshi*. 2009;50:91.

Olsen GL, et al. Use of terbinafine in the treatment protocol of intestinal Cryptococcus neoformans in a dog. *J Am Anim Hosp Assoc*. 2012;48:216.

Quimby JM, et al. Adverse neurologic events associated with voriconazole use in three cats. *J Vet Intern Med*. 2010;24:647.

Singer LM, et al. Antifungal drug susceptibility and phylogenetic diversity among *Cryptococcus* isolates from dogs and cats in North America. *J Clin Microbiol*. 2014;52:2061.

Sykes JE, et al. Clinical signs, imaging features, neuropathology, and outcome in cats and dogs with central nervous system cryptococcosis from California. *J Vet Intern Med*. 2010;24:1427.

Sykes JE, et al. In vivo development of fluconazole resistance in serial Cryptococcus gattii isolates from a cat. *Med Mycol*. 2017;55: 396.

Tangeman L, et al. Abdominal cryptococcosis in two dogs: diagnosis and medical management. *J Am Anim Hosp Assoc*. 2015;51:107.

Tintelnot K, et al. Pitfalls in serological diagnosis of *Cryptococcus gattii* infections. *Med Mycol*. 2015;53:874.

Trivedi SR, et al. Clinical features and epidemiology of cryptococcosis in cats and dogs in California: 93 cases (1988-2010). *J Am Vet Med Assoc*. 2011a;239:357.

Trivedi SR, et al. Feline cryptococcosis: impact of current research on clinical management. *J Feline Med Surg*. 2011b;13:163.

Vorathavorn VI, et al. Cryptococcosis as an emerging systemic mycosis in dogs. *J Vet Emerg Crit Care (San Antonio)*. 2013;23:489.

Histoplasmosis

Bromel C, Sykes JE. Histoplasmosis in dogs and cats. *Clin Tech Small Animal Pract*. 2005;20:227.

Clinkenbeard KD, et al. Feline disseminated histoplasmosis. *Comp Cont Ed Pract Vet*. 1989;11:1223.

Cook AK, et al. Clinical evaluation of urine Histoplasma capsulatum antigen measurement in cats with suspected disseminated histoplasmosis. *J Feline Med Surg*. May 24, 2012;[Epub ahead of print].

Cunningham L, et al. Sensitivity and specificity of *Histoplasma* antigen detection by enzyme immunoassay. *J Am Anim Hosp Assoc*. 2015;51:306.

Hanzlicek AS, et al. Antigen concentrations as an indicator of clinical remission and disease relapse in cats with histoplasmosis. *J Vet Intern Med*. 2016;30:1065.

Hodges RD, et al. Itraconazole for the treatment of histoplasmosis in cats. *J Vet Intern Med*. 1994;8:409.

Jarchow A, et al. Antigenemia without antigenuria in a cat with histoplasmosis. *JFMS Open Rep*. 2015;1:2055116915618422.

Johnson LR, et al. Histoplasmosis infection in two cats from California. *J Am Anim Hosp Assoc*. 2004;40:165.

Kirsch EJ, et al. Evaluation of Coccidioides antigen detection in dogs with coccidioidomycosis. *Clin Vaccine Immunol*. 2012;19:343.

Lin Blache J, et al. Histoplasmosis. *Compend Contin Educ Vet*. 2011;33:E1.

Pearce J, et al. Management of bilateral uveitis in a *Toxoplasma gondii*-seropositive cat with histopathologic evidence of fungal panuveitis. *Vet Ophthalmol*. 2007;10:216.

Reinhart JM, et al. Feline histoplasmosis: fluconazole therapy and identification of potential sources of *Histoplasma* species exposure. *J Feline Med Surg*. 2012;14:841.

Renschler JS, et al. Reduced susceptibility to fluconazole in a cat with histoplasmosis. *JFMS Open Rep*. 2017;3:2055116917743364.

Schulman RL, et al. Use of corticosteroids for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by chronic histoplasmosis: 16 cases (1979-1997). *J Am Vet Med Assoc*. 1999;214:1345.

Smith KM, et al. Utility of antigen testing for the diagnosis of ocular histoplasmosis in four cats: a case series and literature review. *J Feline Med Surg*. 2017;19:1110.

Ward JI, et al. Acute histoplasmosis: clinical, epidemiologic and serologic finding of an outbreak associated with exposure to a fallen tree. *Am J Med*. 1979;66:587.

CHAPTER 98

Polysystemic Protozoal Infections



BABESIOSIS

Etiology and Epidemiology

Babesiosis in dogs is most commonly associated with *Babesia canis*, *B. rossi*, *B. vogeli*, *B. gibsoni,* and *B. conradae*. These protozoans parasitize red blood cells (RBCs) and are most frequently associated with development of anemia and associated signs. The worldwide distribution, vectors, and virulence of *Babesia* spp. varies. *B. rossi* is transmitted by *Haemaphysalis elliptica* (previously *leachi*) and is the most pathogenic; *B. canis* is transmitted by *Dermacentor* spp. and *Rhipicephalus sanguineus* and is moderately pathogenic; *B. vogeli* is the least pathogenic and is transmitted by *R. sanguineus*. *Babesia vogeli* is the most common *B. canis* subspecies infecting dogs in the United States. *B. gibsoni* is transmitted by *Haemaphysalis longicornis* and *Haemaphysalis bispinosa* in some countries; the vector in the United States is unknown, but *R. sanguineus* has been proposed. Presence of *B. gibsoni* DNA in blood of dogs in the United States has been associated with a history of a dog bite, especially by an American Pit Bull Terrier, suggesting that fighting is a route of transmission (Birkenheuer et al., 2003b). *Babesia conradae* induces hemolytic anemia in dogs in southern California; the vector is unknown but is suspected to be *R. sanguineous* (Kjemtrup et al., 2006). *Theleiria annae* and *B. vulpes* are *Babesia microti*-like organisms that has been detected in dogs of Europe and North America that may be transmitted by *Ixodes* spp. (Solano-Gallego and Baneth, 2011; Solano-Gallego et al., 2016).

In one survey in North America, *Babesia* spp. infections were detected in 29 states and Ontario (Birkenheuer et al., 2005). Other novel *Babesia* spp. that genetically vary considerably from other *B. canis* or *B. gibsoni* isolates have been described in the United States; however, the prevalence rate for these infections is unknown (Meinkoth et al., 2000; Birkenheuer et al., 2004a). *Babesia* spp. can also be transmitted by blood transfusions so screening is recommended for blood donors (Wardrop et al., 2016).

Babesiosis in cats appears to be less common than in dogs. Cats have been shown to be infected by *B. cati* (India), *B. felis* (Africa, southern Asia, Europe; Qatar), *B. herpailuri* (South America, Africa), *B. canis presentii* (Israel), *B. canis* (Europe), and *B. vogeli* (Brazil, Thailand, Qatar, United States). *Babesia vogeli* DNA was amplified from *Ctenocephalides felis* collected from cats in Jerusalem (Kamani et al., 2018). Whether this just reflects ingestion of *B. vogeli* in blood by the flea or whether the flea is involved in transmission of *B. vogeli* has not been determined.

After infection with pathogenic strains of *B. canis, B. vogeli*, or *B. gibsoni,* the incubation period varies from several days to several weeks. The degree of parasitemia varies by the organism studied but can be detected transiently in some dogs as soon as day 1. The organisms replicate intracellularly in RBCs, resulting in intravascular or extravascular hemolytic anemia. Immune-mediated reactions against the parasites or altered self-antigens worsen the hemolytic anemia and commonly result in a positive direct Coombs test. Activation of macrophages leads to fever and hepatosplenomegaly. Severe hypoxia occurs because of rapid breakdown of RBCs. Disseminated intravascular coagulation occurs in some infected dogs during acute infection.

The severity of disease depends on the species and strain of *Babesia* and the host's immune status; chronic, subclinical infection is common. Administration of glucocorticoids or splenectomy may reactivate chronic carriers into an acute disease state. Splenectomized experimentally infected dogs develop more severe *B. vogeli* clinical and laboratory manifestations of disease (Wang et al., 2018). Presence of coinfections such as *Bartonella* spp. may increase the pathogenic potential.

Clinical Features

The clinical features most commonly associated with *Babesia* spp. infecting dogs worldwide have been reviewed (Solano-Gallego and Baneth, 2011). In the United States, subclinical *Babesia* spp. infections are most common. Peracute or acute *Babesia* spp. infections result in anemia and fever, leading to pale mucous membranes, tachycardia, tachypnea, depression, anorexia, and weakness. Icterus, petechiae, and hepatosplenomegaly are present in some dogs depending on the stage of infection and the presence of disseminated intravascular coagulation. Severe anemia, disseminated

intravascular coagulation, metabolic acidosis, and renal disease are most common during acute infection and are generally most severe with *B. rossi* infections in South Africa. Tissue hypoxemia is important in the pathogenesis of disease in severely affected dogs. The main differential diagnoses for acute babesiosis is primary immune-mediated hemolytic anemia and immune-mediated thrombocytopenia. Chronically infected dogs commonly have weight loss and anorexia. Ascites, gastrointestinal signs, central nervous system (CNS) disease, edema, and clinical evidence of cardiopulmonary disease occur in some dogs with atypical infection. *Babesia canis* or *B. gibsoni* DNA has been amplified from the blood or effusion (one dog; *B. gibsoni*) of some dogs with pericardial effusion (Tabar et al., 2018).

Diagnosis

Spherocytic regenerative anemia, hyperbilirubinemia, bilirubinuria, hemoglobinuria, thrombocytopenia, metabolic acidosis, azotemia, polyclonal gammopathy, proteinuria, and cylindruria are common in dogs infected with pathogenic *Babesia* spp. Presence of the organism in RBCs detected by Wright or Giemsa stains on thin blood smears (see Chapter 91) can be used to support the diagnosis, but parasitemia can be intermittent, giving falsely negative results; capillary blood is the preferred source for blood smear evaluation. In the United States, *B. vogeli* is typically found as single or paired, piriform bodies measuring 2.5 × 4.5 µm, *B. gibsoni* is typically found as single annular bodies (more than one per cell are common) measuring 1.0 × 3.0 µm, and *B. conradae* is typically found as ring or ameboid bodies measuring 0.3 × 3 µm.

Serologic and polymerase chain reaction (PCR) assays are usually used in the diagnosis of babesiosis. Indirect fluorescent antibody tests for *B. vogeli* and *B. gibsoni* are available commercially in the United States. However, serologic cross-reactivity can exist, so antibody test results cannot be used to determine the infective species definitively. Demonstration of increasing titers over 2 to 3 weeks is consistent with recent or active infection. No standardization between laboratories exists, so suggested positive cutoff titers vary. False-negative serologic test results can occur in some dogs, particularly in those with peracute disease or concurrent immunosuppression. Many dogs are seropositive but clinically normal, so serology alone cannot be used to make a definitive diagnosis of clinical babesiosis.

Positive results in PCR assays performed on blood prove current infection and can be used to differentiate amongst the *Babesia* spp. However, as subclinical carriers exist, positive results do not always correlate with clinical illness. In addition, not all PCR assays performed in commercial laboratories are equivalent.

The acute phase proteins like serum amyloid A, haptoglobin, and paraoxonase-1 have been studied in small numbers of animals in an attempt to differentiate subclinical *Babesia* spp. carriers from those with clinical manifestations of disease. In naturally infected cats with *B. vogeli* infections, serum haptoglobin concentrations were increased and paraoxonase-1 concentrations were decreased when compared with healthy client-owned cats (Vilhena et al., 2017). These types of assays may prove to be of clinical benefit in the future.

Treatment

Supportive care, including blood transfusions, sodium bicarbonate therapy for acidosis, and fluid therapy, should be administered as indicated. A number of drugs, including diminazene aceturate, phenamidine, pentamidine isethionate, parvaquone, atovaquone, and niridazole, have also been used in an attempt to treat different *Babesia* spp. infections. In the United States, if clinical disease associated with *B. vogeli* is suspected, imidocarb diproprionate may be effective when administered (5-6.6 mg/kg subcutaneously or intramuscularly) twice, 14 days apart or (7.5 mg/kg subcutaneously or intramuscularly) once. Adverse effects include transient salivation, diarrhea, dyspnea, lacrimation, necrosis at the injection site, and depression.

Imidocarb as a single agent is not as effective for the treatment of *B. gibsoni* infection. In the United States, if clinical disease associated with *B. gibsoni* or *B. conradae* is suspected, azithromycin (10 mg/kg by mouth [PO] q24h for at least 10 days) and atovaquone (13.3 mg/kg PO q8h for at least 10 days) is currently recommended. However, this combination does not always result in elimination of infection, and *B. gibsoni* resistance to these drugs has been recognized (Birkenheuer et al., 2004b; Di Cicco et al., 2012; Jefferies et al., 2007). In Asia the combination of clindamycin, diminazene, and imidocarb was used successfully for the treatment of *B. gibsoni* infection in 11 of 13 dogs (Lin et al., 2012) and should be considered for atovaquone resistant strains (Baneth, 2018). Oral administration of a doxycycline-enrofloxacin-metronidazole combination led to clinical improvement in 85.7% of dogs infected with Asian strains of *B. gibsoni* (Lin and Huang, 2010). Although success rates with this protocol have not been reported with North American strains, it could be considered for use with infected dogs if atovaquone or diminazene are not immediately available or is ineffective. Because no drugs are known to eliminate infection consistently, treatment of healthy, seropositive dogs is unlikely to be of benefit.

Zoonotic Aspects and Prevention

No evidence currently exists to suggest that *Babesia* spp. infecting dogs and cats can cause human disease. However, some *Babesia* spp. that infect people *(B. microti)* are genetically similar to those infecting dogs, so ticks should be controlled if possible. Minimal cross-protection exists between species; a dog that has recovered from babesiosis may still become ill if infected with another species. Administration of immunosuppressive drugs or splenectomy should be avoided in previously infected dogs. Dog bites should be avoided. Vaccines against some *Babesia* spp. are available in some countries but not the United States. For blood donor programs, high-risk breeds (American Pit Bull Terrier; Greyhounds) or dogs from endemic areas should be screened for

Babesia spp. infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2016).

Babesia canis has been shown to be transmitted to 50% of experimentally infected dogs by *D. reticulatus* after 8 hours of feeding (Varloud et al., 2018). Thus acaricides that repel or have a rapid kill time are indicated in endemic areas. In one field study, an imidacloprid/flumethrin collar was 99.7% against tick infestation, and had an efficacy of 91.6% for the prevention of *A. platys* and 91.6% for *B. vogeli* (Dantas-Torres et al., 2013).

CYTAUXZOONOSIS

Etiology and Epidemiology

Cytauxzoon felis is a protozoal disease of cats in the southeastern, mid-Atlantic, and south-central United States that is often fatal when clinical illness occurs unless appropriate treatment is administered. *Cytauxzoon* spp. infection has also been documented in a number of other countries including Italy (Carli et al., 2012), France (Legroux et al., 2017), Spain (Díaz-Regañón et al., 2017), and Portugal (Alho et al., 2016). However, clinical illness has only occasionally been detected in the cats infected in Europe suggesting it is a different strain or variant of *C. felis* (Gallusová et al., 2016).

In contrast, isolates from domestic cats have been genetically similar between studies in the United States (Birkenheuer et al., 2006b). Bobcats are usually subclinically affected and may therefore be the natural host of the organism. Recent genetic analysis performed on *C. felis* from bobcats and pumas suggests multiple strains of the organism exist in wild felids (Shock et al., 2012). Domestic cats can be infected by different genotypes, alone or in combinations (Cohn et al., 2011). The organism can be passed experimentally from infected bobcats to domestic cats by *Dermacentor variabilis* (American dog tick) and *Amblyomma americanum* (Lone Star tick), but based on geographical distribution of infected cats, *A. americanum* is likely most important. Clinical illness occurs after an incubation period of 5 to 20 days. The majority of cases are diagnosed in April, May, and June (Reichard et al., 2008). After infection, schizonts and macroschizonts form in mononuclear phagocytes. The infected macrophages line the lumen of veins throughout the body. Merozoites released from the infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by the mononuclear infiltrates and from hemolytic anemia. Domestic cats occasionally survive infection, suggesting that variants that are less virulent to cats also exist in the United States. Perinatal infection did not occur from 2 queens to their 14 kittens (Lewis et al., 2012).

Clinical Features

Most cases of cytauxzoonosis are in cats allowed to go outdoors. Fever, anorexia, dyspnea, depression, icterus, pale mucous membranes, and death are the most common clinical findings. A primary differential diagnosis is hemoplasmosis. Ticks are rarely identified on affected cats.

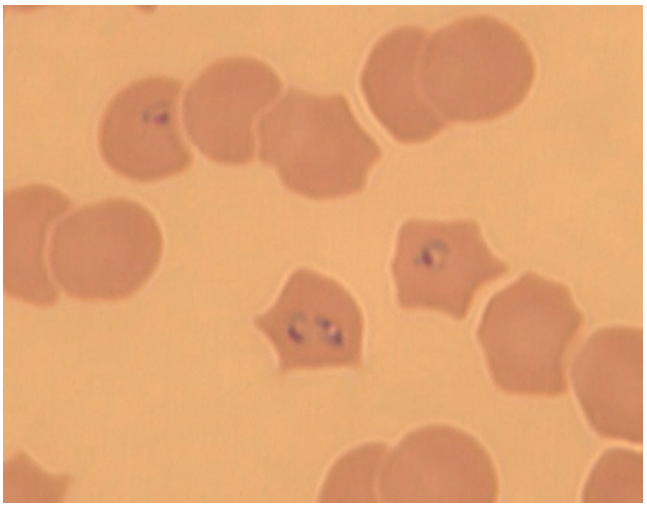


FIG 98.1
Cytauxzoon felis in the red blood cells of a cat. (Courtesy Dr. Terry M. Curtis, Gainesville, FL.)

Diagnosis

Regenerative anemia, pancytopenia, and neutrophilic leukocytosis are the most common hematologic findings; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, hyperbilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears (Fig. 98.1) stained with Wright or Giemsa stains (see Chapter 91). Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates. The organism is easily identified on histopathologic evaluation of most organs. Serologic testing is not commercially available. PCR can be used to amplify organism DNA from blood, and positive test results prove current infection.

Treatment

Supportive care includes fluid therapy and blood transfusion administered as indicated. Recently, a prospective study compared survival in cats treated with atovaquone at 15 mg/kg PO q8h and azithromycin at 10 mg/kg PO q24h to cats treated with imidocarb at 3.5 mg/kg IM (Cohn et al., 2011). The survival rates for the atovaquone/azithromycin combination and imidocarb were 60% and 26%, respectively. Diminazene administered at 2 mg/kg IM twice, 7 days apart was used in five cats that survived infection (Greene et al., 1999). However, some cases fail treatment with diminazene, and side-effects including monoparesis at the injection site, signs of nausea, and potential hepatotoxicity can occur (Lewis et al., 2014).

Zoonotic Aspects and Prevention

Cytauxzoon felis is not known to be zoonotic. The disease can only be prevented by avoiding exposure.

Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity. *Cytauxzoon felis* has been shown to be transmitted by *A. americanum* between 36 and 48 hours after feeding (Thomas et al., 2018). An imidacloprid/flumethrin collar was effective at blocking transmission by *A. americanum* in one experimental study (Reichard et al., 2013). Known *C. felis*-positive cats should not be used as blood donors, and cats to be used as blood donors in endemic areas should be shown negative by PCR assay (Wardrop et al., 2016).

HEPATOZOONOSIS

Etiology and Epidemiology

Hepatozoonosis in dogs is caused by the protozoal agents *Hepatozoon canis* and *Hepatozoon americanum.* In North America, *H. americanum* predominates, is transmitted by *Amblyomma maculatum* (Gulf Coast tick), and is most common in the Texas Gulf Coast, Mississippi, Alabama, Georgia, Florida, Louisiana, and Oklahoma. In Africa, southern Europe, and Asia, *H. canis* predominates and is transmitted by *R. sanguineus* (brown dog tick). In South America, *H. canis* is transmitted by *R. sanguineus* and *A. ovale*. *Hepatozoon canis* can also be transmitted transplacentally. Cystozoites are an infectious stage of *Hepatozoon* spp. that form in the tissue of paratenic hosts like rabbits, mice, and some rats and can initiate infection in dogs after predation (Johnson et al., 2009a,b). In one study of 614 dogs with suspected hepatozoonosis in the United States, the prevalence rates for *H. americanum, H. canis,* or both were 27.2%, 2.3%, and 2.3%, respectively (Li et al., 2008).

At least three *Hepatozoon* species can be detected in the blood of cats in Europe (Díaz-Regañón et al., 2017; Giannelli et al., 2017), and the organism can be amplified from ticks removed from cats (Duplan et al., 2018). The routes of transmission and clinical disease associations are currently unclear, but the cats are commonly co-infected with feline leukemia virus or feline immunodeficiency virus.

Vertebrate hosts develop macrogametes and microgametes in neutrophils and monocytes after infection by a *Hepatozoon* spp. The tick ingests the organism during a blood meal and oocysts develop. After a dog ingests an infected tick, sporozoites are released and infect mononuclear phagocytes and endothelial cells of the spleen, liver, muscle, lungs, and bone marrow, and ultimately form cysts containing macromeronts and micromeronts. Micromeronts develop into micromerozoites, which infect leukocytes and develop into gamonts. Tissue phases induce pyogranulomatous inflammation, resulting in clinical disease. Glomerulonephritis or amyloidosis may occur as a result of chronic inflammation and immune complex disease. Infected dogs can serve as a source of infection for ticks for months to years (Ewing et al., 2002).

Clinical Features

Although subclinical infection is common, both *H. americanum* and *H. canis* can be primary pathogens, resulting in clinical illness without concurrent immune deficiency. Clinically affected dogs have been in all age groups, but disease is most commonly recognized in puppies. Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, meningoencephalomyelitis, and bloody diarrhea occur in some dogs. Cutaneous lesions consisting of a pruritic swelling were described in one dog (Little and Baneth, 2011). Clinical signs can be intermittent and recurrent.

Diagnosis

Neutrophilic leukocytosis (20,000-200,000 cells/μL) with a left shift is the most common hematologic finding for dogs infected with *H. americanum*. Thrombocytopenia is unusual unless co-infection with *Ehrlichia canis*, *Anaplasma* spp., or *Leishmania* spp occurs. Normocytic, normochromic, nonregenerative anemia is common and is likely from chronic inflammation. Increased activity of alkaline phosphatase but not creatine kinase occurs in *H. americanum*–infected dogs. Hypoalbuminemia, hypoglycemia, and, rarely, polyclonal gammopathy occur in some dogs. Periosteal reactions from the inflammatory response directed at tissue phases in muscle can occur in any bone except the skull, are most common in young dogs, do not occur in every case, and are not pathognomonic for hepatozoonosis. Definitive diagnosis is based on identification of gamonts in neutrophils or monocytes in Giemsa or Leishman stained blood smears or by demonstration of the organism in muscle biopsy sections. However, the organisms can be detected in the blood of healthy dogs and cats. Serologic tests are available in some countries and because the tissue phases are not cleared, positive test results suggest that the dog is infected. However, because subclinical infection can occur, presence of serum antibodies does not prove the clinical manifestations are from *Hepatozoon* spp. infection. PCR assays are now available in some laboratories, and positive results confirm infection (Li et al., 2008; Modrý et al., 2017). Quantitative PCR assay results may be used to follow treatment responses in the future.

Treatment

No therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues. However, clinical disease resolves rapidly with several drug protocols. For treatment of *H. americanum,* the combination of trimethoprim-sulfadiazine (15 mg/kg PO q12h), pyrimethamine (0.25 mg/kg PO q24h), and clindamycin (10 mg/kg PO q8h) for 14 days is highly successful in the acute stage (Macintire et al., 2001). Use of decoquinate (10-20 mg/kg q12h) with food lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate (5-6 mg/kg intramuscularly or subcutaneously) administered once or twice 14 days apart is the drug of

choice for treatment of *H. canis* and may also be effective for *H. americanum*. A recent study showed administration of ponazuril as a single therapeutic agent did not clear the infection (Allen et al., 2010). Administration of nonsteroidal antiinflammatory agents may lessen discomfort for some dogs. Administration of doxycycline or oxytetracycline has been used in some cats in Europe suspected as having hepatozoonosis (Lloret et al., 2015).

Zoonotic Aspects and Prevention

No evidence exists for zoonotic transfer of *H. americanum* or *H. canis* from infected dogs to people. Tick control is the best form of prevention. Glucocorticoid administration should be avoided because it may exacerbate clinical disease. However, prednisone was used in the management of one case with meningoencephalomyelitis without obvious exacerbation of infection (Marchetti et al., 2009).

LEISHMANIOSIS

Etiology and Epidemiology

Leishmania spp. are flagellates that cause cutaneous, mucocutaneous, and visceral diseases in dogs, human beings, and other mammals. Rodents and dogs are primary reservoirs of *Leishmania* spp., people and cats are probably incidental hosts, and sandflies are the vector in most endemic regions other than the United States. Cats are also commonly exposed in areas with endemic canine infection. In one study, sandflies could be infected by feeding on a naturally infected cat, suggesting this species should be further evaluated as a potential reservoir (Maroli et al., 2007).

Leishmaniosis was considered unimportant in the United States until recently, with cases only reported occasionally. In 1999, *Leishmania infantum* infection was confirmed in multiple dogs in a Foxhound kennel in New York State (Gaskin et al., 2002). Further investigation of more than 12,000 Foxhounds and other canids documented *L. infantum* infection in 18 states and two Canadian provinces (Duprey et al., 2006). Infection of canids other than Foxhounds appears to be uncommon in North America. In the United States, *Leishmania* spp. appear to be transmitted vertically (Freeman et al., 2010).

In other countries, flagellated promastigotes develop in the sandfly and are injected into the vertebrate host when the sandfly feeds. Promastigotes are engulfed by macrophages and disseminate through the body. After an incubation period of 1 month to 7 years, amastigotes (nonflagellate) form and cutaneous lesions develop; sandflies are infected during feeding. In Foxhounds in the United States transmission appears to be primarily from dog to dog (Duprey et al., 2006). Transmission by fighting, shared needles, blood transfusions, breeding, and vertical transmission can occur (Boggiatto et al., 2011; Duprey et al., 2006; de Freitas et al., 2006). *Leishmania infantum* DNA has been amplified from *Rhipicephalus sanguineous* ticks collected off naturally infected dogs; further study of this potential route of transmission is necessary (Solano-Gallego et al., 2012). The intracellular organism induces extreme immune responses; polyclonal gammopathies (and occasionally monoclonal); proliferation of macrophages, histiocytes, plasma cells, and lymphocytes in lymphoreticular organs; and immune complex formation resulting in glomerulonephritis and polyarthritis are common. Co-infections like Ehrlichia canis may potentiate the development of clinical manifestations of disease (Attipa et al., 2018).

Cats have generally been believed to be more resistant that dogs to leishmaniosis. However, when illness occurs, the syndrome usually includes cutaneous lesions (Pennisi et al., 2015).

Clinical Features

Dogs generally develop visceral leishmaniosis. A subclinical phase of infection may persist for months or years. Weight loss in the face of a normal to increased appetite, polyuria, polydipsia, muscle wasting, depression, vomiting, diarrhea, cough, petechiae, ecchymosis, epistaxis, sneezing, and melena are common presenting complaints. Splenomegaly, lymphadenopathy, facial alopecia, fever, rhinitis, dermatitis, increased lung sounds, icterus, swollen painful joints, uveitis, and conjunctivitis are commonly identified on physical examination. Cutaneous lesions are characterized by hyperkeratosis, scaling, thickening, mucocutaneous ulcers, and intradermal nodules on the muzzle, pinnae, ears, and foot pads (Fig. 98.2). Bone lesions are detected in some dogs. Infertility and prostatitis were detected in a chronically infected dog (Mir et al., 2012). Most dogs die or are euthanized as a consequence of chronic kidney disease. Cats are usually subclinically infected; when infection occurs, the major clinical manifestations are cutaneous. The skin lesions are usually nodular and ulcerative on the pinnae and less commonly on the muzzle and periorbital skin (Navarro et al., 2010; Trainor et al., 2010). Histopathology reveals



FIG 98.2
Characteristic *Leishmania* spp.–associated skin lesion on the foot of a dog in Spain. (Courtesy Dr. Arturo Font, Barcelona, Spain.)

granulomatous inflammation with numerous amastigotes within macrophages.

Diagnosis

The principal clinicopathologic abnormalities include hyperglobulinemia, hypoalbuminemia, proteinuria, increased liver enzyme activities, anemia, thrombocytopenia, azotemia, lymphopenia, and leukocytosis with left shift. The hyperglobulinemia is usually polyclonal, but an immunoglobulin G (IgG) monoclonal gammopathy has been reported. Neutrophilic polyarthritis occurs in some dogs as a manifestation of a type III hypersensitivity reaction. Demonstration of amastigotes (2.5-5.0 μm × 1.5-2.0 μm) in lymph node aspirates, bone marrow aspirates, or skin imprints stained with Wright or Giemsa stain gives a definitive diagnosis (Fig. 98.3). The organism can also be identified by histopathologic or immunoperoxidase evaluation of skin or organ biopsy, culture, inoculation of hamsters, or PCR. Antibodies against *Leishmania* can be detected in serum by a variety of techniques and point care assays are available in some countries. In general, IgG titers develop 14 to 28 days after infection and decline 45 to 80 days after treatment. Serologic cross-reactivity occurs between *Trypanosoma cruzi* and *Leishmania,* so positive antibody test results do not always correlate with *Leishmania* infection. Use of vaccines against *Leishmania* spp. in some countries has complicated the diagnosis of leishmaniosis by use of antibody tests in vaccinated dogs (Solano-Gallego et al., 2017). Because dogs are unlikely to eliminate infection spontaneously, most true-positive antibody test dogs are currently infected. PCR can be performed on ethylenediamine tetraacetic acid anticoagulated blood, bone marrow, spleen, or lymph node aspirates. Real-time PCR assays can be used to monitor response to therapy (Francino et al., 2006).

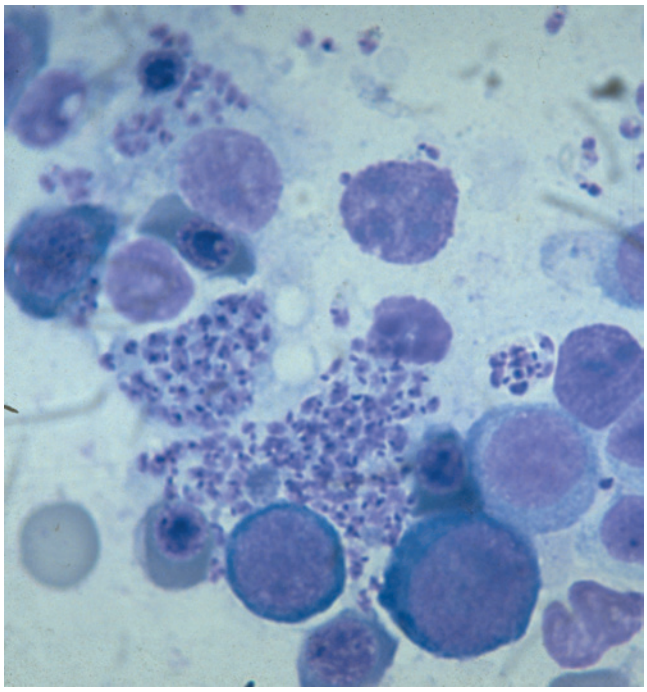


FIG 98.3
Impression smear of a lymph node of a *Leishmania* spp.–infected dog showing intracellular amastigotes. (Courtesy Dr. Arturo Font, Barcelona, Spain.)

Treatment

The management of canine leishmaniosis can be completed and the LeishVet group has published recommendations (Solano-Gallego et al., 2012). Dogs that are seropositive, cytologically positive, or PCR-positive with clinical disease manifestations consistent with leishmaniosis should be treated. Although clinical signs of disease often improve with drug administration, the prognosis for visceral leishmaniosis in dogs is variable; most cases are recurrent. No drug or drug combination has been used to clear *Leishmania* from the body successfully. The combination of antimony compounds and allopurinol (15 mg/kg PO q12h) was superior to treatment with either drug alone (Denerolle et al., 1999), but even long-term therapy does not always eliminate infection (Manna et al., 2008). In one study of dogs treated with meglumine antimoniate (50 mg/kg subcutaneously q12h) until clinical and clinicopathologic abnormalities resolved and allopurinol (15 mg/kg PO q12h administered for 6 months), relapses were not reported in 1 year of monitoring, and the disease-free interval for some dogs was as long as 65 months (Paradies et al., 2012). Miltefosine and domperidone are available in some countries. Miltefosine when given with allopurinol (Miró et al., 2009) and domperidone given as a single agent also have shown therapeutic efficacy for canine leishmaniosis (Gómez-Ochoa et al., 2009). Because antimony drugs are not available in the United States, infected dogs should be started on allopurinol therapy initially. In one study, marbofloxacin was effective in vitro and may be considered for the treatment of infected dogs if other drugs are not available (Vouldoukis et al., 2006). Liposomal or lipid-emulsified amphotericin B at varying doses (0.8-3.3 mg/kg IV for varying numbers of treatments) has been prescribed with good clinical results, but recurrences can still occur (Cortadellas, 2003). Dogs with chronic kidney disease have a poor prognosis, but one study showed administration of allopurinol to be beneficial (Plevraki et al., 2006). In cats, long-term administration of allopurinol at 10-20 mg/kg PO q12h or q24h can be clinically beneficial (Pennisi et al., 2015).

Zoonotic Aspects and Prevention

Reviews of control measures for leishmaniosis are available (Solano-Gallego et al., 2011; Miro et al., 2017). The primary zoonotic risk for canine leishmaniosis is from dogs acting as a reservoir host for the organism. Direct contact with amastigotes in draining lesions is unlikely to result in human infection. None of the 185 persons with potential exposure to infected Foxhounds had evidence of infection (Duprey et al., 2006). Avoidance of infected sandflies is the primary means of prevention in endemic areas. In endemic areas, animals should stay indoors during night hours and breeding places of sandflies should be controlled. Use of 10%

imidacloprid/50% permethrin may lessen transmission in sandfly-endemic areas (Otranto et al., 2007). In one study, the authors suggested that 65% permethrin applied every 2 to 3 weeks would be efficacious (Molina et al., 2012). Many vaccines have been studied and are available for use with dogs in some countries (Dantas-Torres, 2006; Fernández Cotrina, et al., 2018; Palatnik-de-Sousa, 2012). For blood donor programs, high-risk breeds (e.g., Foxhounds) or dogs from endemic areas should be screened for *Leishmania* spp. infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2016).

NEOSPOROSIS

Etiology and Epidemiology

Neospora caninum is a coccidian previously confused with *Toxoplasma gondii* because of similar morphology. The sexual cycle is completed in the gastrointestinal tract of canids and results in the passage of oocysts in feces. Oocyst shedding can continue for several months in some dogs (McGarry et al., 2003). Sporozoites develop in oocysts within 24 hours of passage. Tachyzoites (rapidly dividing stage) and tissue cysts containing hundreds of bradyzoites (slowly dividing stage) are the other two life stages. In one study, dogs fed sporulated oocysts were infected and seroconverted but did not shed oocysts (Bandini et al., 2011). Dogs are infected by ingestion of bradyzoites but not tachyzoites. Infection has been documented after ingestion of a number of different infected bovine tissues. Dogs can also become infected from ingesting intermediate hosts such as white-tailed deer, and the organism has been detected in the tissues of free-ranging chickens (Gondim et al., 2004; Gonçalves et al., 2012). Thus free-roaming dogs appear to be at increased risk of infection. Transplacental infection has been well documented; dams that give birth to infected offspring can repeat transplacental infection during subsequent pregnancies. Because repeated transplacental infections occur, puppies from a bitch who previously birthed infected puppies are at an increased risk. Canine neosporosis has been reported in many countries around the world. Seroprevalence of infection has varied from 0% to 100% depending on the country and lifestyle of the dog (Dubey et al., 2007a). In one paper from Australia, the canine prevalence rate increased over a 20-year period (Sloan et al., 2017). Oocysts are rarely reported in fecal surveys; in one study of 24,677 dog samples, oocysts consistent with *N. caninum* were detected in 0.3% (Barutzki and Schaper, 2011). DNA of *N. caninum* has been amplified from feces of coyotes as well (Klein et al., 2018). The pathogenesis of the disease is primarily related to the intracellular replication of tachyzoites. Although organism replication occurs in many tissues, including the lungs, in dogs clinical illness is primarily neuromuscular. Administration of glucocorticoids may activate bradyzoites in tissue cysts, resulting in clinical illness.

Encephalomyelitis and myositis develop in experimentally infected kittens, and seropositive, naturally exposed cats have been detected (Bresciani et al., 2007), but clinical disease in naturally infected cats has not been reported. *N. caninum* seropositive, nondomestic felids also have been reported (Spencer et al., 2003; Sedlák et al., 2014). *Neospora caninum* infection can lead to great economic losses as a result of abortion in cattle. Strategies for control of the infection in cattle have been reviewed (Dubey et al., 2007a).

Clinical Features

Ascending paralysis with hyperextension of the hindlimbs in congenitally infected puppies is the most common clinical manifestation of the disease. Muscle atrophy occurs in many cases. Polymyositis and multifocal CNS disease can occur alone or in combination. Cerebral ataxia and atrophy is a recently recognized clinical syndrome associated with neosporosis (Garosi et al., 2010). Clinical signs can be evident soon after birth or may be delayed for several weeks. Neonatal death is common. Although disease tends to be most severe in congenitally infected puppies, dogs as old as 15 years have been clinically affected. In one dog presented primarily for respiratory disease, cough was the principal sign. Myocarditis, dysphagia, ulcerative dermatitis, pneumonia, and hepatitis occur in some dogs. Whether clinical disease in older dogs is from acute, primary infection or exacerbation of chronic infection is unknown. Administration of glucocorticoids with or without cyclosporine may activate bradyzoites in tissue cysts, resulting in clinical illness. Disease is caused by intracellular replication of *N. caninum* tachyzoites. Infection of CNS structures generally causes mononuclear cell infiltrates, which suggests an immune-mediated component to the pathogenesis of disease. Intact tissue cysts in neural structures are generally not associated with inflammation, but ruptured tissue cysts induce inflammation. Untreated disease generally results in death.

Diagnosis

Hematologic and biochemical findings are nonspecific. Myositis commonly results in increased creatine kinase and aspartate aminotransferase activities. Cerebrospinal fluid (CSF) abnormalities include increased protein concentration (20-50 mg/dL) and a mild, mixed pleocytosis (10-50 cells/μL) consisting of monocytes, lymphocytes, neutrophils, and, rarely, eosinophils. Interstitial and alveolar patterns can be noted on thoracic radiographs. Magnetic resonance imaging of seven dogs with cerebellar disease showed marked bilaterally symmetric cerebellar atrophy surrounded by an area T2-weighted hyperintense and T1-weighted hypointense signal (Garosi et al., 2010).

Definitive diagnosis is based on demonstration of the organism in CSF or tissues. Tachyzoites are rarely identified on cytologic examination of CSF, imprints of dermatologic lesions, and bronchoalveolar lavage. Mixed inflammation with neutrophils, lymphocytes, eosinophils, plasma cells, macrophages, and tachyzoites was noted on transthoracic aspirate of one dog with lung disease. *N. caninum* tissue cysts have a wall thicker than 1 μm; *T. gondii* tissue cysts have a wall thinner than 1 μm (Fig. 98.4). Oocysts can be detected

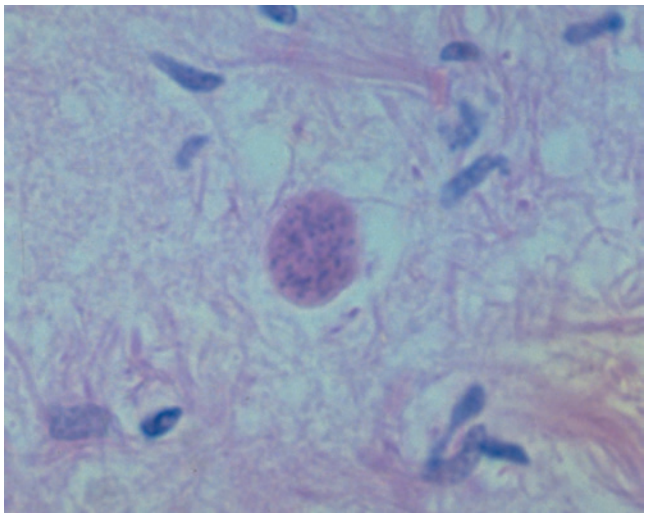


FIG 98.4
Neospora caninum cyst filled with bradyzoites in canine central nervous system tissue.

in feces by microscopic examination after flotation or by PCR. The organism can be differentiated from *T. gondii* by electron microscopy, immunohistochemistry, and PCR. A multiplex PCR assay that detects both *T. gondii* and *N. caninum* for use with tissues or CSF has been reported (Schatzerg et al., 2003). In a group of dogs with cerebellar disease related to *N. caninum* infection, four of five dogs tested were positive for DNA of the organism by PCR assay performed on CSF.

A presumptive diagnosis of neosporosis can be made by combining appropriate clinical signs of disease and positive serology or presence of antibodies in CSF with the exclusion of other etiologies inducing similar clinical syndromes, particularly *T. gondii*. Serologic cross-reactivity between *T. gondii* and *N. caninum* exist in some assays. IgG antibody titers of at least 1:200 have been detected in most dogs with clinical neosporosis; minimal serologic cross-reactivity occurs with *T. gondii* at titers of 1:50 or higher when using the immunofluorescent assay test.

Treatment

Although many dogs with neosporosis die, some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine; sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine; or clindamycin alone. While different doses of have recommended by different authors, administration of trimethoprim-sulfadiazine (15 mg/kg PO q12h) with pyrimethamine (1 mg/kg PO q24h) for 4 weeks or clindamycin (10 mg/kg PO q8h) for 4 weeks has been used frequently treatment of canine neosporosis. If improvement is noted, treatment should be continued. A 7-week-old Irish Wolfhound with *N. caninum*–associated myositis had significant clinical improvement after 18 weeks of treatment with clindamycin (Crookshanks et al., 2007). In one recent study of naturally infected Beagle puppies, administration of clindamycin alone (75 mg/puppy at 9 weeks of age PO q12h [dose doubled at 13 weeks] for 6 months) lessened clinical signs of disease but did not eliminate the infection (Dubey et al., 2007b). Four of six dogs with cerebellar disease associated with *N. caninum* infection treated with different combinations of clindamycin, trimethoprim, sulfadiazine, and pyrimethamine had a positive response (Garosi et al., 2010). Ponazuril is a cidal drug and may prove to be effective for the treatment of neosporosis at 20 mg/kg, PO, daily (Silva et al., 2016). Treatment of clinically affected dogs should be initiated before the development of extensor rigidity, if possible. The prognosis for dogs presented with severe neurologic involvement is grave.

Zoonotic Aspects and Prevention

Neospora caninum antibodies have been detected in people, but in one study no link was found to repeated abortion (Petersen et al., 1999). In addition, the organism has not been isolated from human tissues, so the zoonotic potential is still unproven. An epidemiologic link has been shown between dogs and cattle; efforts should be made to lessen dog fecal contamination of livestock feed, and dogs should not be allowed to ingest bovine placentas. Consuming raw meat is a risk factor for dogs and should be avoided (Reichel et al., 2007). Hunting behavior of dogs should be restricted if possible. Bitches that whelp clinically affected puppies should not be bred. Glucocorticoids should not be administered to seropositive animals, if possible, because a potential exists for activation of infection.

FELINE TOXOPLASMOSIS

Etiology and Epidemiology

Toxoplasma gondii is one of the most prevalent parasites infecting warm-blooded vertebrates. Only cats complete the coccidian life cycle and pass environmentally resistant oocysts in feces. Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity. Tachyzoites disseminate in blood or lymph during active infection and replicate rapidly intracellularly until the cell is destroyed. Bradyzoites are slowly dividing, persistent tissue stages that form in the extraintestinal tissues of infected hosts as immune responses attenuate tachyzoite replication. Tissue cysts form readily in the CNS, muscles, and visceral organs. Bradyzoites may persist in tissues for the life of the host. There are different genotypes of *T. gondii,* which may vary in pathogenic potential, partially explaining why even some immunocompetent cats can become ill.

Infection of warm-blooded vertebrates occurs after ingestion of any of the three life stages of the organism or transplacentally. Most cats are not coprophagic and so are infected most commonly by ingesting *T. gondii* bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants

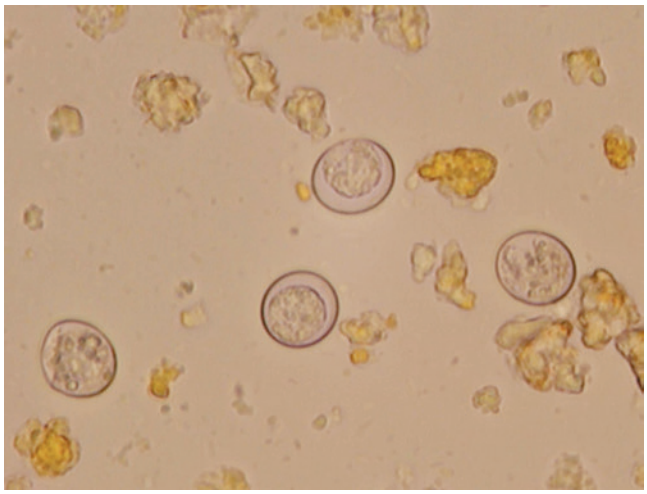


FIG 98.5
Unstained *Toxoplasma gondii* unsporulated oocysts. The oocysts are 10 × 12 µm.

(Fig. 98.5). Results of a research study confirm that the *T. gondii* oocyst-shedding prepatent period is stage-dependent (ingestion of bradyzoites has a shorted prepatent period than ingestion of sporozoites) and not dose-dependent (Dubey et al., 2006). In addition, transmission of *T. gondii* is most efficient when cats consume tissue cysts (carnivorism) and when intermediate hosts consume oocysts (fecal-oral transmission). *Toxoplasma gondii* infection of rodents changes the behavior of the prey species, making it less averse to cats, potentially increasing the likelihood the definitive host (felid) will become infected and potentiate the sexual phase of the organism (Vyas et al., 2007). A number of studies have now evaluated whether *T. gondii* infection is associated with behavioral abnormalities in people with mixed results (see Chapter 99). In one study of clinically ill cats in the United States, *T. gondii* antibodies were detected in 31.6% of the 12,628 cats tested (Vollaire et al., 2005) so cats are commonly exposed to the agent, likely from predation in most.

Clinical Features

Approximately 10% to 20% of experimentally inoculated cats develop self-limiting, small-bowel diarrhea for 1 to 2 weeks after primary oral inoculation with *T. gondii* tissue cysts; this is presumed to be from enteroepithelial replication of the organism. However, detection of *T. gondii* oocysts in feces is rarely reported in studies of naturally exposed cats with or without diarrhea because of the short shedding period. For example, in a study in Germany the oocyst-shedding rate was estimated at 0.8% in 8640 cats (Barutzki and Schaper, 2011). *Toxoplasma gondii* enteroepithelial stages were found in intestinal tissues from two cats with inflammatory bowel disease. Positive response to anti-*Toxoplasma* drugs in these two cats suggests that toxoplasmosis may occasionally induce inflammatory bowel disease.

Fatal extraintestinal toxoplasmosis can develop from overwhelming intracellular replication of tachyzoites after primary infection; hepatic, pulmonary, CNS, and pancreatic



FIG 98.6
Punctate chorioretinitis caused by *Toxoplasma gondii* in an experimentally inoculated cat.

tissues are commonly involved. Kittens infected by the transplacental or transmammary routes develop the most severe signs of extraintestinal toxoplasmosis and generally die of pulmonary or hepatic disease. Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, and fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea.

If a host with chronic toxoplasmosis is immunosuppressed, bradyzoites in tissue cysts can replicate rapidly and disseminate again as tachyzoites; this is common in people with acquired immunodeficiency syndrome (AIDS). Disseminated toxoplasmosis has been documented in cats concurrently infected with feline leukemia, feline immunodeficiency, or feline infectious peritonitis viruses, as well as after cyclosporine administration for skin disease or after renal transplantation (Barrs et al; 2006). The acute respiratory distress syndrome was recently documented in a cat with disseminated toxoplasmosis (Evans et al., 2017).

Sublethal, chronic toxoplasmosis occurs in some cats. *Toxoplasma gondii* infection should be on the list of differential diagnoses for cats with anterior or posterior uveitis, cutaneous lesions, fever, muscle hyperesthesia, myocarditis with arrhythmias, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, or pancreatitis (Fig. 98.6). Cutaneous toxoplasmosis is characterised by hyperemic nodules that may or may not be ulcerated. On the basis of results of *T. gondii*–specific aqueous humor antibody and PCR studies, toxoplasmosis appears to be a common infectious cause of uveitis in cats. Distal polyneuropathies can occur in dogs or cats (Mari et al., 2016).

Kittens infected transplacentally or lactationally commonly develop ocular disease. Immune complex formation and deposition in tissues and delayed hypersensitivity reactions may be involved in chronic, sublethal clinical toxoplasmosis. Although chronic tissue infection and immune complex formation are common, there was no association between *T. gondii* antibodies and chronic kidney disease in one study (Hsu et al., 2011). None of the anti-*Toxoplasma* drugs totally clear the body of the organism, so recurrence of disease may occur in some cats, and serum IgG titers rarely become negative.

Diagnosis

Cats with clinical toxoplasmosis can have a variety of clinicopathologic and radiographic abnormalities, but none documents the disease. Nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, and bilirubinuria, as well as increases in serum protein and bilirubin concentrations, creatinine kinase, alanine aminotransferase, alkaline phosphatase, and lipase activities occur in some cats. Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns or pleural effusion. Mass lesions may be detected on computed tomography or magnetic resonance imaging examinations. CSF protein concentrations and cell counts are often higher than normal. The predominant white blood cells in CSF are small mononuclear cells, but neutrophils are also commonly found.

The antemortem definitive diagnosis of feline toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon, particularly in association with sublethal disease. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF. Visualization of 10×12 µm oocysts in feces in cats with diarrhea suggests toxoplasmosis but is not definitive because *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts.

Toxoplasma gondii–specific antibodies (IgM, IgG, IgA), antigens, and immune complexes can be detected in the serum of normal cats, as well as in those with clinical signs of disease, so antemortem diagnosis of clinical toxoplasmosis is impossible on the basis of these tests alone. Of the serum tests, IgM correlates the best with clinical feline toxoplasmosis because this antibody class is rarely detected in serum of healthy cats. The antemortem diagnosis of clinical toxoplasmosis can be tentatively based on the combination of the following:

- Demonstration of antibodies in serum, which documents exposure to *T. gondii*
- Demonstration of an IgM titer above 1:64 or a fourfold or greater increase in IgG titer, which suggests recent or active infection
- Clinical signs of disease referable to toxoplasmosis
- Exclusion of other common causes for the clinical syndrome
- Positive response to appropriate treatment

Some cats with clinical toxoplasmosis will have reached their maximal IgG titer or have undergone antibody class shift from IgM to IgG by the time they are serologically evaluated, so the failure to document an increasing IgG titer or a positive IgM titer does not exclude the diagnosis of clinical toxoplasmosis. Because some healthy cats have extremely high serum antibody titers and some clinically ill cats have low serum antibody titers, the magnitude of titer is relatively unimportant in the clinical diagnosis of toxoplasmosis. Because the organism cannot be cleared from the body, most cats will be antibody positive for life, so repeating serum antibody titers after the clinical disease has resolved is not necessary.

The combination of aqueous humor or CSF *T. gondii*–specific antibody detection and *T. gondii* DNA amplification by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis (www.dlab.colostate.edu; Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins). For example, in one study of six cats with uveitis, five had *T. gondii* DNA in blood or aqueous humor but were seronegative for *T. gondii* antibodies (Powell et al., 2010). Whereas *T. gondii*–specific IgA, IgG, and *T. gondii* DNA can be detected in aqueous humor and CSF of both normal and clinically ill cats, *T. gondii*–specific IgM has only been detected in the aqueous humor or CSF of clinically ill cats and therefore may be the best indicator of clinical disease. Because *T. gondii* DNA can be amplified from the blood of healthy cats, positive PCR results do not always correlate to clinical disease (Burney et al., 1999).

Treatment

Supportive care should be instituted as needed. Clindamycin hydrochloride (10-12 mg/kg PO q12h) administered for 4 weeks has been used most frequently by the author for the treatment of clinical feline toxoplasmosis. Azithromycin (10.0 mg/kg PO q24h) has been used successfully in a limited number of cats, but the optimal duration of therapy is unknown. Ponazuril was apparently successful for the treatment of *T. gondii* infection in a dog and also has been shown to have anti-*T. gondii* effects in a mouse model (Mitchell et al., 2004). Ponazuril is known to be safe in cats for the treatment of *Isospora* spp. infection and should be studied further for use in affected cats. Trimethoprim-sulfonamide combination has been used at 15 mg/kg PO q12h for 4 weeks in some cats with toxoplasmosis but is not tolerated by many cats. Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in vomiting or inappetance and can cause anemia in cats. Cats with systemic clinical signs of toxoplasmosis, such as fever or muscle pain combined with uveitis, should be treated with anti-*Toxoplasma* drugs in combination with topical, oral, or parenteral corticosteroids to avoid secondary lens luxations and glaucoma. *Toxoplasma gondii*–seropositive cats with uveitis that are otherwise normal can be treated with topical glucocorticoids alone unless the uveitis is recurrent or persistent. In these situations,

administration of a drug with anti–*T. gondii* activity may be beneficial.

Clinical signs not involving the eyes or the CNS usually resolve within the first 2 to 3 days of clindamycin or azithromycin administration; ocular and CNS toxoplasmosis respond more slowly to therapy. If fever or muscle hyperesthesia does not decrease after 3 days of treatment, other causes should be considered. Recurrence of clinical signs may be more common in cats treated for less than 4 weeks. No evidence suggests that any drug can totally clear the body of the organism, so recurrences are common and infected cats will always be seropositive. The prognosis is poor for cats with hepatic or pulmonary disease caused by organism replication, particularly in those that are immunocompromised.

Zoonotic Aspects and Prevention

Toxoplasma gondii is a major zoonosis. Primary infection of mothers during gestation can lead to clinical toxoplasmosis in the fetus; stillbirth, CNS disease, and ocular disease are common clinical manifestations. Primary infection in immunocompetent individuals results in self-limiting fever, malaise, and lymphadenopathy. As T-helper cell counts decline, approximately 10% of people with AIDS develop toxoplasmic encephalitis from activation of bradyzoites in tissue cysts.

People most commonly acquire toxoplasmosis transplacentally or by ingesting sporulated oocysts or tissue cysts. Avoiding the ingestion of undercooked meats and carefully washing or cooking produce are two of the most important ways to prevent toxoplasmosis (Box 98.1). In a study of 6282 meat samples from 698 retail meat stores, *T. gondii* was not found in any of the beef or chicken samples tested (by bioassay in cats) and only a small number of pork samples were positive (Dubey et al., 2005). However, the organism has been detected in tissues from free-ranging chickens that were likely infected by ingestion of sporulated oocysts (Gonçalves et al., 2012). Sporulated oocysts are also infectious, so ingestion of materials that may be contaminated with old cat feces (e.g., contaminated soil or unwashed vegetables) should be avoided. There is also an association between toxoplasmosis and ingestion of certain uncooked shellfish that can concentrate the organism from contaminated water (Jones et al., 2009). Touching individual cats is probably not a common way to acquire toxoplasmosis for the following reasons:

- Cats generally only shed oocysts for days to several weeks after primary inoculation.
- Reactivation of oocyst shedding is rare in cats with chronically infected healthy cats, even in cats treated with clinical doses of glucocorticoids or cyclosporine, or in those infected with feline immunodeficiency virus or feline leukemia virus.
- Repeat shedding can occur if chronically infected cats are re-exposed, but generally smaller numbers of oocysts are shed (Zulpo et al., 2018).

BOX 98.1

Prevention of Human Toxoplasmosis

Prevention of Oocyst Ingestion

Avoid feeding undercooked meats to cats.
Do not allow cats to hunt.
Clean the litter box daily, and incinerate or flush the feces.
Clean the litter box periodically with scalding water or use a litter box liner.
Wear gloves when working with soil.
Wash hands thoroughly with soap and hot water after gardening.
Wash fresh vegetables well or cook before ingestion.
Keep children's sandboxes covered.
Boil water for drinking that has been obtained from the general environment.
Control potential transport hosts.
Treat oocyst shedding cats with anti-*Toxoplasma* drugs.

Prevention of Tissue Cyst Ingestion

Cook all meat products to 66° C.
Wear gloves when handling meats.
Wash hands thoroughly with soap and hot water after handling meats.
Freeze all meat for a minimum of 3 days before cooking.

- Cats are quite fastidious and usually do not allow feces to remain on their skin for periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.
- Increased risk of acquired toxoplasmosis was not associated with cat ownership in people with AIDS or in most studies of veterinary health care providers.

However, in the minority of studies evaluating risk factors, the association between cat contact and toxoplasmosis has been made. For example, the risk was associated with owning three or more kittens in one study (Jones et al., 2009). Thus hands should always be washed after handling kittens and cat feces. If a fecal sample from a cat is shown to contain oocysts measuring 10 × 12 µm, the organism is assumed to be *T. gondii.* The feces should be collected daily until the oocyst-shedding period is complete. Historically, administration of clindamycin (25-50 mg/kg PO divided q12h) can reduce levels of oocyst shedding. Because human beings are not commonly infected with *T. gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. Fecal examination is an adequate procedure to determine when cats are actively shedding oocysts but cannot predict when a cat has shed oocysts in the past. No serologic assay accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding;

most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their physician for testing.

CANINE TOXOPLASMOSIS

Etiology and Epidemiology

Dogs do not produce *T. gondii* oocysts like cats, but they can mechanically transmit oocysts after ingesting feline feces. The tissue phases of *T. gondii* infection occur in dogs and can induce clinical disease. Approximately 20% of dogs in the United States are seropositive for *T. gondii* antibodies (Levy et al., 2011). Before 1988, many dogs diagnosed with toxoplasmosis based on histologic evaluation were truly infected with *Neospora caninum* (see Neosporosis section). Transplacental infection occurs in dogs with both *T. gondii* and *N. caninum*. In one study of 41 stillborn puppies, 78.6% were positive for *T. gondii* (Taques et al., 2016). Toxoplasma gondii strains from dogs in Brazil were shown to be from four different genotypes of which all were proven to be virulent to mice (da Silva et al., 2017).

Clinical Features

Respiratory, gastrointestinal, or neuromuscular infection resulting in fever, vomiting, diarrhea, dyspnea, and icterus occurs most commonly in dogs with generalized toxoplasmosis. Generalized toxoplasmosis is most common in immunosuppressed dogs such as those with canine distemper virus infection or those receiving cyclosporine to prevent rejection of a transplanted kidney. Neurologic signs depend on the location of the primary lesions and include ataxia, seizures, tremors, cranial nerve deficits, paresis, and paralysis. Dogs with myositis present with weakness, stiff gait, or muscle wasting. Rapid progression to tetraparesis and paralysis with lower motor neuron dysfunction can occur. One study associated *T. gondii* antibodies with polyradiculoneuritis in dogs (Holt et al., 2011). Some dogs with suspected neuromuscular toxoplasmosis probably have neosporosis. Myocardial infection resulting in ventricular arrhythmias occurs in some infected dogs. Dyspnea, vomiting, or diarrhea occurs in dogs with polysystemic disease. Retinitis, anterior uveitis, iridocyclitis, and optic neuritis occur in some dogs with toxoplasmosis, but they are less common than in cats. Cutaneous disease has also been reported.

Diagnosis

As in cats, clinicopathologic and imaging abnormalities are not specific. Hyperglobulinemia can occur in dogs with chronic infection (Yarim et al., 2007). Increased protein concentrations and mixed inflammatory cell infiltrates occur in dogs with CNS toxoplasmosis.

Demonstration of the organism associated with inflammation in tissues or exudates can lead to a definitive diagnosis. More commonly an antemortem diagnosis is based on the combination of appropriate clinical signs, exclusion of other likely etiologies, positive serum antibody tests, exclusion of *N. caninum* infection by serologic testing, and response to an anti-*Toxoplasma* drug. Interpretation of serum, aqueous humor, and CSF antibody and PCR test results is as discussed for toxoplasmosis in cats.

Treatment

Clindamycin hydrochloride (10-12 mg/kg PO q12h) has been used most frequently for treatment of canine toxoplasmosis by the author. Trimethoprim-sulfa (15 mg/kg PO q12h) is an alternative protocol. Treatment should be continued for a minimum of 4 weeks. Ponazuril at 20 mg/kg PO q24h for 28 days was used successfully to treat a dog with suppurative keratitis and necrotizing conjunctivitis (Swinger et al., 2009). If uveitis is detected, topical glucocorticoid treatment should also be used.

Zoonotic Aspects and Prevention

Dogs do not complete the enteroepithelial phase of *T. gondii* but can mechanically transmit oocysts after ingesting feline feces. Like all other warm-blooded vertebrates, dogs are infected by the ingestion of sporulated oocysts or tissue cysts. Repeated infection can occur in dogs, and it appears that venereal infection can also occur (Arantes et al., 2009; Taques et al., 2016). Toxoplasmosis in dogs can be prevented by not allowing dogs to be coprophagic and to feed only cooked meat and meat by-products.

AMERICAN TRYPANOSOMIASIS

Etiology and Epidemiology

Trypanosoma cruzi is a flagellate that infects many mammals and causes American trypanosomiasis. The disease is diagnosed primarily in South America, but multiple cases have been detected in dogs of North America. *Trypanosoma caninum* is a new species identified in dogs in Brazil (Madeira et al., 2014). Continued work is needed to determine the prevalence of this agent in the United States and to define the clinical importance of the agent. *Trypanosoma cruzi* is molecularly diverse, but isolates from California have been shown to be similar to those of Latin America and so are likely of being capable of inducing disease (Shender et al., 2016). The triatomine vectors (reduviid [kissing] bugs) of *T. cruzi* are common in parts of the United States including Texas and California and frequently live in homes and dog kennels (Curtis-Robles et al., 2018). Even though infected reservoir mammals (dogs, cats, raccoons, opossums, armadillos) and vectors are found in the United States, infection in dogs or people is rare; this may relate to differences in vector behavior and sanitation standards in the United States. In one study in Texas, the number of serologically positive dogs increased between 1987 and 1996 (Meurs et al., 1998). Foxhounds infected with *Leishmania* spp. are commonly shown to be co-infected with *T. cruzi* (Duprey et al., 2006). In a study of 860 dogs in Tennessee, 6.4% had positive serum antibody titers suggesting exposure was common (Rowland et al., 2010). In another smaller study, the seroprevalence

rate in Virginia was 1%. Although some cats in Mexico are known to be seropositive, clinical disease in cats has not been characterized (Longoni et al., 2012).

The organism has three life stages: trypomastigotes (flagellated stage found free in blood), amastigotes (nonflagellated intracellular form), and epimastigotes (flagellated form found in the vector). When infected kissing bugs defecate during feeding, epimastigotes enter the vertebrate host, infect macrophages and myocytes, and transform into amastigotes. Amastigotes divide by binary fission until the host cell ruptures, releasing trypomastigotes into the circulation. The vector is then infected by ingesting trypomastigotes during a blood meal. Transmission can also occur transplacentally by vector ingestion, blood transfusion, or ingestion of infected tissues or milk. Coinfection with parasites like *Ancylostoma caninum* may potentiate *T. cruzi* infection (Enriquez et al., 2016). Peak parasitemia occurs 2 to 3 weeks after infection, causing acute disease. Disease in dogs is primarily a cardiomyopathy that develops from parasite-induced damage to myocardial cells or immune-mediated reactions.

Clinical Features

Exercise intolerance and weakness are nonspecific presenting complaints that relate to myocarditis or heart failure during acute infection. Generalized lymphadenopathy, pallor, tachycardia, pulse deficits, hepatomegaly, and abdominal distension can be detected on physical examination. Anorexia, diarrhea, and neurologic signs occasionally occur. Dogs that survive acute infection can present for evaluation of chronic dilative cardiomyopathy. In 537 dogs in Texas that were confirmed serologically or by histopathology, the primary clinical abnormalities included anorexia, ascites, cardiac conduction disturbances, cardiomegaly, lethargy, and respiratory difficulties (Kjos et al., 2008). In another study of 11 dogs with chronic infection, right-sided cardiac disease, conduction disturbances, ventricular arrhythmias, and supraventricular arrhythmias were most common (Meurs et al., 1998).

Diagnosis

Common clinicopathologic abnormalities include lymphocytosis and increased activities of liver enzymes and creatine kinase. Thoracic radiographic, abdominal radiographic, and echocardiographic findings are consistent with cardiac disease and failure but are not specific for trypanosomiasis. The primary electrocardiographic findings are ventricular premature contractions, heart block, and T-wave inversion. Definitive diagnosis is based on organism demonstration. Trypomastigotes (one flagellum, 15-20 μm long) can be identified during acute disease on thick blood film or buffy coat smears stained with Giemsa or Wright stain. The organism is sometimes detected in lymph node aspirates or abdominal effusions. Histopathologic evaluation of cardiac tissue usually reveals myocarditis (98%) and amastigotes (82%) are often identified (Kjos et al., 2008). Serologic assays can be used to prove exposure to *T. cruzi*. PCR assays can also be used to amplify *T. cruzi* DNA from tissues or blood, and positive test results prove infection. Trypomastigotes can be cultured from blood or grown by bioassay in mice.

Treatment

Nifurtimox has been prescribed for Chagas disease, but it is toxic and not readily available in the United States. In a recent study of allopurinol for the treatment of *T. cruzi* infection in an experimentally infected mouse model, a positive response was noted. Thus treating clinically affected dogs with allopurinol as described for *Leishmania* may be prudent. In recent studies, administration of benznidazole or ravuconazole lessened parasitemia but did not prevent infection in dogs (Diniz Lde et al., 2010; Kratz et al., 2018; Santos et al., 2012). Administration of the statin, simvastatin, at 20 mg PO q24h lessened cardiac dysfunction over time in an experimentally infected dog, likely from the immune modulating effects of the drug (Melo et al., 2011). Whether the same benefits will be recognized in naturally infected dogs remains to be proven. DNA vaccines for use as therapy also show promise (Quijano-Hernandez et al., 2008). Glucocorticoid therapy may improve survival of infected dogs. Therapy for arrhythmias or heart failure should be instituted as needed. Most dogs that survive acute infection develop dilative cardiomyopathy. Survival time in 11 dogs ranges from 0 to 60 months.

Zoonotic Aspects and Prevention

Infected dogs can serve as a reservoir of *T. cruzi* for vectors, and blood from infected dogs can be infectious to human beings (Travi, 2018). Vector control is the primary means of prevention. In one study, use of deltamethrin-treated collars reduced *Triatoma infestans* feeding success on dogs (Reithinger et al., 2005; Travi, 2018). However, treatment with fipronil does not provide adequate protection (Gürtler et al., 2009; Amelotti et al., 2012). Dogs should be kept from other reservoir hosts, such as opossums, and should not be fed raw meat. Potential blood donors from endemic areas should be serologically screened. For blood donor programs, high-risk breeds (e.g., Foxhounds) or dogs from endemic areas should be screened for *T. cruzi* infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2016). Experimental vaccine studies in dogs have been shown to lessen parasitemia and potential for development of Chagas disease.

Suggested Readings

Babesiosis

Annoscia G, et al. A new PCR assay for the detection and differentiation of *Babesia canis* and Babesia vogeli. *Ticks Tick Borne Dis*. 2017;8:862.

Baneth G. Antiprotozoal treatment of canine babesiosis. *Vet Parasitol*. 2018;254:58.

Birkenheuer AJ, et al. Babesia gibsoni infections in dogs from North Carolina. *J Am Anim Hosp Assoc*. 1999;35:125.

Birkenheuer AJ, et al. Detection and molecular characterization of a novel large Babesia species in a dog. *Vet Parasitol*. 2004a;124: 151.

Birkenheuer AJ, et al. Development and evaluation of a seminested PCR for detection and differentiation of Babesia gibsoni (Asian genotype) and B. canis DNA in canine blood samples. *J Clin Microbiol*. 2003a;41:4172.

Birkenheuer AJ, et al. Efficacy of combined atovaquone and azithromycin for therapy of chronic Babesia gibsoni (Asian genotype) infections in dogs. *J Vet Intern Med*. 2004b;18:494.

Birkenheuer AJ, et al. Geographic distribution of babesiosis among dogs in the United States and association with dog bites: 150 cases (2000-2003). *J Am Vet Med Assoc*. 2005;227:942.

Birkenheuer AJ, et al. Serosurvey of anti-Babesia antibodies in stray dogs and American pit bull terriers and American Staffordshire terriers from North Carolina. *J Am Anim Hosp Assoc*. 2003b;39:551.

Dantas-Torres F, et al. Efficacy of an imidacloprid/flumethrin collar against fleas, ticks and tick-borne pathogens in dogs. *Parasit Vectors*. 2013;6:245.

Davies S, et al. Prevalence of ticks and tick-borne pathogens: *Babesia* and *Borrelia* species in ticks infesting cats of Great Britain. *Vet Parasitol*. 2017;244:129.

Di Cicco MF, et al. Re-emergence of *Babesia conradae* and effective treatment of infected dogs with atovaquone and azithromycin. *Vet Parasitol*. 2012;187:23.

Freyburger L, et al. Comparative safety study of two commercialised vaccines against canine babesiosis induced by *Babesia canis*. *Parasite*. 2011;18:311.

Jefferies R, et al. *Babesia gibsoni:* detection during experimental infections and after combined atovaquone and azithromycin therapy. *Exp Parasitol*. 2007;117:15.

Jongejan F, et al. The prevention of transmission of *Babesia canis canis* by *Dermacentor reticulatus* ticks to dogs using a novel combination of fipronil, amitraz and (S)-methoprene. *Vet Parasitol*. 2011;179:343.

Kamani J, et al. Pathogenic and endosymbiont apicomplexans in *Ctenocephalides felis* (Siphonaptera: Pulicidae) from cats in Jerusalem, Israel. *Comp Immunol Microbiol Infect Dis*. 2018; 57:29.

Kelly PJ, et al. Survey of vector-borne agents in feral cats and first report of *Babesia gibsoni* in cats on St Kitts, West Indies. *BMC Vet Res*. 2017;13:331.

Kjemtrup AM, et al. *Babesia conradae,* sp. Nov., a small canine Babesia identified in California. *Vet Parasitol*. 2006;138:103.

Lin EC, et al. The therapeutic efficacy of two antibabesial strategies against *Babesia gibsoni*. *Vet Parasitol*. 2012;186:159.

Lin MY, Huang HP. Use of a doxycycline-enrofloxacin-metronidazole combination with/without diminazene diaceturate to treat naturally occurring canine babesiosis caused by *Babesia gibsoni*. *Acta Vet Scand*. 2010;52:27.

Malheiros J, et al. Identification of vector-borne pathogens in dogs and cats from Southern Brazil. *Ticks Tick Borne Dis*. 2016;7:893.

Penzhorn BL. Why is Southern African canine babesiosis so virulent? An evolutionary perspective. *Parasit Vectors*. 2011;4:51.

Solano-Gallego L, Baneth G. Babesiosis in dogs and cats—expanding parasitological and clinical spectra. *Vet Parasitol*. 2011;181:48.

Solano-Gallego L, et al. A review of canine babesiosis: the European perspective. *Parasit Vectors*. 2016;9:336.

Tabar MD, et al. PCR evaluation of selected vector-borne pathogens in dogs with pericardial effusion. *J Small Anim Pract*. 2018;59:248.

Varloud M, et al. Early *Babesia canis* transmission in dogs within 24 h and 8 h of infestation with infected pre-activated male *Dermacentor reticulatus* ticks. *Parasit Vectors*. 2018;11:41.

Vilhena H, et al. Acute phase proteins response in cats naturally infected with *Hepatozoon felis* and *Babesia vogeli*. *Vet Clin Pathol*. 2017;46:72.

Wang J, et al. First description of the pathogenicity of *Babesia vogeli* in experimentally infected dogs. *Vet Parasitol*. 2018;253:1.

Wardrop KJ, et al. Update on canine and feline blood donor screening for blood-borne pathogens. *J Vet Intern Med*. 2016; 30:15.

Wulansari R, et al. Clindamycin in the treatment of *Babesia gibsoni* infections in dogs. *J Am Anim Hosp Assoc*. 2003;39:558.

Cytauxzoonosis

Alho AM, et al. First report of Cytauxzoon sp. infection in a domestic cat from Portugal. *Parasit Vectors*. 2016;9:220.

Birkenheuer AJ, et al. Cytauxzoon felis infection in cats in the mid-Atlantic states: 34 cases (1998.2004). *J Am Vet Med Assoc*. 2006a;228:568.

Birkenheuer AJ, et al. Development and evaluation of a PCR assay for the detection of Cytauxzoon felis DNA in feline blood samples. *Vet Parasitol*. 2006b;137:144.

Brown HM, et al. Identification and genetic characterization of Cytauxzoon felis in asymptomatic domestic cats and bobcats. *Vet Parasitol*. 2010;172:311.

Carli E, et al. Cytauxzoon sp. infection in the first endemic focus described in domestic cats in Europe. *Vet Parasitol*. 2012;183:343.

Cohn LA, et al. Efficacy of atovaquone and azithromycin or imidocarb dipropionate in cats with acute cytauxzoonosis. *J Vet Intern Med*. 2011;25:55.

Díaz-Regañón D, et al. Molecular detection of Hepatozoon spp. and Cytauxzoon sp. in domestic and stray cats from Madrid, Spain. *Parasit Vectors*. 2017;10:112.

Gallusová M, et al. Cytauxzoon infections in wild felids from Carpathian-Danubian-Pontic Space: further evidence for a different Cytauxzoon species in European felids. *J Parasitol*. 2016; 102:377–380.

Greene CE, et al. Administration of diminazene aceturate or imidocarb dipropionate for treatment of cytauxzoonosis in cats. *J Am Vet Med Assoc*. 1999;215:497.

Haber MD, et al. The detection of Cytauxzoon felis in apparently healthy free-roaming cats in the USA. *Vet Parasitol*. 2007;146:316.

Legroux JP, et al. First clinical case report of Cytauxzoon sp. infection in a domestic cat in France. *BMC Vet Res*. 2017;13:81.

Lewis KM, Cohn LA, Birkenheuer AJ. Lack of evidence for perinatal transmission of Cytauxzoon felis in domestic cats. *Vet Parasitol*. 2012;188:172.

Lewis KM, et al. Failure of efficacy and adverse events associated with dose-intense diminazene diaceturate treatment of chronic Cytauxzoon felis infection in five cats. *J Feline Med Surg*. 2014;16:157.

Meinkoth J, et al. Cats surviving natural infection with Cytauxzoon felis: 18 cases (1997-1998). *J Vet Intern Med*. 2000;14:521.

Reichard MV, et al. Confirmation of Amblyomma americanum (Acari: Ixodidae) as a vector for Cytauxzoon felis (Piroplasmorida: Theileriidae) to domestic cats. *J Med Entomol*. 2010;47:890.

Reichard MV, et al. Temporal occurrence and environmental risk factors associated with cytauxzoonosis in domestic cats. *Vet Parasitol*. 2008;152:314.

Reichard MV, et al. Efficacy of an imidacloprid 10 % / flumethrin 4.5 % collar (Seresto®, Bayer) for preventing the transmission of

Cytauxzoon felis to domestic cats by Amblyomma americanum. *Parasitol Res*. 2013;112 Suppl 1:11.
Rizzi TE, et al. Prevalence of Cytauxzoon felis infection in healthy cats from enzootic areas in Arkansas, Missouri, and Oklahoma. *Parasit Vectors*. 2015;8:13.
Sherrill MK, Cohn LA. Cytauxzoonosis: diagnosis and treatment of an emerging disease. *J Feline Med Surg*. 2015;17:940.
Shock BC, et al. Variation in the ITS-1 and ITS-2 rRNA genomic regions of Cytauxzoon felis from bobcats and pumas in the eastern United States and comparison with sequences from domestic cats. *Vet Parasitol*. 2012;190:29.
Thomas JE, et al. Minimum transmission time of Cytauxzoon felis by Amblyomma americanum to domestic cats in relation to duration of infestation, and investigation of ingestion of infected ticks as a potential route of transmission. *J Feline Med Surg*. 2018;20:67.

Hepatozoonosis

Allen K, et al. Treatment of Hepatozoon americanum infection: review of the literature and experimental evaluation of efficacy. *Vet Ther*. 2010;11:E1.
Allen KE, et al. Diversity of Hepatozoon species in naturally infected dogs in the southern United States. *Vet Parasitol*. 2008;154:220.
Allen KE, et al. Hepatozoon spp infections in the United States. *Vet Clin North Am Small Anim Pract*. 2011;41:1221.
Baneth G. Perspectives on canine and feline hepatozoonosis. *Vet Parasitol*. 2011;181:3.
Díaz-Regañón D, et al. Molecular detection of Hepatozoon spp. and Cytauxzoon sp. in domestic and stray cats from Madrid, Spain. *Parasit Vectors*. 2017;10:112.
Duplan F, et al. Anaplasma phagocytophilum, Bartonella spp., haemoplasma species and Hepatozoon spp. in ticks infesting cats: a large-scale survey. *Parasit Vectors*. 2018;11:201.
Ewing SA, et al. Transmission of Hepatozoon americanum (Apicomplexa: Adeleorina) by ixodids (Acari: Ixodidae). *J Med Entomol*. 2002;39:631.
Giannelli A, et al. Three different Hepatozoon species in domestic cats from southern Italy. *Ticks Tick Borne Dis*. 2017;8:721.
Johnson EM, et al. Alternate pathway of infection with Hepatozoon americanum and the epidemiologic importance of predation. *J Vet Intern Med*. 2009b;23:1315.
Johnson EM, et al. Experimental transmission of Hepatozoon americanum to New Zealand White rabbits (Oryctolagus cuniculus) and infectivity of cystozoites for a dog. *Vet Parasitol*. 2009a;164:162.
Li Y, et al. Diagnosis of canine Hepatozoon spp. infection by quantitative PCR. *Vet Parasitol*. 2008;157:50.
Little L, Baneth G. Cutaneous Hepatozoon canis infection in a dog from New Jersey. *J Vet Diagn Invest*. 2011;23:585.
Lloret A, et al. Hepatozoonosis in cats: ABCD guidelines on prevention and management. *J Feline Med Surg*. 2015;17:642.
Macintire DK, et al. Treatment of dogs infected with Hepatozoon americanum: 53 cases (1989-1998). *J Am Vet Med Assoc*. 2001;218:77.
Marchetti V, et al. Hepatozoonosis in a dog with skeletal involvement and meningoencephalomyelitis. *Clin Pathol*. 2009;38:121.
Modrý D, et al. A review of methods for detection of Hepatozoon infection in carnivores and arthropod vectors. *Vector Borne Zoonotic Dis*. 2017;17:66.
Potter TM, Macintire DK. Hepatozoon americanum: an emerging disease in the south-central/southeastern United States. *J Vet Emerg Crit Care (San Antonio)*. 2010;20:70.

Leishmaniasis

Attipa C, et al. Association between canine leishmaniosis and Ehrlichia canis co-infection: a prospective case-control study. *Parasit Vectors*. 2018;11:184.
Ayllón T, et al. Vector-borne diseases in client-owned and stray cats from Madrid, Spain. *Vector Borne Zoonotic Dis*. 2012;12:143.
Boggiatto PM, et al. Transplacental transmission of Leishmania infantum as a means for continued disease incidence in North America. *PLoS Negl Trop Dis*. 2011;5:e1019.
Cavaliero T, et al. Clinical, serologic, and parasitologic follow-up after long-term allopurinol therapy of dogs naturally infected with Leishmania infantum. *J Vet Intern Med*. 1999;13:330.
Coelho WM, et al. Seroepidemiology of Toxoplasma gondii, Neospora caninum, and Leishmania spp. infections and risk factors for cats from Brazil. *Parasitol Res*. 2011;109:1009.
Cortadellas O. Initial and long-term efficacy of a lipid emulsion of amphotericin B desoxycholate in the management of canine leishmaniasis. *J Vet Intern Med*. 2003;17:808.
da Silva SM, et al. Efficacy of combined therapy with liposome-encapsulated meglumine antimoniate and allopurinol in treatment of canine visceral leishmaniasis. *Antimicrob Agents Chemother*. 2012;56:2858.
Dantas-Torres F. Leishmune vaccine: the newest tool for prevention and control of canine visceral leishmaniosis and its potential as a transmission-blocking vaccine. *Vet Parasitol*. 2006;141:1.
de Freitas E, et al. Transmission of Leishmania infantum via blood transfusion in dogs: potential for infection and importance of clinical factors. *Vet Parasitol*. 2006;137:159.
Denerolle P, et al. Combination allopurinol and antimony treatment versus antimony alone and allopurinol alone in the treatment of canine leishmaniasis (96 cases). *J Vet Intern Med*. 1999;13:413.
Duprey ZH, et al. Canine visceral leishmaniasis, United States and Canada. 2000-2003. *Emerg Infect Dis*. 2006;12:440.
Fernández Cotrina J, et al. A large-scale field randomized trial demonstrates safety and efficacy of the vaccine LetiFend® against canine leishmaniosis. *Vaccine*. 2018;36:1972.
Francino O, et al. Advantages of real-time PCR assay for diagnosis and monitoring of canine leishmaniosis. *Vet Parasitol*. 2006;137:214.
Freeman KS, et al. Leishmaniasis in a dog native to Colorado. *J Am Vet Med Assoc*. 2010;237:1288.
Gaskin AA, et al. Visceral leishmaniasis in a New York foxhound kennel. *J Vet Intern Med*. 2002;16:34.
Gómez-Ochoa P, et al. Use of domperidone in the treatment of canine visceral leishmaniasis: a clinical trial. *Vet J*. 2009;179:259.
Maia C, Campino L. Can domestic cats be considered reservoir hosts of zoonotic leishmaniasis? *Trends Parasitol*. 2011;27:341.
Manna L, et al. Real-time PCR assay in Leishmania-infected dogs treated with meglumine antimoniate and allopurinol. *Vet J*. 2008;177:279.
Maroli M, et al. Infection of sandflies by a cat naturally infected with Leishmania infantum. *Vet Parasitol*. 2007;145:357.
Mir F, et al. Subclinical leishmaniasis associated with infertility and chronic prostatitis in a dog. *J Small Anim Pract*. 2012;53:419.
Miró G, et al. Multicentric, controlled clinical study to evaluate effectiveness and safety of miltefosine and allopurinol for canine leishmaniosis. *Vet Dermatol*. 2009;20:397.
Miro G, et al. Novel areas for prevention and control of canine leishmaniosis. *Trends Parasitol*. 2017;33:718.
Molina R, et al. Efficacy of 65% permethrin applied to dogs as a spot-on against Phlebotomus pernicious. *Vet Parasitol*. 2012;187:529.

Navarro JA, et al. Histopathological lesions in 15 cats with leishmaniosis. *J Comp Pathol*. 2010;143:297.
Otranto D, et al. Efficacy of a combination of 10% imidacloprid/50% permethrin for the prevention of leishmaniasis in kennelled dogs in an endemic area. *Vet Parasitol*. 2007;144:270.
Palatnik-de-Sousa CB. Vaccines for canine leishmaniasis. *Front Immunol*. 2012;3:69.
Paradies P, et al. Monitoring the reverse to normal of clinicopathological findings and the disease free interval time using four different treatment protocols for canine leishmaniosis in an endemic area. *Res Vet Sci*. 2012;93:843.
Pena MT, et al. Ocular and periocular manifestations of leishmaniasis in dogs: 105 cases (1993-1998). *Vet Ophthalmol*. 2000;3:35.
Pennisi MG, et al. Leishmaniosis in cats: ABCD guidelines on prevention and management. *J Feline Med Surg*. 2015;15:638.
Petersen CA. New means of canine leishmaniasis transmission in North America: the possibility of transmission to humans still unknown. *Interdiscip Perspect Infect Dis*. 2009;802:712.
Plevraki K, et al. Effects of allopurinol treatment on the progression of chronic nephritis in Canine leishmaniosis (Leishmania infantum). *J Vet Intern Med*. 2006;20:228.
Rosypal AC, et al. Emergence of zoonotic canine leishmaniasis in the United States: isolation and immunohistochemical detection of Leishmania infantum from foxhounds from Virginia. *J Eukaryot Microbiol*. 2003;50:691.
Silva DA, et al. Assessment of serological tests for the diagnosis of canine visceral leishmaniasis. *Vet J*. 2012;195:252.
Solano-Gallego L, et al. Detection of Leishmania infantum DNA mainly in Rhipicephalus sanguineus male ticks removed from dogs living in endemic areas of canine leishmaniosis. *Parasit Vectors*. 2012;5:98.
Solano-Gallego L, et al. LeishVet guidelines for the practical management of canine leishmaniosis. *Parasit Vectors*. 2011;4:86.
Solano-Gallego L, et al. Diagnostic challenges in the era of canine Leishmania infantum vaccines. *Trends Parasitol*. 2017;33:706.
Solcà Mda S, et al. Qualitative and quantitative polymerase chain reaction (PCR) for detection of Leishmania in spleen samples from naturally infected dogs. *Vet Parasitol*. 2012;184:133.
Trainor KE, et al. Eight cases of feline cutaneous leishmaniasis in Texas. *Vet Pathol*. 2010;47:1076.
Vouldoukis I, et al. Canine visceral leishmaniasis: comparison of in vitro leishmanicidal activity of marbofloxacin, meglumine antimoniate and sodium stibogluconate. *Vet Parasitol*. 2006;135:137.

Neosporosis

Bandini LA, et al. Experimental infection of dogs (Canis familiaris) with sporulated oocysts of Neospora caninum. *Vet Parasitol*. 2011;176:151.
Barutzki D, Schaper R. Results of parasitological examinations of faecal samples from cats and dogs in Germany between 2003 and 2010. *Parasitol Res*. 2011;109:S45.
Basso W, et al. First isolation of Neospora caninum from the feces of a naturally infected dog. *J Parasitol*. 2001;87:612.
Bresciani KD, et al. Antibodies to Neospora caninum and Toxoplasma gondii in domestic cats from Brazil. *Parasitol Res*. 2007;100:281.
Cavalcante GT, et al. Shedding of Neospora caninum oocysts by dogs fed different tissues from naturally infected cattle. *Vet Parasitol*. 2011;179:220.
Crookshanks JL, et al. Treatment of canine pediatric Neospora caninum myositis following immunohistochemical identification of tachyzoites in muscle biopsies. *Can Vet J*. 2007;48:506.
Dubey JP, et al. Epidemiology and control of neosporosis and Neospora caninum. *Clin Microbiol Rev*. 2007a;20:323.
Dubey JP, et al. Neosporosis in Beagle dogs: clinical signs, diagnosis, treatment, isolation and genetic characterization of Neospora caninum. *Vet Parasitol*. 2007b;149:158.
Dubey JP, et al. Neosporosis in cats. *Vet Pathol*. 1990a;27:335.
Dubey JP, et al. Newly recognized fatal protozoan disease of dogs. *J Am Vet Med Assoc*. 1988;192:1269.
Dubey JP, et al. Repeated transplacental transmission of Neospora caninum in dogs. *J Am Vet Med Assoc*. 1990b;197:857.
Dubey JP, Schares G. Neosporosis in animals–the last five years. *Vet Parasitol*. 2011;180:90.
Garosi L, et al. Necrotizing cerebellitis and cerebellar atrophy caused by Neospora caninum infection: magnetic resonance imaging and clinicopathologic findings in seven dogs. *J Vet Intern Med*. 2010;24:571.
Gondim LF, et al. Transmission of Neospora caninum between wild and domestic animals. *J Parasitol*. 2004;90:1361.
Klein C, et al. Neospora caninum DNA in coyote fecal samples collected in an urban environment. *J Wildl Dis*. 2018;doi:10.7589/2018-02-027.
McAllister MM, et al. Dogs are definitive hosts of Neospora caninum. *Int J Parasitol*. 1998;28:1473.
McGarry JW, et al. Protracted shedding of oocysts of Neospora caninum by a naturally infected foxhound. *J Parasitol*. 2003;89:628.
Petersen E, et al. Neospora caninum infection and repeated abortions in humans. *Emerg Infect Dis*. 1999;5:278.
Reichel MP, et al. Neosporosis and hammondiosis in dogs. *J Small Anim Pract*. 2007;48:308.
Rosypal AC, et al. Toxoplasma gondii and Trypanosoma cruzi antibodies in dogs from Virginia. *Zoonoses Public Health*. 2010;57:e76.
Schatzerg SJ, et al. Use of a multiplex polymerase chain reaction assay in the antemortem diagnosis of toxoplasmosis and neosporosis in the central nervous system of cats and dogs. *Am J Vet Res*. 2003;64:1507.
Sedlák K, et al. Seroprevalence of Neospora caninum in cats from the Czech Republic. *Acta Parasitol*. 2014;59:359.
Silva RC, Machado GP. Canine neosporosis: perspectives on pathogenesis and management. *Vet Med (Auckl)*. 2016;7:59.
Sloan S, et al. High seroprevalance of Neospora caninum in dogs in Victoria, Australia, compared to 20 years ago. *Parasit Vectors*. 2017;10:503.
Spencer JA, et al. Seroprevalence of Neospora caninum and Toxoplasma gondii in captive and free-ranging nondomestic felids in the United States. *J Zoo Wildl Med*. 2003;34:246.
Taques IIGG, et al. Molecular assessment of the transplacental transmission of Toxoplasma gondii, Neospora caninum, Brucella canis, and Ehrlichia canis in dogs. *Comp Immunol Microbiol Infect Dis*. 2016;49:47.
Tranas J, et al. Serological evidence of human infection with the protozoan Neospora caninum. *Clin Diagn Lab Immunol*. 1999;6:765.

Toxoplasmosis

Arantes TP, et al. Toxoplasma gondii: evidence for the transmission by semen in dogs. *Exp Parasitol*. 2009;123:190.
Barrs VR, et al. Antemortem diagnosis and treatment of toxoplasmosis in two cats on cyclosporin therapy. *Aust Vet J*. 2006;84:30.
Bresciani KD, et al. Transplacental transmission of Toxoplasma gondii in reinfected pregnant female canines. *Parasitol Res*. 2009;104:1213.

Burney DP, et al. Detection of Toxoplasma gondii parasitemia in experimentally inoculated cats. *J Parasitol*. 1999;5:947.
da Silva JR, et al. Isolation and genotyping of Toxoplasma gondii in brazilian dogs. *Korean J Parasitol*. 2017;55:239.
Dabritz HA, Conrad PA. Cats and Toxoplasma: implications for public health. *Zoonoses Public Health*. 2010;57:34.
Davidson MG, et al. Feline immunodeficiency virus predisposes cats to acute generalized toxoplasmosis. *Am J Pathol*. 1993;143: 1486.
Dubey JP, et al. Clinical Sarcocystis neurona, Sarcocystis canis, Toxoplasma gondii, and Neospora caninum infections in dogs. *Vet Parasitol*. 2006;137:36.
Dubey JP, et al. Histologically confirmed clinical toxoplasmosis in cats: 100 cases (1952-1990). *J Am Vet Med Assoc*. 1556;203:1993a.
Dubey JP, et al. Neonatal toxoplasmosis in littermate cats. *J Am Vet Med Assoc*. 1546;203:1993b.
Dubey JP, et al. Prevalence of viable Toxoplasma gondii in beef, chicken, and pork from retail meat stores in the United States: risk assessment to consumers. *J Parasitol*. 2005;91:1082.
Evans NA, et al. Acute respiratory distress syndrome and septic shock in a cat with disseminated toxoplasmosis. *J Vet Emerg Crit Care (San Antonio)*. 2017;27:472.
Gonçalves IN, et al. Molecular frequency and isolation of cyst-forming coccidia from free ranging chickens in Bahia State, Brazil. *Vet Parasitol*. 2012;190:74.
Holt N, et al. Seroprevalence of various infectious agents in dogs with suspected acute canine polyradiculoneuritis. *J Vet Intern Med*. 2011;25:261.
Hsu V, et al. Prevalence of IgG antibodies to Encephalitozoon cuniculi and Toxoplasma gondii in cats with and without chronic kidney disease from Virginia. *Vet Parasitol*. 2011;176:23–26.
Jones JL, et al. Risk factors for Toxoplasma gondii infection in the United States. *Clin Infect Dis*. 2009;49:878.
Lappin MR, et al. Polymerase chain reaction for the detection of Toxoplasma gondii in aqueous humor of cats. *Am J Vet Res*. 1589;57:1996a.
Lappin MR, et al. Primary and secondary Toxoplasma gondii infection in normal and feline immunodeficiency virus-infected cats. *J Parasitol*. 1996b;82:733.
Levy JK, et al. Prevalence of infectious diseases in cats and dogs rescued following Hurricane Katrina. *J Am Vet Med Assoc*. 2011;238:311.
Lindsay DS, et al. Mechanical transmission of Toxoplasma gondii oocysts by dogs. *Vet Parasitol*. 1997;73:27.
Mari L, et al. Distal polyneuropathy in an adult Birman cat with toxoplasmosis. *JFMS Open Rep*. 2016;2:2055116916630335.
Mitchell SM, et al. Efficacy of ponazuril in vitro and in preventing and treating Toxoplasma gondii infections in mice. *J Parasitol*. 2004;90:639.
Plugge NF, et al. Occurrence of antibodies against Neospora caninum and/or Toxoplasma gondii in dogs with neurological signs. *Rev Bras Parasitol Vet*. 2011;20:202.
Powell CC, et al. Bartonella species, feline herpesvirus-1, and Toxoplasma gondii PCR assay results from blood and aqueous humor samples from 104 cats with naturally occurring endogenous uveitis. *J Feline Med Surg*. 2010;12:923.
Powell CC, Lappin MR. Clinical ocular toxoplasmosis in neonatal kittens. *Vet Ophthalmol*. 2001;4:87.
Swinger RL, et al. Keratoconjunctivitis associated with Toxoplasma gondii in a dog. *Vet Ophthalmol*. 2009;12:56.
Taques IIGG, et al. Molecular assessment of the transplacental transmission of Toxoplasma gondii, Neospora caninum, Brucella canis and Ehrlichia canis in dogs. *Comp Immunol Microbiol Infect Dis*. 2016;49:47.
Torrey EF, et al. Toxoplasma oocysts as a public health problem. *Trends Parasitol*. 2013;29:380.
Vollaire MR, et al. Seroprevalence of Toxoplasma gondii antibodies in clinically ill cats in the United States. *Am J Vet Res*. 2005;66:874.
Vyas A, et al. Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. *Proc Natl Acad Sci USA*. 2007;104:6442.
Wallace MR, et al. Cats and toxoplasmosis risk in HIV-infected adults. *JAMA*. 1993;269:76.
Yarim GF, et al. Serum protein alterations in dogs naturally infected with Toxoplasma gondii. *Parasitol Res*. 2007;101:1197.
Zulpo DL, et al. Toxoplasma gondii: a study of oocyst re-shedding in domestic cats. *Vet Parasitol*. 2018;249:17.

American Trypanosomiasis

Amelotti I, et al. Effects of fipronil on dogs over Triatoma infestans, the main vector of Trypanosoma cruzi, causative agent of Chagas disease. *Parasitol Res*. 2012;111:1457.
Barr SC, et al. Trypanosoma cruzi infection in Walker Hounds from Virginia. *Am J Vet Res*. 1995;56:1037.
Barr SC. Canine Chagas' disease (American trypanosomiasis) in North America. *Vet Clin North Am Small Anim Pract*. 2009;39:1055.
Curtis-Robles R, et al. Analysis of over 1500 triatomine vectors from across the US, predominantly Texas, for Trypanosoma cruzi infection and discrete typing units. *Infect Genet Evol*. 2018;58:171–180.
de Oliveira Tda S. Report of new cases of Trypanosoma caninum in Brazil. *Rev Soc Bras Med Trop*. 2015;48:347.
de Paula Costa G, et al. Doxycycline and benznidazole reduce the profile of Th1, Th2, and Th17 chemokines and chemokine receptors in cardiac tissue from chronic Trypanosoma cruzi-infected Dogs. *Mediators Inflamm*. 2016;3694714.
Diniz Lde F, et al. Effects of ravuconazole treatment on parasite load and immune response in dogs experimentally infected with Trypanosoma cruzi. *Antimicrob Agents Chemother*. 2010;54:2979.
Enriquez GF, et al. Is the infectiousness of dogs naturally infected with Trypanosoma cruzi associated with poly-parasitism? *Vet Parasitol*. 2016;223:186.
Gobbi P, et al. Allopurinol is effective to modify the evolution of Trypanosoma cruzi infection in mice. *Parasitol Res*. 2007;101:1459.
Gürtler RE, et al. Effects of topical application of fipronil spot-on on dogs against the Chagas disease vector Triatoma infestans. *Trans R Soc Trop Med Hyg*. 2009;103:298.
Jimenez-Coello M, et al. Efficacy of recombinase polymerase amplification to diagnose Trypanosoma cruzi infection in dogs with cardiac alterations from an endemic area of mexico. *Vector Borne Zoonotic Dis*. 2018;18:417.
Kjos SA, et al. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. 2008;152:249.
Kratz JM, et al. Clinical and pharmacological profile of benznidazole for treatment of Chagas disease. *Expert Rev Clin Pharmacol*. 2018;doi:10.1080/17512433.2018.1509704.
Longoni SS, et al. Detection of different Leishmania spp. and Trypanosoma cruzi antibodies in cats from the Yucatan Peninsula (Mexico) using an iron superoxide dismutase excreted as antigen. *Comp Immunol Microbiol Infect Dis*. 2012;35:469.
Madeira MF, et al. Trypanosoma caninum, a new parasite described in dogs in Brazil: aspects of natural infection. *J Parasitol*. 2014;100:231.

Melo L, et al. Low doses of simvastatin therapy ameliorate cardiac inflammatory remodeling in Trypanosoma cruzi-infected dogs. *Am J Trop Med Hyg*. 2011;84:325.

Meurs KM, et al. Chronic Trypanosoma cruzi infection in dogs: 11 cases (1987-1996). *J Am Vet Med Assoc*. 1998;213:497.

Patel JM, et al. Isolation, mouse pathogenicity, and genotyping of Trypanosoma cruzi from an English Cocker Spaniel from Virginia, USA. *Vet Parasitol*. 2012;187:394.

Pinto AG, et al. Evaluation of 18S rDNA PCR assay using skin fragments as a diagnostic test for Trypanosoma caninum. *Vet Parasitol*. 2014;205:343.

Quijano-Hernandez IA, et al. Therapeutic DNA vaccine against Trypanosoma cruzi infection in dogs. *Ann N Y Acad Sci*. 2008;1149:343.

Reithinger R, et al. Chagas disease control: deltamethrin-treated collars reduce Triatoma infestans feeding success on dogs. *Trans R Soc Trop Med Hyg*. 2005;99:502.

Rowland ME, et al. Factors associated with Trypanosoma cruzi exposure among domestic canines in Tennessee. *J Parasitol*. 2010;96:547.

Santos FM, et al. Cardiomyopathy prognosis after benznidazole treatment in chronic canine Chagas' disease. *J Antimicrob Chemother*. 2012;67:1987.

Shender LA, et al. Molecular Diversity of Trypanosoma cruzi Detected in the Vector Triatoma protracta from California, USA. *PLoS Negl Trop Dis*. 2016;10:e0004291.

Travi BL. Considering dogs as complementary targets of Chagas Disease control. *Vector Borne Zoonotic Dis*. 2018;doi:10.1089/vbz.2018.2325.

CHAPTER 99

Zoonoses



Zoonotic diseases are defined as being common to, shared by, or naturally transmitted between humans and other vertebrates. Most of the agents discussed in this chapter can infect and cause disease in immunocompetent people, but disease is generally more prevalent or more severe in immunodeficient people. Immunosuppression is common in humans. People with acquired immunodeficiency syndrome (AIDS) are discussed most frequently, but the population also includes the very old, the very young, and those receiving chemotherapy for immune-mediated diseases, organ transplantation, or neoplasia. Immunosuppressed people are sometimes advised to give up their pets. However, humans are unlikely to contract zoonotic diseases from contact with their healthy pets, so in most cases this is not necessary. All human and other animal healthcare providers should provide accurate information to pet owners concerning the risks and benefits of pet ownership so that an informed decision about acquiring and keeping pets can be made. The Centers for Disease Control and Prevention website "Healthy Pets Health People" is an excellent source of information physicians, veterinarians, and pet owners (https://www.cdc.gov/healthypets/index.html).

Many infectious agents can infect humans by direct contact with pets, their exudates, or their excrement (Table 99.1). These agents are the most important to veterinary healthcare providers and to dog and cat owners, and are discussed in this chapter by likely route of exposure. For some zoonoses, including *Anaplasma* spp. (ticks), *Bartonella* spp. (fleas and possibly ticks), *Borrelia burgdorferi* (ticks), *Ehrlichia* spp. (ticks), and *Rickettsia* spp. (fleas for *R. felis*; ticks for *R. rickettsii*), the pet brings the vector of the organism into the environment, resulting in potential exposure of the person. With some zoonoses, including *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis,* and *Cryptococcus neoformans,* the owner and pet are infected by shared environmental exposure to the agent.

The following is a brief description of the more common canine and feline zoonoses encountered in small animal practice. General guidelines for the avoidance of zoonotic transfer of disease for veterinarians and pet owners are listed in Boxes 99.1 and 99.2, respectively.

ENTERIC ZOONOSES

Multiple infectious agents of the gastrointestinal tract can be shared between animals and humans. Many veterinarians in United States now use commercial diagnostic laboratories for fecal flotation, which has allowed for the publication of results on large sample sizes (Little et al., 2009). For example, results from 1,199,293 dog samples showed overall national prevalence rates for ascarids (2.2%), hookworms (2.5%), and *Giardia* (4.0%). Other manuscripts have shown high prevalence rates of enteric zoonotic agents in cats as well (De Santis et al., 2006a; De Santis et al., 2006b). These findings emphasize that diagnostic workups for enteric infections in pets with gastrointestinal signs of disease are indicated because of potential human health risks.

The minimal diagnostic plan to assess for enteric zoonoses in pets with diarrhea includes a fecal flotation and a *Giardia* antigen test or fluorescent antibody assay. In one study, a fecal polymerase chain reaction (PCR) assay was less sensitive than other assays, likely due to fecal PCR inhibitors, thus this technique should not be the screening procedure for *Giardia* (Hascall et al., 2016). Fecal bacterial culture should be considered if infection with *Salmonella* spp. or *Campylobacter* spp. is on the list of differential diagnoses.

NEMATODES

Visceral larva migrans can be induced by infection of humans with *Toxocara cati, Toxocara canis,* or *Baylisascaris procyonsis* (see Table 99.1). In the United States, infection of humans is still common; the age-adjusted seroprevalence is approximately 14% (Won et al., 2008). These common roundworms are passed as eggs in feces. The eggs larvate and become infectious after 1 to 3 weeks and can survive in the environment for months. Humans are infected after ingesting embryonated eggs. Embryonated *Toxocara* spp. eggs have been transmitted by earthworms, filth flies, and cockroaches, and have been found on the fur of pets (Sasmal et al., 2008; Overgaauw et al., 2009). Dogs are considered more of a significant problem than cats for the spread of eggs. However, areas such as children's sandboxes and vegetable gardens may be contaminated with *T. cati* because of

TABLE 99.1

Common Zoonotic Infections of Dogs and Cats

ROUTE OF EXPOSURE	AGENT	AFFECTED	PRINCIPLE CLINICAL SYNDROMES
Bites, Scratches, Exudates			
Bartonella spp.[a]	Bacteria	Cats and dogs	Subclinical, fever, hyperglobulinemia, uveitis, lymphadenopathy, others
		Humans	Fever, malaise, lymphadenopathy, bacillary angiomatosis, bacillary peliosis, others
Capnocytophaga canimorsus	Bacterium	Dogs and cats	Subclinical oral carriage
		Humans	Bacteremia
Dermatophytes	Fungi	Cats and dogs	Superficial dermatologic disease
		Humans	Superficial dermatologic disease
Francisella tularensis[b]	Bacterium	Cats and dogs	Septicemia, pneumonia
		Humans	Ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of inoculation)
Rabies	Virus	Cats and dogs	Progressive central nervous system disease
		Humans	Progressive central nervous system disease
Sporothrix spp.[b]	Fungal	Cats	Draining cutaneous tracts
		Humans	Draining cutaneous tracts
Yersinia pestis[b]	Bacterium	Cats and dogs	Bubonic, bacteremic, or pneumonic (depending on route of inoculation)
		Humans	Bubonic, bacteremic, or pneumonic (depending on route of inoculation)
Enteric Agents			
Ancylostoma spp.[c]	Hookworm	Dogs and cats	Blood loss anemia, diarrhea, unthrifty
		Humans	Cutaneous larva migrans; esosinophilic pain
Baylisascaris procyanosis	Roundworm	Dogs	Failure to thrive
		Humans	Visceral larva migrans; CNS disease
Campylobacter jejuni and *Campylobacter coli*	Bacteria	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Cryptosporidium spp.[d]	Coccidian	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Escherichia coli	Bacteria	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Echinococcus multilocularis	Cestode	Dogs and cats	Subclinical infection
		Humans	Polysystemic disease
Echinococcus granulosa	Cestode	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Entamoeba histolytica[e]	Amoeba	Dogs	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Giardia spp.[f]	Flagellate	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Helicobacter spp.[g]	Bacterium	Dogs and cats	Vomiting
		Humans	Reflux disease and vomiting
Salmonella spp.	Bacteria	Dogs and cats	Diarrhea and vomiting
		Humans	Diarrhea and vomiting
Strongyloides stercoralis	Hookworm	Dogs and cats	Blood loss anemia, failure to thrive
		Humans	Cutaneous larva migrans

Continued

TABLE 99.1

Common Zoonotic Infections of Dogs and Cats—cont'd

ROUTE OF EXPOSURE	AGENT	AFFECTED	PRINCIPLE CLINICAL SYNDROMES
Toxocara canis and *T. cati* (C)[c]	Roundworms	Dogs and cats Humans	Vomiting, failure to thrive Ocular and visceral larva migrans
Toxoplasma gondii[h]	Coccidian	Cats Humans	Rarely diarrhea, polysystemic disease Ocular, CNS, polysystemic disease
Uncinaria stenocephala[c]	Hookworm	Dogs and cats Humans	Blood loss anemia, diarrhea, unthrifty Cutaneous larva migrans
Yersinia enterocolitica	Bacterium	Dogs and cats Humans	Subclinical infection Diarrhea and vomiting
Respiratory or Ocular			
Bordetella bronchiseptica	Bacterium	Dogs and cats Humans	Sneeze and cough Pneumonia in immunosuppressed
Chlamydia felis	Bacterium	Cats Humans	Conjunctivitis, sneezing Conjunctivitis
Francisella tularensis[i]	Bacterium	Cats Humans	Septicemia, pneumonia Ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of infection)
Streptococcus group A	Bacterium	Dogs and cats Humans	Subclinical, transient carrier "Strep throat," septicemia
Yersinia pestis[i]	Bacterium	Cats	Bubonic, bacteremic, or pneumonic
		Humans	Bubonic, bacteremic, or pneumonic
Urogenital			
Brucella canis	Bacterium	Dogs Humans	Orchitis, epididymitis, abortion, stillbirth, vaginal discharge, uveitis, fever Fever, malaise
Leptospira spp.	Spirochetes	Dogs Humans	Fever, malaise, inflammatory urinary tract or hepatic disease, uveitis, CNS Fever, malaise
Coxiella burnetii[i]	*Rickettia*	Cats Humans	Subclinical, abortion, or stillbirth Fever, pneumonitis, lymphadenopathy, myalgia, arthritis
Flea-borne			
Bartonella spp.[a]	Bacteria	Cats and dogs Humans	Subclinical, fever, hyperglobulinemia, uveitis, lymphadenopathy, others Fever, malaise, lymphadenopathy, bacillary angiomatosis, bacillary peliosis, others
Rickettsia felis	Rickettsia	Cats Humans	Subclinical, fever Fever, CNS
Yersinia pestis	Bacterium	Cats Humans	Bubonic, bacteremic, or pneumonic (depending on the route of inoculation) Bubonic, bacteremic, or pneumonic (depending on the route of inoculation)
Tick-borne[j]			
Anaplasma phagocytophilum	Rickettsia	Dogs and cats Humans	Fever, polyarthritis Fever, polysystemic

TABLE 99.1

Common Zoonotic Infections of Dogs and Cats—cont'd

ROUTE OF EXPOSURE	AGENT	AFFECTED	PRINCIPLE CLINICAL SYNDROMES
Borrelia burgdorferi	Spirochete	Dogs	Subclinical infection, fever, polyarthritis, nephropathy
		Humans	Polyarthropathy, cardiac and CNS disease
Ehrlichia spp.	Rickettsia	Dogs	Subclinical infection, fever, polysystemic
		Humans	Fever, polysystemic
Rickettsia rickettsii	Rickettsia	Dogs	Subclinical infection, fever, polysystemic
		Humans	Fever, polysystemic

[a]*Bartonella henselae*, *Bartonella koehlerae*, and *Bartonella clarridgeaie* are transmitted among cats and dogs by *C. felis* and are therefore listed under flea-borne disease. Other *Bartonella* spp. have zoonotic implications. Cats generally develop a higher level of bacteremia than dogs and are therefore epidemiologically linked more frequently to human disease. The vector is unknown for some *Bartonella* spp.
[b]Dogs rarely shed enough organisms to be a public health risk.
[c]Larvation of eggs occurs after passage into the environment, so direct transmission is less likely than exposure through environmental contamination.
[d]Most dogs and cats are infected by *Cryptosporidium canis* or *C. felis*, respectively, and these host-adapted species are rarely associated with disease in humans.
[e]Infection of dogs in the United States is thought to be rare.
[f]Host-adapted and zoonotic assemblages exist. Dogs and cats can harbor zoonotic assemblages, but whether levels of infection result in reinfection of humans is not established.
[g]Most *Helicobacter* spp. found in dogs and cats are host-adapted species. When *Helicobacter pylori* is detected in a dog or cat, it is likely from reverse zoonotic transmission.
[h]Sporulation of oocysts occurs after passage into the environment, so direct transmission is less likely than exposure through environmental contamination.
[i]Also can be vector-borne.
[j]*Bartonella* spp. DNA have been amplified from some ticks, but the extent of the role ticks play in the transmission of these agents has not been fully ascertained.

BOX 99.1

General Guidelines for Veterinarians to Avoid Zoonotic Transfer of Disease

- Veterinarians and their staff should familiarize themselves with zoonotic issues and take an active role in discussing the health risks and benefits of pet ownership with clients so that logical decisions concerning ownership and management of individual animals can be made.
- The veterinary clinic should communicate that the staff understands conditions associated with immune deficiency, is discreet, and is willing to help; signs or posters can be effective for this purpose.
- Pet owners should be provided information concerning veterinary or public health aspects of zoonoses, but veterinarians should not diagnose diseases in humans or discuss specific treatments.
- Clinically ill pet owners should always be referred to a physician for additional information and treatment.
- Veterinarians and physicians have different experiences concerning zoonoses; veterinarians should volunteer to speak to the pet owner's physician to clarify zoonotic issues when indicated.
- When public health–related advice is offered, it should be documented in the medical record.
- When reportable zoonotic diseases are diagnosed, appropriate public health officials should be contacted.
- Diagnostic plans to assess for presence of organisms with zoonotic potential should be offered, particularly to owners with clinically ill pets.
- All dogs and cats should be vaccinated for rabies.
- Dogs and cats should be routinely administered drugs that kill hookworms and roundworms.
- Flea and tick control should be maintained at all times.
- Veterinary clinic staff members should teach owners techniques to avoid being bitten or scratched.
- Avoid needle sticks contaminated with blood or effusions.

BOX 99.2

General Guidelines for Pet Owners to Avoid Zoonotic Transfer of Disease

- If a new pet is to be adopted, the dog or cat least likely to be a zoonotic risk is a clinically normal, arthropod-free, adult animal from a private family.
- Once the animal to be adopted is identified, it should be quarantined from any immunocompromised person until a thorough physical examination and zoonoses risk assessment is performed by a veterinarian.
- Veterinary care should be sought for all clinically ill pets.
- Physical examination and fecal examination should be performed at least once or twice yearly.
- Fecal material produced in the home environment should be removed daily, preferably by someone other than an immunocompromised individual.
- Use litterbox liners and periodically clean the litterbox with scalding water and detergent.
- Do not allow dogs or cats to drink from the toilet.
- Wear gloves when gardening and wash hands thoroughly when finished.
- Filter or boil water from sources in the environment.
- Wash your hands after handling animals.
- Do not handle animals that you are unfamiliar with.
- Clinically ill animals should not be handled by immunocompromised people, if possible.
- Pets should be maintained within the home environment to lessen exposure to other animals that may carry zoonotic agents, exposure to excrement of other animals, and exposure to fleas and ticks.
- Pets should only be fed commercially processed food.
- People should not share food utensils with pets.
- Avoid being licked by animals.
- Claws of cats should be clipped frequently to lessen the risk of skin penetration.
- To lessen the risk of bites and scratches, do not tease or physically restrain dogs and cats.
- If bitten or scratched by a dog or cat, seek medical attention.
- Control potential transport hosts, such as flies and cockroaches, that may bring zoonotic agents into the home.
- Cook meat for human consumption to 80° C for 15 minutes minimum (medium-well).
- Wear gloves when handling meat and wash hands thoroughly with soap and water when finished.

the defecation habits of cats. Human infection after direct contact with dogs or cats is extremely unlikely because the eggs are not immediately infectious.

Dogs and cats can be subclinically affected or may develop poor haircoats, poor weight gain, and gastrointestinal signs. In people, eosinophilic granulomatous reactions involving the skin, lungs, central nervous system (CNS), or eyes then occur, potentially leading to clinical signs of disease. Clinical signs and physical examination abnormalities in affected individuals include skin rash, fever, failure to thrive, CNS signs, cough, pulmonary infiltrates, and hepatosplenomegaly. Peripheral eosinophilia is common. Ocular larva migrans most commonly involves the retina and can cause reduced vision; uveitis and endophthalmitis can also occur. Visceral larva migrans is most common in children between 1 and 4 years of age, whereas ocular larva migrans is most common in older children. Diagnosis in human beings is confirmed by biopsy or can be presumed in cases with classic clinical manifestations, eosinophilia, and positive serology.

Ancylostoma caninum, Ancylostoma braziliense, Ancylostoma tubaeformis, Uncinaria stenocephala, and *Strongyloides stercoralis* have been associated with cutaneous larva migrans in the United States. Prevalence rates of hookworm infection vary by the study and have changed over the years. In one large study of more than 1 million dogs examined at 547 private veterinary hospitals in 44 U.S. states, 4.5% of samples contained eggs of *Ancyclostoma* spp. (Little et al., 2009). In high-risk areas and animals, infection rates can be much higher. For example, *A. tubaeforme* and *A. braziliense* were found in feces of 26 of 40 (65%) of the feral cats tested in one study in Florida (Liotta et al., 2012). After the passage of hookworm eggs into the environment in feces, infectious larvae are released after incubating for 1 to 3 days; humans are infected by skin penetration. In addition, eosinophilic enteritis in humans was reported after ingestion of larvated *A. caninum* eggs (Landmann and Prociv, 2003).

Animals are either subclinically ill or have nonspecific signs such as poor haircoats, failure to gain weight, vomiting, or diarrhea. Heavily infected puppies and kittens may have pale mucous membranes from blood loss anemia. In humans, the larvae cannot penetrate the dermoepidermal junction and usually die in the epidermis. Clinical signs are related to migration of the larvae, which results in an erythematous, pruritic cutaneous tunnel. Cutaneous signs usually resolve within several weeks. Abdominal pain is the most common clinical sign in humans with *A. caninum* intestinal infection.

Trichuris vulpis, the dog whipworm, is most commonly associated with large-bowel diarrhea in dogs. The organism is common in dogs of the United States (overall prevalence = 1.2%; Little et al., 2009) and has been detected in feces in some people (George et al., 2017).

Prevention of hookworms and roundworms is achieved by control of animal excrement in human environments. All puppies and kittens should have a fecal flotation performed and should be routinely treated with an anthelmintic that has efficacy against roundworms and hookworms. The Companion Animal Parasite Council (http://www.capcvet.org) maintains current guidelines on how to optimally control zoonotic parasitic infections of dogs and cats.

CESTODES

Dipylidium caninum, Echinococcus granulosa, and *Echinococcus multilocularis* are cestodes of dogs or cats that can infect humans. Wild carnivores are more common definitive hosts of *Echinococcus* spp. and shed infective eggs into the environment. *Echinococcus granulosa* eggs can be transmitted in feces of dogs after ingestion of infected sheep or rabbit tissues; *Echinococcus multilocularis* can be transmitted in feces of dogs or cats after ingestion of an infected rodent. Transmission to humans occurs after ingestion of the intermediate host (flea, *Dipylidium*) or eggs (*Echinococcus* spp.). Infection of dogs and cats with cestodes is generally subclinical. *Dipylidium* infection is most common in children after accidental ingestion of fleas and can lead to diarrhea and pruritus ani. In humans, after ingestion of eggs, which are immediately infectious, *Echinococcus* enters the portal circulation and spreads throughout the liver and other tissues. *Echinococcus multilocularis* is most common in the northern and central parts of North America but seems to be spreading with the fox population (most common definitive host). Prevention or control of cestodes is based on sanitation procedures and use of taeniacides. Praziquantel is labeled for the treatment of *Echinococcus* spp. Restricting hunting behavior of dogs and cats and feeding only processed or cooked foods should lessen potential exposure to *Echinococcus* spp. Monthly administration of praziquantel should be considered in dogs and cats allowed to hunt in endemic areas. Flea control should be maintained to lessen risk of *D. caninum* infection.

COCCIDIANS

Cryptosporidium spp. inhabit the respiratory and intestinal epithelium of many vertebrates, including birds, mammals, reptiles, and fish. Once thought to be a commensal, *Cryptosporidium* spp. are now known to cause gastrointestinal tract disease in several mammalian species, including rodents, dogs, cats, calves, and humans. The organisms have an enteric life cycle similar to that of other coccidians that culminates in the production of thin-walled, autoinfective oocysts and thick-walled, environmentally resistant oocysts that are passed in feces (Fig. 99.1). Oocysts (4-6 µm in diameter) are passed sporulated and are immediately infectious to other hosts. Multiple species of *Cryptosporidium* spp. exist, including *Cryptosporidium parvum*, *Cryptosporidium hominis*, *Cryptosporidium felis,* and *Cryptosporidium canis.* Although some *Cryptosporidium* infect multiple animal species, others have a limited host range. However, strains that infect both pets and people cannot be differentiated by light microscopy from those that infect only pets, so all *Cryptosporidium* spp. should be considered potentially zoonotic. *Cryptosporidium parvum* infection of humans after exposure to infected calves has been recognized for years, and it is now known that most human infections are from *C. hominus*. The most common *Cryptosporidium* spp. isolated from dogs and cats are the host-adapted *C. canis* and *C. felis,* respectively, and so most consider pets with *Cryptosporidium* spp. infections to not be significant risks for humans (Lucio-Forster et al., 2010). In one study, cat or dog ownership was not statistically associated with cryptosporidiosis in human immunodeficiency virus (HIV)-infected people (Glaser et al., 1998).

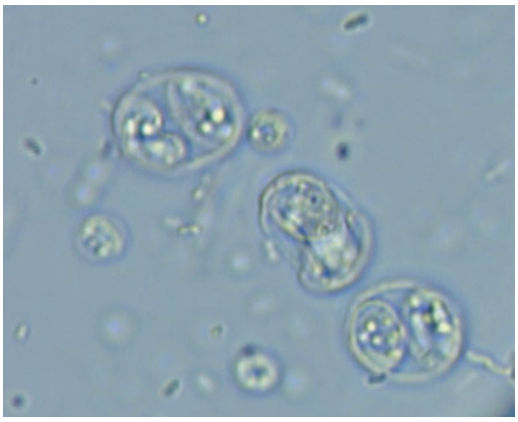


FIG 99.1
Cryptosporidium parvum and *Toxoplasma gondii* oocysts on a fecal flotation. The *C. parvum* oocysts are approximately 4 × 5 µm, and the *T. gondii* oocysts are approximately 10 × 12 µm.

Infection of dogs and cats by *Cryptosporidium* spp. is usually subclinical, but small-bowel diarrhea occurs in some cases. Immunosuppression may potentiate disease; several dogs and cats had concurrent FeLV infection, canine distemper virus infection, or intestinal lymphoma. Clinical cryptosporidiosis is characterized by small-bowel diarrhea and is generally self-limiting in immunocompetent people, but fatal infection is common in those with AIDS.

The small size (approximately 4-6 µm in diameter) of *Cryptosporidium* spp. oocysts leads to difficulty in diagnosis. Routine salt solution flotation and microscopic examination at ×100 magnification commonly lead to false-negative results. The combination of concentration techniques with fluorescent antibody staining or acid-fast staining appears to be more sensitive. Multiple enzyme-linked immunosorbent assays for the detection of *C. parvum* antigen in feces are commercially available but do not accurately detect *C. felis* or *C. canis.* PCR assay is the most sensitive test to date and is now routinely available but not standardized among laboratories.

No drug has been shown to eliminate *Cryptosporidium* spp. from the gastrointestinal tract. However, clinical signs usually resolve when azithromycin is administered orally at 10 mg/kg q24h, tylosin is administered orally at 10 to 15 mg/kg q8h, or nitazoxanide is administered orally at 37.5-75 mg/kg twice, 14 days between doses. Optimal duration of therapy is unknown; some cases have required administration of azithromycin for several weeks before clinical signs resolve. Avoiding exposure is the most effective prevention. Routine disinfectants require extremely long contact with the organism to be effective. Drying, freeze thawing, and steam cleaning can inactivate the organism. Surface water collected in the field for drinking should be boiled or filtered. If the

owner of a dog or cat with *Cryptosporidium* spp. infection would like to know whether the pet is carrying a pet species or zoonotic species, genotyping can be performed commercially in the United States (www.dlab.colostate.edu).

Toxoplasma gondii is a ubiquitous coccidian with worldwide distribution (Lappin et al., 2010). Most seroprevalence studies performed in the United States suggest that at least 30% of cats and humans have previously been exposed. Cats are the only known definitive host of the organism, completing the enteroepithelial cycle (sexual phase) that results in the passage of environmentally resistant unsporulated oocysts in feces. Oocyst sporulation occurs in 1 to 5 days in the presence of oxygen; sporulated oocysts are infectious to most warm-blooded vertebrates (see Fig. 99.1). After infection by *T. gondii,* an extraintestinal phase that ultimately leads to the formation of tissue cysts containing the organism develops. Infection by *T. gondii* occurs after ingestion of sporulated oocysts, after ingestion of tissue cysts, or transplacentally. Transplacental infection of humans and cats usually occurs only if the mother is infected for the first time during gestation.

In dogs and cats, clinical disease from *T. gondii* infection occurs occasionally and is manifested most commonly by fever, uveitis, pulmonary disease, hepatic disease, and CNS disease (see Chapter 98). Infected immunocompetent humans are generally asymptomatic; self-limiting fever, lymphadenopathy, and malaise occur occasionally. Transplacental infection of humans results in clinical manifestations, including stillbirth, hydrocephalus, hepatosplenomegaly, and retinochoroiditis. Presence of *T. gondii* antibodies has been associated with presence of behavioral abnormalities in people, but a direct cause and effect has not been established (Fuglewicz et al., 2017). Chronic tissue infection in humans can be reactivated by immunosuppression, leading to dissemination and severe clinical illness; this has been commonly associated with drug-induced immunosuppression and AIDS. Approximately 10% of humans with AIDS develop toxoplasmic encephalitis.

Toxoplasma gondii oocysts are most effectively demonstrated in cat feces after sugar or other centrifugation techniques. Clinical toxoplasmosis is difficult to diagnose in humans, dogs, and cats but usually involves the combination of clinical signs, serologic test results, organism demonstration techniques, and response to anti-*Toxoplasma* drugs (Lappin, 2010; see Chapter 98).

Although *T. gondii* is recognized as one of the most common zoonoses, humans are usually not infected by direct contact with cats. The oocyst-shedding period usually lasts several days to several weeks (≈7-10 days if the cat was infected by tissue cyst ingestion). Because oocysts have to sporulate to be infectious, contact with fresh feces cannot cause infection. Cats are quite fastidious and usually do not allow feces to remain on their skin for periods long enough to lead to oocyst sporulation. Oocysts were not isolated from the fur of cats 7 days after completion of the oocyst-shedding period in one study. Most studies evaluating cat ownership as a risk factor for human toxoplasmosis has showed minimal associations including one study of HIV-infected individuals (Wallace et al., 1993). In addition, one study of veterinary staff members who worked frequently with cats had low seroprevalence rates suggesting exposure to cats did not increase their risk for acquiring *T. gondii* infection (Shuhaiber et al., 2003). Cats infected by *T. gondii* usually do not shed or shed lower numbers of oocysts on secondary exposures (Zulpo et al., 2018) and did not have repeat oocyst shedding after being administered cyclosporine in a recent study (Lappin et al., 2015). Cats do not need to be removed from households with immunodeficient people or pregnant women because of the risk for acquiring toxoplasmosis (www.cdc.gov/parasites/toxoplasmosis/gen_info/pregnant.html). Prevention of *T. gondii* infection is summarized in Box 98.1.

FLAGELLATES, AMOEBA, AND CILIATES

Giardia spp. (flagellate), *Entamoeba histolytica* (amoeba), and *Balantidium coli* (ciliate) are enteric protozoans that can be transmitted to humans by contact with feces; the cysts do not require an incubation period to become infectious. *Entamoeba histolytica* infection is extremely rare in dogs and cats; *B. coli* infection is rare in dogs and has not been reported in cats.

Giardia spp. infection of dogs and cats is common and can be detected in feces of normal dogs and cats, and in those with small-bowel diarrhea (and occasionally mixed-bowel diarrhea in cats). Clinical signs of disease are generally more severe in immunodeficient individuals. Because the organism is immediately infectious when passed as cysts in stool, direct zoonotic transfer is possible. Genetic studies have detected multiple *Giardia* spp., and most dogs and cats are infected with the host-adapted assemblages C, D, and F (Scorza et al., 2012). However, as is the case with *Cryptosporidium,* because determining zoonotic strains of *Giardia* spp. by microscopic examination is not possible, assume that feces from all dogs and cats infected with *Giardia* spp. are a potential human health risk. Fecal examination should be performed on all dogs and cats at least yearly, and treatment with drugs with anti-*Giardia* activity, such as fenbendazole, metronidazole, or febantel/praziquantel/pyrantel, should be administered if indicated (see Chapter 28). Febantel/praziquantel/pyrantel is now labeled for the treatment of giardiasis in dogs in some countries. Centrifugation techniques (zinc sulfate or sugar) are considered by most parasitologists to be optimal for demonstration of cysts. If fresh stool is available from dogs or cats with diarrhea, examination of a wet mount to detect the motile trophozoites may improve sensitivity (see also Chapter 91). Monoclonal antibody-based immunofluorescent antibody tests, fecal antigen tests, and PCR assays are available but should be used in addition to, not in lieu of, fecal flotation, which can also reveal other parasites. The combination of a fecal centrifugation technique with a *Giardia* antigen test has approximately 97% sensitivity. Fecal PCR assay results can be less sensitive due to presence of fecal PCR inhibitors (Hascall et al., 2016). The Companion Animal Parasite Council does not recommend treating

healthy carriers with more than one drug (www.capcvet.org). If a pet is healthy but persistently *Giardia*-positive, genotyping can be performed to determine whether the assemblage is zoonotic (www.dlab.colostate.edu).

Giardia vaccines for dogs or cats are no longer commercially available in the United States. Prevention of zoonotic giardiasis includes boiling or filtering surface water for drinking and washing hands that have handled fecally contaminated material, even if gloves were worn. In dogs and cats treated for giardiasis, infection can be documented again several weeks later in approximately 75% of animals. Thus the primary goal for the treatment of giardiasis is elimination of diarrhea. Whether these cases are a treatment failure or a reinfection is unknown.

BACTERIA

Campylobacter spp., *Escherichia coli, Helicobacter* spp. *Salmonella* spp., and *Yersinia enterocolitica* can each infect dogs and cats, and can cause disease in humans. When pets with *Clostridium difficile* are identified, the animal was likely infected by a human and usually is a subclinical carrier. Transmission from animals to humans is by fecal-oral contact. Dogs can be subclinical carriers of *Shigella* spp., but humans are the natural hosts. Although *Helicobacter pylori* was isolated from a colony of cats, whether dogs and cats are a common source of *Helicobacter* infection in humans is unclear. However, on the basis of epidemiologic studies, it is unlikely. In most studies on prevalence of enteric zoonoses, *Salmonella* spp. and *Campylobacter* spp. infections were uncommon in pet dogs and cats. The prevalence of *Salmonella* and *Campylobacter* infections is greater in young animals housed in unsanitary or crowded environments.

Gastroenteritis can occur in dogs or cats after infection by *Salmonella* spp., *Campylobacter* spp., or *E. coli; Y. enterocolitica* is probably a commensal agent in animals but causes fever, abdominal pain, polyarthritis, and bacteremia in humans. *Helicobacter* infections cause gastritis, which is commonly manifested as vomiting, belching, and pica. *Salmonella* spp. infection in dogs and cats is often subclinical. Approximately 50% of clinically affected cats have gastroenteritis; many present with signs of bacteremia that usually include fever (Tauni et al., 2000). Salmonellosis of cats and humans has been associated with songbirds (songbird fever). Abortion, stillbirth, and neonatal death can result from in utero infection. Diagnosis of *Salmonella* spp., *Campylobacter jejuni, E. coli,* and *Y. enterocolitica* is based on culture of feces (see Chapter 91). A single negative culture may not rule out infection. Although PCR assays are available, culture is superior because antimicrobial susceptibility can be determined.

Antibiotic therapy can control clinical signs of disease from infection by *Salmonella* spp. or *Campylobacter* spp. (see Chapter 28) but should not be administered orally to pets because of the risk for antibiotic resistance. Parenteral drugs should be administered if bacteremia is suspected. Strains of *Salmonella* resistant to most antibiotics have been detected in several cats. Prevention of enteric bacterial zoonoses is based on sanitation and control of exposure to feces. Immunodeficient people should avoid young animals and animals from crowded or unsanitary housing, particularly if clinical signs of gastrointestinal tract disease occur.

BITE, SCRATCH, OR EXUDATE EXPOSURE ZOONOSES

BACTERIA

It is estimated that, between 2005 and 2009, there were approximately 300,000 nonfatal dog bite injuries per year in the United States (Quirk, 2012). Most of the aerobic and anaerobic bacteria associated with bite or scratch wounds cause only local infection in immunocompetent individuals. However, 28% to 80% of cat bites become infected, and severe sequelae, including meningitis, endocarditis, septic arthritis, osteoarthritis, and septic shock, can occur. The majority of the aerobic and anaerobic bacteria associated with dog or cat bite or scratch wounds lead only to local infection in immunocompetent individuals. Immunodeficient humans or those exposed to *Pasteurella* spp., *Capnocytophaga canimorsus* (DF-2), or *Capnocytophaga cynodegmi* more consistently develop systemic clinical illness. Splenectomized humans are at increased risk for developing bacteremia.

Dogs and cats are subclinical carriers of multiple bacteria in the oral cavity. After a person is bitten or scratched, local cellulitis is noted initially, followed by evidence of deeper tissue infection. Bacteremia and the associated clinical signs of fever, malaise, and weakness are common, and death can occur within hours after infection with *Capnocytophaga* spp. in immunodeficient or splenectomized humans. Diagnosis is confirmed by culture. Treatment of carrier animals is not necessary. Treatment of clinically affected humans includes local wound management and parenteral antibiotic therapy. Penicillin derivatives are highly effective against most *Pasteurella* infections; penicillins and cephalosporins are effective against *Capnocytophaga* spp. in vitro.

Normal dogs and cats, as well as those with clinical signs of disease, can carry methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP) on the skin. These agents can be spread among veterinary or human patients and doctors, so this is a significant problem in hospitals (Febler et al., 2018; Weese et al., 2006). A recent study of nasal and perianal samples completed in an open admission shelter showed MRSA in 0.5% of cat samples, MRSA in 0.5% of dog samples, and MRSP in 3% of dog samples (Gingrich et al., 2011). These prevalence rates are generally lower than those from dogs or cats from veterinary hospitals. These animals are generally not a risk for immunocompetent and otherwise healthy people, but care should be taken to avoid contamination of open wounds if an infected animal is being cared for. It is wise for veterinary hospitals to have an MRSA and MRSP policy for staff members; if repeated infections occur in veterinary cases, a staff member could be a carrier, so testing may been necessary.

Mycoplasma spp. infections of humans resulting from cat bites, one with cellulitis and one with septic arthritis, have been reported. L-form bacteria are cell wall–deficient organisms associated with chronic draining skin wounds in cats commonly resistant to cell wall–inhibiting antibiotics such as penicillins and cephalosporins. Infection of a human being after a cat bite has been documented. Diagnosis can be confirmed only by histologic examination of tissue. Doxycycline has been used to treat cats and people successfully. Gloves should be worn when attending cats with draining tracts, and hands should be cleansed thoroughly.

Bartonella henselae can infect both dogs and cats, and is the most common cause of cat scratch disease, as well as bacillary angiomatosis and bacillary peliosis—common disorders in humans with AIDS (Breitschwerdt et al., 2010). Dogs and cats can also be infected with several other *Bartonella* spp., including *Bartonella clarridgeiae, Bartonella koehlerae, Bartonella vinsonii* (dogs), and *Bartonella quintana* (see Chapter 94). *Bartonella henselae* has been isolated from the blood of subclinically ill, seropositive cats and also from some cats with a variety of clinical manifestations such as fever, lethargy, lymphadenopathy, uveitis, gingivitis, and neurologic diseases. Infection of dogs has also been associated with clinical illness. Seroprevalence in cats varies by region, but up to 93% of cats in some geographic areas of the United States are *Bartonella* spp. seropositive. *Bartonella* spp. have also been detected in dog saliva, and dogs have been associated with bartonellosis in people (see Chapter 94). *Bartonella henselae*, *B. clarridgeiae,* and *B. koehlerae* are transmitted between cats by fleas, so the prevalence is greatest in cats from states where fleas are common (Breitschwerdt et al., 2010). Transmission to humans commonly occurs after cat bites or scratches; the disease appears to be transmitted most commonly from kittens. *B. henselae* survives in flea frass for at least 9 days, so the cat's claws and teeth are likely contaminated with *B. henselae* during grooming, which emphasizes the maintenance of flea control on dogs and cats (Fig. 99.2). In one study of cats with *C. felis* infestation, *Bartonella* spp. DNA could be amplified from the skin (31%) and claw beds (18%) of the cats (Lappin and Hawley, 2009).

Humans with cat scratch disease develop a variety of clinical signs, such as lymphadenopathy, fever, malaise, weight loss, myalgia, headache, conjunctivitis, skin eruptions, and arthralgia (Breitschwerdt et al., 2007; Breitschwerdt et al., 2010). Bacillary angiomatosis is a diffuse disease resulting in vascular cutaneous eruptions. Bacillary peliosis is a diffuse systemic vasculitis of parenchymal organs, particularly the liver. The incubation period for cat scratch disease is approximately 3 weeks. Most cases of cat scratch disease are self-limiting but may take several months to completely resolve. Recently, *B. henselae* has been documented as a cause of chronic disease syndromes like fever, headaches, polyarthritis, and chronic fatigue; immunocompetent veterinary healthcare providers or *Bartonella* researchers may be overrepresented from increased risk of exposure (Breitschwerdt et al., 2007). Most medical doctors may not recognize this differential and should be informed if a patient is exhibiting these problems.



FIG 99.2
Ctenocephalides felis frass and eggs that can contain live *Bartonella* spp. or *Rickettsia felis*. (Courtesy the HESKA Corporation.)

Blood culture, blood PCR, and serologic testing can be used to determine the risk of individual cats, dogs, or people (see Chapter 94). The use of Bartonella alpha proteobacteria growth medium (BAPGM) culture media with PCR assay has been shown to be one of the most sensitive ways to prove *Bartonella* spp. bacteremia in dogs and people. This assay is available at a commercial laboratory (www.galaxydx.com). In dogs and cats, although serologic testing can be used to determine whether an individual has been exposed, both seropositive and seronegative cats can be bacteremic, limiting the diagnostic utility of serologic testing. Thus testing healthy cats or dogs for *Bartonella* spp. infection is not currently recommended by the Centers for Disease Control and Prevention (Kaplan et al., 2009) or the American Association of Feline Practitioners (Brunt et al., 2006). Testing should be reserved for cats with suspected clinical bartonellosis.

In experimental studies, administration of doxycycline, tetracycline, erythromycin, amoxicillin-clavulanate, or enrofloxacin can limit bacteremia but does not cure infection in all cats and has not been shown to lessen the risk of cat scratch disease. Azithromycin was commonly administered to cats with suspected clinical bartonellosis but is now considered contraindicated for feline bartonellosis due to rapid induction of antimicrobial resistance (Biswas et al., 2010). Thus antibiotic treatment of healthy bacteremic cats is controversial and not currently recommended by the Centers for Disease Control (Kaplan et al., 2009) and Prevention or the American Association of Feline Practitioners (Brunt et al., 2006). Treatment should be reserved for cats with suspected clinical bartonellosis. Strict flea control should be maintained because the administration of monthly imidacloprid topically or in an 8-month collar has been shown to block transmission of *B. henselae* among cats (Bradbury and Lappin, 2010; Lappin et al., 2013). Immunodeficient people

should avoid kittens. Cat claws should be kept clipped, and cats should never be teased. Cat-induced wounds should immediately be cleansed, and medical advice sought.

Plague in cats and dogs is caused by *Yersinia pestis,* a gram-negative coccobacillus found most commonly in Midwestern and far Western states, particularly Arizona, New Mexico, and Colorado. Rodents are the natural hosts for this bacterium; cats are most commonly infected by ingestion of bacteremic rodents or lagomorphs or by being bitten by *Yersinia*-infected rodent fleas. Humans are most commonly infected by rodent flea bites, but many cases of transmission by exposure to wild animals and infected domestic cats have been documented. From 1977 to 1998, 23 cases of human plague (88% of the total cases) resulted from contact with infected cats (Gage et al., 2000). Infection can be induced by inhalation of respiratory secretions of cats with pneumonic plague, through bite wounds, or by contamination of mucous membranes or abraded skin with secretions or exudates.

Bubonic, septicemic, and pneumonic plague can develop in cats and humans; each form has accompanying fever, headache, weakness, and malaise. Because cats are most commonly infected by ingestion of bacteremic rodents, suppurative lymphadenitis (buboes) of the cervical and submandibular lymph nodes is the most common clinical manifestation. Exudates from cats with lymphadenopathy should be examined cytologically for the presence of large numbers of the characteristic bipolar rods (see Fig. 94.3). The diagnosis is usually confirmed by PCR assays that amplify the DNA of *Y. pestis* in exudates or aspirates. The diagnosis can also be confirmed by fluorescent antibody staining of exudates; culture of exudates, the tonsillar area, and saliva; and documentation of increasing antibody titers. People who are exposed to infected cats should be urgently referred to physicians for antimicrobial therapy, and public health officials should be alerted. Doxycycline, fluoroquinolones, chloramphenicol, or aminoglycosides can be used successfully for the treatment of plague. Parenteral antibiotics should be used during the bacteremic phase. Cats or dogs with suppurative lymphadenitis should be considered plague suspects, and extreme caution should be exercised when handling exudates or treating draining wounds. Suspect animals should be treated for fleas and housed in isolation. Pets are generally not considered infectious to humans after 4 days of antibiotic treatment.

Francisella tularensis is the gram-negative bacillus found throughout the continental United States that causes tularemia. The agent has several ticks capable of transmitting the agent. Human tularemia occurs most commonly after exposure to ticks and less commonly from contact with infected animals. However, human cases after exposure to dogs or cats have been reported (Capellan et al., 1993; Rimawi et al., 2015; Salit et al., 2013).

Infected cats exhibit generalized lymphadenopathy and abscess formation in organs such as the liver and spleen, which leads to fever, anorexia, icterus, and death. Ulceroglandular, oculoglandular, glandular, oropharyngeal, pneumonic, and typhoidal forms have been described in humans and develop depending on the route of exposure. Unlike the situation with plague, the organism is not often recognized in exudates or lymph node aspirates from infected cats. PCR assays, cultures, and documentation of increasing antibody titers can be used to confirm the diagnosis in pets and humans. Most cases of tularemia in pets have been diagnosed at necropsy, so optimal treatment is unknown. Streptomycin and gentamicin are the drugs used most commonly to treat humans. Tetracycline or chloramphenicol can be used in cases not requiring hospitalization but may be associated with relapses. Avoiding exposure to rabbits, ticks, and infected dogs or cats prevents the disease. All dogs or cats dying with bacteremia should be handled carefully at necropsy.

FUNGI

Of the many fungal agents that infect both humans and animals, only *Sporothrix* spp. and the dermatophytes have been shown to infect humans on direct exposure. *Histoplasma, Blastomyces, Coccidioides, Aspergillus,* and *Cryptococcus* infections of humans and animals can occur in the same household but generally result from a common environmental exposure (see Chapter 97).

Sporothrix spp. are cosmopolitan in distribution, and the soil is believed to be the natural reservoir. Early studies usually reported *S. schenckii* as the primary zoonotic agent. However, in Brazil, *S. brasiliensis* is most common and frequently a zoonosis (Della Terra et al., 2017). Dogs generally do not produce large numbers of *Sporothrix* in exudates and are not as great a zoonotic risk as cats. Infection of cats and humans usually occurs after the organism contaminates broken skin. Cats are believed to be infected by scratches from contaminated claws of other cats; infection is most common in outdoor males. Humans can be infected by contamination of cutaneous wounds with exudates from infected cats. *Sporothrix* infection in cats can be cutaneolymphatic, cutaneous, or disseminated. Chronic draining cutaneous tracts are common. Cats commonly produce large numbers of the organism in feces, tissues, and exudates; thus veterinary care personnel are at high risk when treating infected cats (Fig. 99.3). The clinical disease in humans is similar to that in cats. The organism can be demonstrated by cytologic examination of exudates or culture. Fluconazole, itraconazole, or ketoconazole are effective treatments. Gloves should be worn when attending cats with draining tracts, and hands should be cleansed thoroughly.

VIRUSES

Rabies is still the only relevant direct small animal viral zoonosis in the United States. See Chapter 64 for a discussion of this agent, as well as the Compendium on Rabies Control 2016 (Brown et al., 2016). Pseudorabies is a herpesvirus that infects pigs; dogs and humans can develop self-limiting pruritic skin disease after exposure. Dogs occasionally develop CNS disease characterized by depression and seizures. Diagnosis is suspected on the basis of the exposure history, and prevention is by avoiding exposure. To date, there is no



FIG 99.3
Sporothrix schenckii-associated skin lesions in a cat in Colorado.

evidence suggesting that the three retroviruses of cats—feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and feline foamy virus (FeFV)—infect humans. In one study, 204 veterinarians and others potentially exposed to feline retroviruses were assessed for antibodies against FIV and FeFV, FeLV p27 antigen, and FeLV provirus; test results on all were negative (Butera et al., 2000). Because both FeLV and FIV can induce immune deficiency, infected cats should be considered more likely than retrovirus-naïve cats to be carrying other potential zoonotic agents, particularly if gastrointestinal tract signs are present.

RESPIRATORY TRACT AND OCULAR ZOONOSES

BACTERIA

Bordetella bronchiseptica is a bacterium that induces respiratory tract infections in dogs and cats (see Chapter 21). The classic clinical manifestation is tracheobronchitis, but the organism can also cause pneumonia, sneezing, and nasal discharge. Humans rarely develop clinical disease caused by *B. bronchiseptica* unless they are immunologically compromised (see Table 99.1). Most cases of *B. bronchiseptica* infection in humans have been in patients that were immunodeficient (Dworkin et al., 1999; Wernli et al., 2011). *Bordetella bronchiseptica* infection in humans has been associated with cats and dogs. Amoxicillin-clavulanate, chloramphenicol, enrofloxacin, and tetracycline derivatives are all effective treatments. Animals with upper or lower respiratory tract inflammatory disease should be kept away from immunodeficient people until the animals are clinically normal. However, treated animals can still shed the organism.

Chlamydia felis (formerly *Chlamydia psittaci*) causes mild conjunctival disease and rhinitis in cats. Conjunctivitis in humans after direct contact with ocular discharges from cats has been described. A human isolate of *Chlamydia* spp. was inoculated into cats, resulting in conjunctivitis and persistent infection, suggesting that the isolate was a feline strain. Occasionally the organism is associated with systemic disease; atypical pneumonia was diagnosed in an apparently immunocompetent 48-year-old man, malaise and cough were diagnosed in an immunosuppressed woman, and endocarditis and glomerulonephritis were diagnosed in a 40-year-old woman. Diagnosis is based on organism demonstration by culture, cytologic documentation of characteristic inclusion bodies, or fluorescent antibody staining of conjunctival scrapings. Tetracycline- or chloramphenicol-containing eye ointments are generally effective in the treatment of infection. Oral administration of doxycycline is still considered the optimal way to clear the carrier state. Care should be taken to avoid direct conjunctival contact with discharges from the respiratory or ocular secretions of cats, especially by immunosuppressed persons (see Box 99.2). Employees should be directed to wear gloves or wash hands carefully when attending cats with conjunctivitis.

Humans are the principal natural hosts for *Streptococcus* group A bacteria; *Streptococcus pyogenes* is the most common cause of "strep throat" in humans. Dogs and cats in close contact with infected humans can develop transient, subclinical colonization of pharyngeal tissues and can transmit the infection to other humans. However, this is poorly documented and believed to be unusual (Wilson et al., 1995). The organism can be cultured from the tonsillar crypts. Culture-positive animals should be treated with penicillin derivatives. If animals are to be treated in a household with chronic, recurrent "strep throat," all humans should also be treated because they could be chronic subclinical carriers.

Yersinia pestis and *F. tularensis* can be transmitted from cats to humans in respiratory secretions. In endemic areas, cats with clinical signs or radiographic abnormalities consistent with pneumonia should be handled as plague or tularemia suspects. Gloves, mask, gown, and eye protection should be worn while performing transoral airway washings in suspect cats.

VIRUSES

Influenza A viral infections have been detected in some cats after close exposure to infected birds (Leschnik et al., 2007). In studies of naturally exposed and experimentally infected cats, some cats developed respiratory disease and others have become asymptomatic carriers. Results of studies assessing transmission between infected cats have been variable. Very rarely, cats infected with an influenza virus are associated with clinical disease in humans (Lee et al., 2017).

GENITAL AND URINARY TRACT ZOONOSES

Coxiella burnetii is a rickettsial agent found throughout the world, including North America (see Table 99.1). Many ticks, including *Rhipicephalus sanguineus,* are naturally infected with *C. burnetii.* Cattle, sheep, and goats are

commonly subclinically infected and pass the organism into the environment in urine, feces, milk, and parturient discharges. Seropositive dogs have been detected, but zoonotic transfer to humans from dogs has not been documented. Infection of cats most commonly occurs after tick exposure, ingestion of contaminated carcasses, or aerosolization from a contaminated environment. Fever, anorexia, and lethargy developed in some experimentally infected cats. Infection has been associated with abortion in cats, but the organism can also be isolated from normal parturient cats. Infection of cats appears to be common; 20% of cats from a shelter in southern California and 20% of cats in Maritime Canada were seropositive, the organism was grown from the vagina of healthy cats in Japan, and DNA of the organism was amplified from uterine tissues of cats in Colorado (Cairns et al., 2007).

Human illness associated with direct contact with infected cats occurs after aerosol exposure to the organism passed by parturient or aborting cats; clinical signs develop 4 to 30 days after contact. Humans commonly develop acute clinical signs similar to those associated with other rickettsial diseases, including fever, malaise, headache, pneumonitis, myalgia, and arthralgia (Marrie, 1995). After primary infection, chronic Q fever develops in approximately 1% and can manifest as hepatic inflammation or valvular endocarditis. Tetracyclines, chloramphenicol, and quinolones are usually effective therapeutic agents in humans. Gloves and masks should be worn when attending to parturient or aborting cats. People who develop fever or respiratory tract disease after exposure to parturient or aborting cats should seek medical attention.

Leptospira spp. can be transmitted in urine from infected dogs and cats to humans, resulting in clinical disease (Sykes et al., 2010). Host-adapted species cause subclinical infection; infection by non-host-adapted species commonly results in clinical illness. The organisms enter the body through abraded skin or intact mucous membranes. (See Chapter 94 for a detailed discussion of the clinical manifestations of this disease and its treatment in dogs and cats.) Human clinical syndromes vary with the serovar but are similar to those that occur in the dog. Animals with suspected leptospirosis should be handled while wearing gloves. Contaminated surfaces should be cleaned with detergents and disinfected with iodine-containing products. Vaccines containing four leptospire serovars should be considered (see Chapter 93).

Brucella canis is a bacterium that preferentially infects the testicles, prostate, uterus, and vagina of dogs (see Chapters 55 and 56). The infection is maintained in dogs primarily by venereal transmission. Humans can be infected by direct contact with vaginal and preputial discharges from dogs. Clinical syndromes in dogs are diverse but commonly include abortion, stillbirth, failure to conceive, orchitis, epididymitis, vaginal discharge, uveitis, discospondylitis, and bacteremia. Intermittent fever, depression, and malaise are common in infected people. Diagnosis is based on serologic testing or demonstration of the organism by culture or PCR assay. Dogs with clinical signs of brucellosis should be evaluated serologically for *Brucella* infection with the 2-mercaptoethanol rapid slide agglutination card test. Seronegative dogs are unlikely to harbor *Brucella* unless the clinical syndrome is peracute. Seropositive dogs should have results confirmed by tube agglutination or agar gel immunodiffusion. Long-term antibiotic treatment (tetracyclines, aminoglycosides, quinolones) usually does not clear the infection, thus some recommend euthanasia of infected dogs. Ovariohysterectomy or castration will lessen contamination of the environment. Genital tract secretions should be avoided.

SHARED VECTOR ZOONOSES

Some zoonotic agents are transmitted between animals and humans by shared vectors such as fleas, ticks, or mosquitoes. *Rickettsia rickettsii* (ticks), *Rickettsia felis* (fleas), *Ehrlichia* spp. (ticks), *Anaplasma phagocytophilum* (ticks), *Borrelia burgdorferi* (ticks), *Bartonella* spp. (fleas and ticks), *Dipylidium caninum* (fleas), *Dirofilaria immitis* (mosquitoes), and West Nile virus (mosquitoes) are examples of vector-borne zoonoses common in the United States. For the flea- and tick-borne zoonoses, the pet brings the vector of the organism into the environment, resulting in exposure of the human being. Veterinary healthcare providers could have a slightly increased risk of exposure because they handle many animals infested with fleas and ticks. However, the vector, not direct contact with the infested animal, results in infection of the person. Flea and tick control should always be maintained with animals, and infested animals seen in the clinic should be treated immediately. See other sections of this textbook for detailed discussions of these agents.

SHARED ENVIRONMENT ZOONOSES

Some agents that infect both animals and man are not commonly transmitted between the pet and the owner by direct contact but are acquired from the same environmental source. Notable examples include *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Cryptococcus neoformans,* and *Aspergillus* spp. See Chapter 97 for detailed discussions of these agents.

Suggested Readings

Biswas S, et al. Comparative activity of pradofloxacin, enrofloxacin, and azithromycin against Bartonella henselae isolates collected from cats and a human. *J Clin Microbiol*. 2010;48:617.

Bradbury CA, Lappin MR. Evaluation of topical application of 10% imidacloprid-1% moxidectin to prevent Bartonella henselae transmission from cat fleas. *J Am Vet Med Assoc*. 2010;236:869.

Breitschwerdt EB, et al. Bartonellosis: an emerging infectious disease of zoonotic importance to animals and human beings. *J Vet Emerg Crit Care (San Antonio)*. 2010;20:8.

Breitschwerdt EB, et al. *Bartonella* species in blood of immunocompetent persons with animal and arthropod contact. *Emerg Infect Dis*. 2007;13:938.

Brown CM, et al; the compendium of animal rabies prevention and control committee. Compendium of animal rabies prevention and control, 2016. *J Am Vet Med Assoc*. 2016;248:505–517.

Brunt J, et al. Association of Feline Practitioners 2006 Panel report on diagnosis, treatment, and prevention of Bartonella spp. infections. *J Feline Med Surg*. 2006;8:213.

Butera ST, et al. Survey of veterinary conference attendees for evidence of zoonotic infection by feline retroviruses. *J Am Vet Med Assoc*. 2000;217:1475.

Capellan J, et al. Tularemia from a cat bite: case report and review of feline-associated tularemia. *Clin Infect Dis*. 1993;16:472.

Cairns K, et al. Prevalence of Coxiella burnetii DNA in vaginal and uterine samples from healthy cats of north-central Colorado. *J Feline Med Surg*. 2007;9:196.

De Santis AC, et al. Estimated prevalence of nematode parasitism among pet cats in the United States. *J Am Vet Med Assoc*. 2006a;228:885.

De Santis-Kerr AC, et al. Prevalence and risk factors for *Giardia* and coccidia species of pet cats in 2003-2004. *J Feline Med Surg*. 2006b;8:292.

Della Terra PP, et al. Exploring virulence and immunogenicity in the emerging pathogen *Sporothrix brasiliensis*. *PLoS Negl Trop Dis*. 2017;11(8):e0005903.

Dworkin MS, et al. *Bordetella bronchiseptica* infection in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1999;28:1095.

Dunston RW, et al. Feline sporotrichosis: a report of five cases with transmission to humans. *J Am Acad Dermatol*. 1986;15:37.

Eidson M, et al. Clinical, clinicopathologic and pathologic features of plague in cats: 119 cases (1977-1988). *J Am Vet Med Assoc*. 1991;199:1191.

Febler AT, et al. Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) among employees and in the environment of a small animal hospital. *Vet Microbiol*. 2018;221:153–158.

Fuglewicz AJ, et al. Relationship between toxoplasmosis and schizophrenia: a review. *Adv Clin Exp Med*. 2017;26:1031–1036.

Gage KL, et al. Cases of cat-associated human plague in the Western US, 1977-1998. *Clin Infect Dis*. 2000;30:893.

George S, et al. The molecular speciation of soil-transmitted helminth eggs collected from school children across six endemic countries. *Trans R Soc Trop Med Hyg*. 2017;doi:10.1093/trstmh/trw078. Jan 18, [Epub ahead of print].

Gingrich EN, et al. Prevalence of methicillin-resistant staphylococci in northern Colorado shelter animals. *J Vet Diagn Invest*. 2011;23:947.

Glaser CA, et al. Association between *Cryptosporidium* infection and animal exposure in HIV-infected individuals. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17:79–82.

Hartley JC, et al. Conjunctivitis due to Chlamydophila felis (Chlamydia psittaci feline pneumonitis agent) acquired from a cat: case report with molecular characterization of isolates from the patient and cat. *J Infect*. 2001;43:7.

Hascall KL, et al. Prevalence of enteropathogens in dogs attending 3 regional dog parks in Northern California. *J Vet Intern Med*. 2016;30:1838–1845.

Kaplan JE, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations and Reports. *MMWR*. 2009;58(RR04):1.

Landmann JK, Prociv P. Experimental human infection with the dog hookworm, *Ancylostoma caninum*. *Med J Aust*. 2003;178:69.

Lappin MR, Hawley JR. Presence of *Bartonella* species and *Rickettsia* species DNA in the blood, oral cavity, skin and claw beds of cats in the United States. *Vet Dermatol*. 2009;20:509.

Lappin MR. Update on the diagnosis and management of *Toxoplasma gondii* infection in cats. *Top Companion Anim Med*. 2010;25:136.

Lappin MR, et al. A flea and tick collar containing 10% imidacloprid and 4.5% flumethrin prevents flea transmission of Bartonella henselae in cats. *Parasit Vectors*. 2013;25(6):26.

Lappin MR, et al. Effect of oral administration of cyclosporine on *Toxoplasma gondii* infection status of cats. *Am J Vet Res*. 2015;764:351–357.

Lee CT, et al; the Influenza A (H7N2) Response Team. Outbreak of Influenza A (H7N2) among cats in an animal shelter with Cat-to-Human transmission - New York City, 2016. *Clin Infect Dis*. 2017;doi:10.1093/cid/cix668. Jul 28, [Epub ahead of print].

Leschnik M, et al. Subclinical infection with avian Influenza A (H5N1) virus in cats. *Emerg Infect Dis*. 2007;13:243.

Liotta JL, et al. Prevalence of *Ancylostoma braziliense* in cats in three northern counties of Florida, United States. *J Parasitol*. 2012;98:1032–1033.

Little SE, et al. Prevalence of intestinal parasites in pet dogs in the United States. *Vet Parasitol*. 2009;166:144.

Lucio-Forster A, et al. Minimal zoonotic risk of cryptosporidiosis from pet dogs and cats. *Trends Parasitol*. 2010;26:174.

Marrie TJ. Coxiella burnetii (Q fever) pneumonia. *Clin Infect Dis*. 1995;21(suppl):S253.

O'Rourke GA, Rothwell R. *Capnocytophaga canimorsis* a cause of septicaemia following a dog bite: a case review. *Aust Crit Care*. 2011;24:93.

Overgaauw PA, et al. Zoonotic parasites in fecal samples and fur from dogs and cats in The Netherlands. *Vet Parasitol*. 2009; 163:115.

Quirk JT. Non-fatal dog bite injuries in the U.S.A., 2005-2009. *Public Health*. 2012;126:300.

Rimawi RH, et al. Hunting for tularaemia - a review of cases in North Carolina. *Zoonoses Public Health*. 2015;62:159–164.

Salit IE, et al. Tularemia endocarditis from domestic pet exposure. *Am J Med*. 2013;126:1.

Sasmal NK, Pahari TK, Laha R. Experimental infection of the cockroach Periplaneta americana with *Toxocara canis* and the establishment of patent infections in pups. *J Helminthol*. 2008;82:97.

Scorza AV, et al. Comparisons of mammalian Giardia duodenalis assemblages based on the β-giardin, glutamate dehydrogenase and triose phosphate isomerase genes. *Vet Parasitol*. 2012;189:182.

Shuhaiber S, et al. Seroprevalence of *Toxoplasma gondii* infection among veterinary staff in Ontario, Canada (2002): implications for teratogenic risk. *BMC Infect Dis*. 2003;3:8.

Souza MJ, et al. *Baylisascaris procyonis* in raccoons (Procyon lotor) in eastern Tennessee. *J Wildl Dis*. 2009;45:1231–1234.

Sykes JE, et al. 2010 ACVIM small animal consensus statement on leptospirosis: diagnosis, epidemiology, treatment, and prevention. *J Vet Intern Med*. 2011;25:1–13.

Talan DA, et al. Bacteriologic analysis of infected dog and cat bites. *N Engl J Med*. 1999;340:84.

Tauni MA, et al. Outbreak of *Salmonella typhimurium* in cats and humans associated with infection in wild birds. *J Small Anim Pract*. 2000;41:339.

Thiry E, et al. Highly pathogenic avian influenza H5N1 virus in cats and other carnivores. *Vet Microbiol*. 2007;122:25.

Torrey EF, et al. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. *Schizophr Bull*. 2007;33:729.

Valtonen M, et al. *Capnocytophaga canimorsus* septicemia: fifth report of a cat-associated infection and five other cases. *Eur J Clin Microbiol Infect Dis*. 1995;14:520.

Wallace M, et al. Cats and toxoplasmosis risk in HIV-infected adults. *J Am Med Assoc*. 1993;269:76.

Weese JS, et al. Suspected transmission of methicillin-resistant *Staphylococcus aureus* between domestic pets and humans in veterinary clinics and in the household. *Vet Microbiol*. 2006;6115:148.

Wendte JM, et al. In vitro efficacy of antibiotics commonly used to treat human plague against intracellular Yersinia pestis. *Antimicrob Agents Chemother*. 2011;55:3752.

Wernli D, et al. Evaluation of eight cases of confirmed Bordetella bronchiseptica infection and colonization over a 15-year period. *Clin Microbiol Infect*. 2011;17:201–203.

Wilson KS, Maroney SA, Gander RM. The family pet as an unlikely source of group A beta-hemolytic streptococcal infection in humans. *Pediatr Infect Dis J*. 1995;14:372–375.

Won KY, et al. National seroprevalence and risk factors for zoonotic *Toxocara* spp. Infection. *Am J Trop Med Hyg*. 2008;79:552.

Zulpo DL, et al. *Toxoplasma gondii*: a study of oocyst re-shedding in domestic cats. *Vet Parasitol*. 2018;249:17–20.

This page intentionally left blank

INDEX

A

A-a gradient. *see* Alveolar-arterial gradient
ABCB1 gene, 1276
Abdomen
  distention of, 7*f*, 408–411, 410*b*
  enlargement of, 408–411, 410*b*
  radiographic imaging of, 419–420, 419*f*
Abdominal carcinomatosis, 513
Abdominal effusion, 407, 519
Abdominal hemangiosarcoma, 513
Abdominal pain, 408, 410*b*, 519
  cranial, 625*f*–626*f*
Abdominal ultrasonography
  cancer staging using, 1288–1289
  hyperadrenocorticism evaluations, 862–864, 862*b*, 863*f*–865*f*
Abdominocentesis, 422, 543–544, 544*t*
Abducent nerve, 1055, 1056*t*
Abiotrophy, 1080–1081
Abortifacient, 1034*t*–1036*t*
Abortion, bacteria associated with, 965–966
Abscess, 612–613, 979*f*
  carnassial tooth root, 245–246
  epididymal, 1001*f*
  prostatitis with, 1003*f*
  retrobulbar, 1124*f*
  splenic, 1412–1413
  subcutaneous, site of glucose administration, 1012*f*
Absorption tests, 423
Acanthocytosis, 1345*t*
Acanthomatous ameloblastoma, 448*t*
Accelerated idioventricular rhythm, 41
Accessory nerve, 1056*t*
Acepromazine, 19–20, 386*t*–388*t*, 733*t*–734*t*
  hypertension treated with, 217*t*
  neurologic disorders treated with, 1185*t*–1186*t*
  stress relief using, 380*t*
Acetamides, 1437*t*–1438*t*
Acetaminophen, 629*t*–630*t*
Acetazolamide, 1079–1080
Acetylcholine, 1041–1042
Acetylcholine receptors
  antibodies to, 424
  myasthenia gravis caused by deficiency of, 1250
Acetylcholinesterase, 1041–1042
Acetylsalicylic acid, 1197*t*, 1209*t*–1210*t*
Acholic feces, 529*f*
Acid-base balance
  blood gas analysis of, 318
  in Greyhounds, 1362, 1362*t*
Acquired chronic polyneuropathies, 1164–1168
Acquired endocardial disease, 119–140
Acquired esophageal weakness, 454–455, 454*f*
Acquired valvular disease, 119–140
Acromegaly, feline, 749–753
  clinical features of, 750–751, 751*f*
  clinical pathology of, 751–752
  clinical signs of, 750*b*
  diagnosis of, 752, 752*f*
  etiology of, 749–750
  hyperadrenocorticism *versus*, 752
  insulin-resistant diabetes mellitus management in, 753
Acromegaly, feline *(Continued)*
  magnetic resonance imaging of, 750*f*
  prognosis for, 753
  radiation therapy for, 753
  treatment of, 753
Acrosomes, 946–947
Activated charcoal, 1185*t*–1186*t*
Activated partial thromboplastin time, 228
Acute abdomen, 407–408, 408*b*, 409*f*
Acute addisonian crisis, 886–888
Acute bronchitis, 330*b*
Acute canine polyradiculoneuritis (ACP), 1166–1168, 1167*t*, 1168*f*
Acute diarrhea, 398–399, 398*b*, 474–476
  acute enteritis, 474–475
  dietary-induced, 475–476
  enterotoxemia and, 475
Acute enteritis, 474–475
Acute gastritis, 462
Acute hemorrhagic diarrheal syndrome (AHDS), 462–463, 482
Acute hepatitis, 598–599, 598*b*
Acute intervertebral disk disease
  cervical disk extrusion, 1138*t*, 1139
  clinical features of, 1136, 1136*f*
  description of, 1135–1141
  diagnostic approach, 1136–1137, 1137*f*–1139*f*
  magnetic resonance imaging of, 1137
  myelography for, 1137, 1138*f*
  thoracolumbar disk extrusion, 1138*t*, 1139–1141, 1140*f*, 1140*t*
  treatment of, 1137–1141
Acute kidney injury (AKI), 686–692
  causes of, 687*b*
  chronic kidney disease *versus*, 687*t*
  clinical findings of, 689
  clinicopathologic findings of, 689–690
  dialysis for, 692
  diuretics for, 691
  fluid administration for, 690
  hyperphosphatemia in, 691
  metabolic acidosis in, 691
  nonsteroidal anti-inflammatory drugs as cause of, 686–687
  oliguria in, 688*f*
  overhydration associated with, 692
  pathophysiology of, 686–689, 687*f*–688*f*
  phases of, 687, 689*f*
  prognosis for, 692
  renal biopsy of, 690
  treatment of, 690–692
  ultrasonographic findings, 690*f*
Acute leukemias
  in cats, 1313*t*, 1319–1320
    chemotherapy for, 1317*b*
    clinical features of, 1320
    diagnosis of, 1320, 1320*f*
    hematologic features of, 1320
    prevalence of, 1319–1320
    treatment of, 1320
  in dogs, 1313–1316, 1313*t*
    chemotherapy for, 1317*b*
    clinical features of, 1313, 1314*f*
    diagnosis of, 1314–1316, 1316*b*
    hematologic features of, 1313–1314, 1314*f*–1315*f*
    prevalence of, 1313
    remission of, 1316
    treatment of, 1316
Acute lower motor neuron tetraparesis, 1166, 1167*t*
Acute lung injury (ALI), 356
Acute lymphoblastic leukemia, 1312*t*, 1313
Acute myelogenous leukemia, 1312*t*, 1313
Acute myelomonocytic leukemia, 1312*t*
Acute pancreatitis
  analgesia for, 628–631, 629*t*–630*t*
  antibiotics for, 633
  antiemetics for, 632–633
  biliary tract obstruction and, 633
  in cats, 624*f*
  chronic pancreatitis *versus*, 623*t*
  clinical features of, 621–625, 623*t*, 624*f*
  description of, 620
  diagnosis of, 625–627
  diagnostic imaging of, 626–627, 627*f*
  etiology of, 621, 623*t*
  fluid analysis for, 627
  gastroprotectants for, 633
  histopathology of, 627
  intravenous fluids and electrolytes for, 628
  necrotizing, 628
  nutrition for, 631–632, 631*b*, 632*f*
  pancreatic enzyme assays, 625–626
  pathogenesis of, 621, 623*t*
  plasma transfusion for, 628
  practice for feeding in, 631*b*
  prognosis for, 627–633
  prognostic factors of, 626
  risk factors for, 623*t*
  treatment of, 627–633
  ultrasonography of, 627*f*
Acute posterior paresis, 226
Acute proctitis, 504
Acute respiratory distress syndrome (ARDS), 356
Acute septic prostatitis, 1003
Acute tubular necrosis, 687*f*
Acute tumor lysis syndrome, 1276, 1286, 1286*f*
Acute vestibular attacks, 1116
Acute-phase proteins, 1420
Acute-phase reactants, 1420
Ad libitum feeding, 904–906
Adenocarcinoma, 503
  intestinal, 503
  prostatic, 1003, 1003*f*
Adenoma(s)
  hepatic cystadenoma, 575*f*
  macroadenoma, 749
  parathyroid, 758–759, 759*f*
  thyroid, 800
Adenosine triphosphatase pump, 931
Adrenal cortex, 872*f*
Adrenal gland, disorders of, 857–895
Adrenal insufficiency, primary, 888–889
Adrenal mass, incidental, 892–893, 893*f*–894*f*
Adrenal tumors
  aldosterone-secreting, 892–893
  cortisol-secreting, 875–876
  progesterone-secreting, 893, 894*f*
  types of, 891*t*
Adrenalectomy, 875–876, 883
α_1-Adrenergic blockers, 217*t*, 218
β-Adrenergic receptors, 93
Adrenocortical tumors, 857–858, 858*f*
Adrenocorticotropic hormone
  endogenous concentration of, 866*t*, 871, 882
  stimulation test for, 866*t*, 870, 870*f*, 881*t*, 882, 885–886
Adriamycin. *see* Doxorubicin
Adulticides
  for heartworm disease
    in cats, 206
    in dogs, 199*b*, 200–201
  pulmonary thromboembolic complications, 201–203
Advantage. *see* Imidocloprid/moxidectin
Aelurostrongylus abstrusus
  in airway washing, 1429*f*
  lower respiratory tract diseases caused by, 288–289, 297*f*, 297*t*
  pulmonary parenchymal diseases caused by, 345
Aerobic infection, 1441*t*
Afebrile neutropenia, 1279–1280, 1375
Aflatoxin, 598–599
Agalactia, 978, 1034*t*–1036*t*
Agenesis, 1014
Aggression, fear-induced, 975
Aglepristone, 960, 1034*t*–1036*t*
Airway(s)
  extrathoracic, 380–381, 381*f*
  hydration of
    in bacterial pneumonia, 341*b*
    nebulization for, 342
  intrathoracic, 381
  obstruction of, extrathoracic, 380–381
  suctioning of, 347
  treatment of, 347
Albon. *see* Sulfadimethoxine
Albuterol, 327*b*
Aldosterone, 1363–1364
  adrenal tumors that secrete, 892–893
  physiologic effects of, 56–57
Aldosterone receptors, 56–57
Alendronate, 927, 934*t*
Alimentary lymphoma, 502–503, 1294, 1309, 1496
Alimentary tract disease
  diagnostic tests for, 412–431
    bacterial fecal culture, 414
    barium contrast enemas, 423
    biopsy, 429–430
    coagulation, 412
    complete blood count, 412
    contrast-enhanced gastrograms, 422
    contrast-enhanced studies, 422–423
    electron microscopy, 415
    endoscopy, 424–429, 424*f*
    enzyme-linked immunosorbent assay, 399, 413
    fecal digestion tests, 413–414
    fecal flotation, 413
    IFA, 399, 414
    laboratory evaluation routine, 412–413
    other special tests for, 424
    peritoneal fluid analysis, 423
    physical examination, 412
    polymerase chain reaction fecal analysis, 414
    radiographs, 415
    serum biochemistry profile, 405–406, 412–413
    serum cortisol, 413
    trypsin-like immunoreactivity, 413
    ultrasonography, 415
    urinalysis, 405–406, 413
  tenesmus caused by, 403
Alimentary tract parasites, 485–491
  coccidiosis, 488
  cryptosporidia, 488–489
  giardiasis, 489–490, 489*f*
  heterobilharzia, 491
  hookworms, 487
  roundworms, 486–487, 486*f*

Page numbers followed by "*f*" indicate figures, "*t*" indicate tables, and "*b*" indicate boxes.

Alimentary tract parasites *(Continued)*
strongyloidiasis, 488
tapeworms, 487–488
trichomoniasis, 490–491, 490*f*
whipworms, 485–486, 485*f*
Alimentary tract perforation, 422
Alizine. *see* Aglepristone
Alkaline phosphatase, 564–565, 861, 880–881
Alkylating agents, 1272–1273, 1273*b*
Allantoin, 719–720, 720*f*
Allergic bronchitis, 329*t*, 337
Allergic pneumonitis, 201
Allergic reactions, to insulin, 827
Allergic rhinitis, 266
clinical features of, 266
diagnosis of, 266
etiology of, 266
prognosis for, 266
radiographic signs of, 249*b*
treatment of, 266
Allometric scaling, 23–25
Allopurinol, 720–721
Alopecia
chemotherapy-related, 1282–1283, 1283*f*
endocrine, 747–749, 747*f*, 748*t*–749*t*, 750*f*
Alopecia X, 748–749, 748*t*, 750*f*
Aluminum hydroxide, 439*t*, 515*t*–517*t*, 700–701
Alveolar pattern, 290–292, 291*f*, 291*b*
Alveolar-arterial gradient, 317–318, 317*t*, 318*b*
Amantadine, 1197*t*, 1209*t*–1210*t*
Amastigotes, 1526
Ambulatory electrocardiography, 49–51
Holter monitoring, 49–50
intermittent event recording, 50–51
American trypanosomiasis, 1525–1526
Amiglyde. *see* Amikacin
Amikacin (Amiglyde), 386*t*–388*t*, 515*t*–517*t*, 1437*t*–1438*t*
Aminoglycosides
ototoxicity caused by, 1114–1115
toxicity caused by, 1439*t*
types of, 1437*t*–1438*t*
Aminopentamide, 437
Aminophylline, 62*b*, 327*b*, 386*t*–388*t*
Amiodarone, 95–96
adverse effects of, 96
antiarrhythmic effects of, 95
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Amitriptyline, 716, 728*b*, 733*t*–734*t*
Amlodipine besylate, 62*b*, 63, 97
bioavailability of, 71
chronic heart failure treated with, 64*t*, 71
hypertension treated with, 215, 217*t*
Ammonia, and hepatic encephalopathy, 523*f*
Ammonium biurate crystals, 669*f*
Amoeba, 1538–1539
Amoxicillin, 386*t*–388*t*, 515*t*–517*t*
bacterial infections treated with, 1437*t*–1438*t*
joint disease treated with, 1209*t*–1210*t*
neutrophilic cholangitis treated with, 570
Amoxicillin-clavulanate, 386*t*–388*t*, 1185*t*–1186*t*, 1209*t*–1210*t*, 1437*t*–1438*t*
Amphojel. *see* Aluminum hydroxide
Amphotericin B, 515*t*–517*t*, 1504–1505, 1504*t*, 1509
Amphotericin B deoxycholate, 1504*t*
Ampicillin, 386*t*–388*t*, 515*t*–517*t*, 1209*t*–1210*t*
Ampicillin sodium, 1437*t*–1438*t*
Ampicillin-sulbactam, 386*t*–388*t*, 1437*t*–1438*t*
Amrinone, 62*b*
Amyloid A protein, 679
Amyloidosis, 693*b*
glomerular, 679–680, 679*f*
hepatic, in cats, 575–576
islet, 831*f*
Anabolic steroids, 702
Anaerobes, 1431
Anaerobic infections, 1438–1440
Anal sac (apocrine gland) adenocarcinoma, 506
Anal sacculitis, 505
Analgesia, 1268*t*
for acute pancreatitis, 628–631, 629*t*–630*t*
in cats, 227*b*
Anaphylactic reactions, 1281
Anaplasma spp.
A. phagocytophilum, 1128–1129, 1190*f*, 1430*f*, 1432–1433, 1440*t*, 1443–1444, 1469, 1470*f*, 1470*t*, 1471, 1533*t*–1535*t*
A. platys, 1440*t*, 1470*t*, 1472
Anasarca, 969, 1020
Ancef. *see* Cefazolin
Ancylostoma spp., 1533*t*–1535*t*, 1536
Anechoic, defined, 19
Anemia
aplastic, 1240
blood loss, 1345–1346, 1346*t*
chemotherapy-induced, 1278
of chronic disease, 1352–1353, 1352*t*
in chronic kidney disease, 697
clinical manifestations of, 1340–1345, 1341*b*, 1343*f*
clinicopathologic findings, 1340–1345, 1341*b*, 1343*f*
definition of, 1340
diagnostic tests for, 1218*t*–1219*t*
of endocrine disease, 1351–1352
hemolytic. *see* Hemolytic anemia
iron deficiency, 1354–1355, 1356*f*
in lymphadenopathy, 1414–1415
management of, 1345–1355
nonregenerative, 1218*t*–1219*t*, 1351–1355, 1352*b*, 1358*f*, 1426*t*
pathogenetic classification of, 1344*b*
regenerative, 1218*t*–1219*t*, 1342–1343, 1344*f*, 1358*f*, 1426*t*
in splenomegaly, 1414–1415
transfusion therapy for, 1355–1358, 1357*t*
Anestrus, 937*f*, 938*t*, 949, 955, 1034*t*–1036*t*
Angiocardiography, 52
selective, 52
Angiography
computed tomography pulmonary, 356
selective, 356
Angiotensin II, 56, 67
Angiotensin receptor blockers, chronic kidney disease, 701
Angiotensin-converting enzyme, 56
adverse effects of, 67
aldosterone levels affected by, 67
chronic heart failure treated with, 64*t*, 67–68
dilated cardiomyopathy treated with, 145
hypertrophic cardiomyopathy treated with, 163–164
Angiotensin-converting enzyme inhibitors
chronic heart failure treated with, 128
chronic kidney disease treated with, 701
hypertension treated with, 215, 217*t*
Animal inoculation, 1433
Anorexia
chemotherapy-related, 1281
description of, 407, 407*b*
Antacid drugs, 438–439, 439*t*
Anthelmintic drugs, 443, 444*t*
Antiarrhythmic drugs, 77–99
class I, 88–93, 89*t*
class II, 88, 90*t*–91*t*, 93–95. *see also* β-Blockers
Antiarrhythmic drugs *(Continued)*
class III, 88, 90*t*–91*t*, 95–96
class IV, 88, 90*t*–91*t*, 96–97. *see also* Calcium channel blockers
classification of, 88, 89*t*
dilated cardiomyopathy treated with, 145
dosage of, 90*t*–91*t*
lidocaine. *see* Lidocaine
mechanism of action of, 88
mexiletine, 90*t*–91*t*, 92
phenytoin, 90*t*–91*t*, 93
procainamide. *see* Procainamide
quinidine. *see* Quinidine
ventricular tachyarrhythmias treated with, 84
Antibacterial drugs, 442–443
Antibiotic-responsive enteropathy, 399, 401*b*, 492
Antibiotics. *see also* Antimicrobial drugs
abdominal sepsis treated with, 443
acute pancreatitis treated with, 633
bacterial endocarditis treated with, 1441
bacterial meningoencephalomyelitis treated with, 1123
bacterial pneumonia treated with, 341–342, 341*b*
bacterial rhinitis treated with, 259
brucellosis treated with, 965
canine chronic bronchitis treated with, 328
canine chronic hepatitis treated with, 593
diskospondylitis treated with, 1144
feline chronic rhinosinusitis treated with, 267–268
feline coronavirus treated with, 1491
feline upper respiratory infection treated with, 258
infective endocarditis treated with, 136–137
otitis media-interna treated with, 1113
prophylactic use of, 348
prostatitis treated with, 1441*t*
pyometra treated with, 1441*t*
pyothorax treated with, 371
Antibodies
to acetylcholine receptors, 424
detection of
in body fluids, 1434–1435
in serum, 1433–1434
feline immunodeficiency virus, 1494
insulin-binding, 828
Anticancer drugs. *see also* Chemotherapy
handling of, 1274
mechanism of action, 1272
neurotoxicity caused by, 1285
nonselective nature of, 1276
occupational exposure to, 1274
pharmacokinetics of, 1276
reconstitution of, 1274
spills of, 1274
toxicity of, 1277*t*–1278*t*
types of, 1272–1273, 1273*b*
Anticholinergic drugs, 97
cardiac effects of, 97
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
sick sinus syndrome treated with, 86–87
sinus bradycardia treated with, 86
Anticholinesterase, 1171*b*, 1250
Anticoagulants
arterial thromboembolism in cats treated with, 227*b*
thromboembolism prophylaxis, 1405
Anticonvulsants
chronic, 1101*b*
oral, 1101*b*
phenobarbital, 1101–1102
Antidiarrheals, 474
Antidiuretic hormone, 662
physiologic effects of, 56
secretion of, 57–58
Antiemetics, 437–438, 438*t*, 632–633
chronic kidney disease, 701
Antiepileptic drugs
description of, 1100–1101
diazepam, 1104
for dogs, 1101*t*
felbamate, 1104
gabapentin, 1103–1104
levetiracetam, 1103
potassium bromide, 1102–1103
pregabalin, 1104
Antiestrogens, 959
Antifibrotics, 593
Antigen-specific T lymphocytes, 1451
Antihistamines, 266
Antihypertensive drugs
hypertension treated with, 215, 217*t*
hypotension caused by, 218
Antiinflammatory drugs, 441–442
Antilentiviral drugs, 1494
Antimetabolites, 1273, 1273*b*
Antimicrobial drugs, 1436. *see also* Antibiotics
anaerobic infections treated with, 1438–1440
bacteremia treated with, 1440–1442
bacterial endocarditis treated with, 1440–1442
central nervous system infections treated with, 1440*t*, 1442
gastrointestinal infections treated with, 1440*t*, 1442–1443
hepatic infections treated with, 1442–1443
joint infections treated with, 1440*t*
muscle infections treated with, 1440*t*
musculoskeletal infections with, 1443–1444
respiratory tract infections treated with, 1441*t*, 1444–1445
skin infections treated with, 1445
soft tissue infections treated with, 1445
toxicities, 1439*t*
types of, 1437*t*–1438*t*
urogenital infections treated with, 1441*t*, 1445–1446
Antinuclear antibody test, 1217
Antioxidants, 590–591
Antiplatelet antibodies, 1216–1218
Antiplatelet therapy, 227*b*, 228
Antiprogestational agents, 960
Antiprolactin therapy, 978
Antiprotozoal drugs, 444*t*
Antirobe. *see* Clindamycin
Antisecretory drugs, 441–442
Antithrombin, 684
deficiency of, 223
description of, 1388
Antithyroid drugs
canine thyroid neoplasia treated with, 803–804
hyperthyroidism in cats treated with, 794–797
Antitumor antibiotics, 1273, 1273*b*
Antral mucosal hypertrophy, gastric, 465, 466*f*
Anzemet. *see* Dolasetron
Aortic dilation, 10–11
Aortoiliac thrombosis, 1405
Apatite-containing calculi, 721
Apex, 9
Aplastic anemia, idiopathic, 1240
Apolipoproteins, 908
Apomorphine, 515*t*–517*t*, 1185*t*–1186*t*
Apoptosis, 1269
Arginine vasopressin, 740
diabetes insipidus, 741–742, 745*f*
Arrhythmias, 130
approach to, 77–78
bradyarrhythmias. *see* Bradyarrhythmias
clinical presentation of, 79, 80*b*
development of, 77
diagnosis of, 78–88

Arrhythmias *(Continued)*
management of, 78–88
electrocardiogram interpretation, 78*b*
goals for, 77–78
predisposing factors, 79*b*
tachyarrhythmias. *see* Tachyarrhythmias
Arrhythmogenic right ventricular cardiomyopathy
in Boxers, 148, 1363
in cats, 171
in dogs, 148–150
Arterial hypertension. *see* Hypertension
Arterial pulses, 5–6, 6*b*
Arterial thromboembolism. *see* Thromboembolism, arterial
Arthritis. *see also* Polyarthritis
feline rheumatoid-like, 1208–1209
fungal, 1201
osteoarthritis, 1196*f*, 1197*t*
septic, 1193, 1197–1201, 1198*f*–1199*f*
viral, 1201
Arthrocentesis, 1190, 1190*f*–1192*f*
Artifacts, 7*f*
electrocardiogram, 48, 51*f*
Artificial insemination
intrauterine, 947–948, 947*f*–948*f*
transcervical, 947–948, 948*f*
vaginal, 947
Arytenoid cartilages
evaluation of, 275, 275*f*
in laryngeal paralysis, 277
laryngoscopy evaluation of, 277–278
Ascending descending myelomalacia, 1140–1141
Aspergillosis, nasal, 260–263, 260*f*–262*f*
clinical features of, 260
description of, 242, 242*f*
diagnosis of, 256, 260–261
prognosis for, 263
radiographic signs of, 249*b*, 250*f*, 260
treatment of, 261–263
Aspergillus spp.
A. fumigatus, 260, 261*f*
A. terreus, 260
Aspiration pneumonia, 346–348
bronchoscopy evaluations, 347
clinical features of, 347
diagnosis of, 347
differential diagnosis of, 329*t*
etiology of, 346–347, 346*b*
iatrogenic causes of, 346
laryngeal paralysis as cause of, 278–279
prognosis for, 348
regurgitation and, 346
tracheal wash for, 348
treatment of, 347–348
Aspirin, 227*b*, 228, 1255*t*–1256*t*
Ataxia
description of, 1043*f*, 1045–1046, 1046*f*, 1046*b*
progressive rear limb, 1146*f*
Atelectasis, 294, 294*f*
Atenolol
in cats, 90*t*–91*t*
characteristics of, 94, 94*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
hypertension treated with, 217*t*
Atherosclerosis, 151, 1076
Atlantoaxial instability, 1142, 1154
Atlantoaxial subluxation, 1154, 1154*f*
Atopica. *see* Cyclosporine
Atresia ani, 1017*f*
Atrial fibrillation, 40, 43*f*
algorithm for, 85*f*
digoxin for, 85
dilated cardiomyopathy as cause of, 142
in dogs, 81*f*
electrical cardioversion of, 85
lone, 85–86
M-mode echocardiography of, 81*f*
predisposing conditions, 84
Atrial fibrillation *(Continued)*
rapid, 79
treatment of, 84–85, 85*f*
Atrial flutter, 39
Atrial gallop, 9
Atrial kick, 84, 159
Atrial natriuretic peptide, 13
synthesis of, 58
Atrial premature complexes, 80
Atrial septal defect
clinical features of, 111
diagnosis of, 111
dog breeds affected by, 102*t*
etiology of, 111
pathophysiology of, 111
prognosis for, 112
radiographic findings, 103*t*
treatment of, 112
Atrial standstill, 87
Atrial tachycardia
causes of, 39
management of, 82
sustained, 42*f*
Atrioventricular block, 87–88
first-degree, 43–44, 44*f*
second-degree, 43–44, 44*f*
third-degree, 43–44, 44*f*
Atrioventricular conduction, 87–88
Atrioventricular mode, conduction disturbances within, 43–44, 44*f*
Atrioventricular reciprocating tachycardia, 44–45
Atrioventricular valve disease
clinical features of, 121–122
clinicopathologic findings, 122
compensatory changes associated with, 120
complications of, 120–121, 121*b*, 129–132
diagnosis of, 122–126
in dogs, 119
echocardiographic findings, 123–126, 124*f*
electrocardiographic findings, 123
etiology of, 119–120
heart failure caused by, 119, 125
jugular vein distention associated with, 122
left atrial enlargement associated with, 120, 125*f*–126*f*
monitoring of, 129
pathophysiology of, 119–120
prognosis for, 126
pulmonary edema caused by, 121–122, 121*b*
radiographic findings, 122–123, 123*f*
reevaluation of, 129
treatment of, 127*b*
Atrioventricular valve malformation, 112–113
Atrophic gastritis, 463
Atrophic myositis, 451
Atrophic vaginitis, 982
Atropine, 386*t*–388*t*, 515*t*–517*t*
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
indications for, 97
neurologic disorders treated with, 1185*t*–1186*t*
Atropine challenge test, 88, 97
Attenuated vaccines, 1451
Atypical hypoadrenocorticism, 884, 889
Aura, 1–2, 1093
Aural neoplasia, 1114
Auscultation, 7–11, 7*f*–8*f*
of cardiac murmurs, 7, 9–11
in cats, 7, 7*f*
respiratory tract, 285*f*
stethoscope for, 7, 7*f*
thoracic, 285–286
of transient heart sounds, 8–9
Autoagglutination, 1345*t*, 1348*f*
Autoimmune chronic pancreatitis, 634
Autoimmune diseases, 1212–1213, 1213*t*
organ systems involved, 1214
Autoimmune panels, 1218
Autoimmune polyendocrine syndromes, 773
Autoimmunity, 1212
Autosomal dominant polycystic kidney disease, 656
Avermectins, 203
Axid. *see* Nizatidine
Axillary nerve, 1158*t*
Azathioprine, 442, 515*t*–517*t*, 592–593
adverse effects of, 1223–1224
dosage of, 1225*t*
for glomerular disease, 682
granulomatous meningoencephalitis treated with, 1121*b*
immune-mediated diseases treated with, 1255*t*–1256*t*
description of, 1223–1224, 1225*t*
hemolytic anemia, 1236
polyarthritis, 1204, 1204*t*
joint disease treated with, 1209*t*–1210*t*
masticatory muscle myositis treated with, 1175
myasthenia gravis treated with, 1251*t*
pharmacokinetics of, 1223
prednisone and, 1224
pure red cell aplasia treated with, 1238–1240
Azidothymidine, 1494
Azithromycin, 386*t*–388*t*, 515*t*–517*t*, 1437*t*–1438*t*
Azium. *see* Dexamethasone
Azoospermia, 1003–1004
Azotemia
arterial thromboembolism in cats, 225–226
definition of, 649
heartworm disease as cause of, 197
postrenal, 649
prerenal, 649
Azulfidine. *see* Sulfasalazine

B

Babesia canis, 1514
Babesia gibsoni, 1382, 1514
Babesia vogeli, 1514
Babesiosis, 154, 1514–1516
Bacillary angiomatosis, 1540
Bacillary peliosis, 1540
Bacteremia
antimicrobial drugs for, 1440–1442
infective endocarditis secondary to, 132
Bacterial bronchitis, 329*t*, 1441*t*
Bacterial cholangiohepatitis, 1440*t*
Bacterial cystitis, 704–711
classification of, 704–709, 705*f*, 705*t*
diagnosis of, 706–708, 707*f*–708*f*, 707*t*
lower urinary tract signs, 704
physical examination findings in, 706
recurrent, 705–706, 706*t*
sporadic, 704–705, 705*t*
treatment of, 708
Bacterial diseases, 480–484
bartonellosis
canine, 1457–1458
feline, 1458–1460, 1458*f*
campylobacteriosis, 480–481
clostridial disease, 482, 482*f*
cytology of, 1429–1430
feline plague, 1460–1462, 1461*f*, 1461*b*
histoplasmosis, 483–484, 484*f*
intestinal tract, 480–484
leptospirosis, 1462–1464
miscellaneous bacteria, 483
Mycoplasma and *Ureaplasma*, 1464–1466
protothecosis, 484, 485*f*
pythiosis, 484
salmonellosis, 481–482
zoonoses, 1539
Bacterial encephalitis, 1440*t*
Bacterial endocarditis, 1440–1442
Bacterial fecal culture, 414
Bacterial meningoencephalomyelitis, 1123–1124
Bacterial myocarditis, in dogs, 153
Bacterial pneumonia, 340–343
airway hydration in, 342–343
antibiotics for, 341–342, 341*b*
bronchodilators for, 343
clinical features of, 340–341
diagnosis of, 341
etiology of, 340
expectorants for, 343
microorganisms that cause, 1444
monitoring of, 343
physiotherapy for, 343
prognosis for, 343
pulmonary abscess caused by, 343
radiographic findings, 341
treatment of, 341*b*
Bacterial prostatitis, 710–711, 710*f*
Bacterial rhinitis, 259–260, 259*f*
Bacterial septicemia, neonatal, 1021–1022
Bactrim. *see* Trimethoprim-sulfadiazine
Baermann technique, 1428
Balanoposthitis, 992–993, 993*f*
Balloon valvuloplasty, for pulmonic stenosis, 108
Barbiturates, 49*b*
Barium contrast studies
enema, indications for, 423
esophageal imaging using, 416
Baroreceptors, 56
Barrington's nucleus, 730
Bartonella alpha proteobacteria growth medium, 1540
Bartonella spp., 1533*t*–1535*t*
antibiotics for, 1440*t*
antigen recognition pattern for, 1434*f*
B. henselae, 1457, 1458*f*, 1540
B. vinsonii, 135–136, 153, 1457
idiopathic canine chronic rhinitis and, 268
infective endocarditis caused by, 132
laboratory tests for, 134
Bartonellosis
canine, 1457–1458
feline, 1458–1460, 1458*f*, 1540–1541
Base, 9
Basement membrane disorder, 693*b*
Basophilia, 1377, 1378*b*
Baylisascaris procyonis, 1533*t*–1535*t*
Baytril. *see* Enrofloxacin
β-cell neoplasia, insulin-secreting, 808, 847–853
clinical features of, 848–849
clinical pathology of, 848–849
clinical signs of, 848
diagnosis of, 849–850, 849*f*
etiology of, 847
peripheral neuropathy, 848
physical examination of, 848
signalment for, 848
signs associated with, 848*b*
treatment of, 850–852
diazoxide therapy, 850*b*, 852
glucocorticoid therapy, 852
overview of, 850
postoperative complications, 851–852, 851*f*
prognosis for, 853
somatostatin therapy, 852
streptozotocin therapy, 852
surgery, 850–851, 850*b*, 851*f*
Beagle dogs, hematologic values for, 1014*t*
Bell, of stethoscope, 7
Benadryl. *see* Diphenhydramine
Benazepril
chronic heart failure treated with, 64*t*, 68
hypertension treated with, 217*t*
Benign muscular pyloric hypertrophy, 465
Benign prostatic hyperplasia, 1001–1003, 1002*f*, 1034*t*–1036*t*
Benign rectal stricture, 507
Benzopyrone, for chylothorax, 375
Beta lactams, 1439*t*

Betamethasone, 1222*t*
Bethanechol, 440–441, 456, 515*t*–517*t*, 733*t*–734*t*, 1185*t*–1186*t*
Bicarbonate, 432
  therapy, 842*b*, 844–845
Bicytopenia, 1382*b*
Bifidobacterium, 443
Big kidney, little kidney syndrome, 715, 715*f*
Bigeminy, 6
Bilateral motor paralysis, 1059*f*
Bile duct, obstruction of. *see* Extrahepatic bile duct obstruction
Bile peritonitis, 603
Biliary cysts, feline, 575
Biliary tract
  diseases and disorders of, 599–603
    in cats. *see* Feline biliary tract disease
    cholangitis, 599–600
    cholecystitis, 599–600
    extrahepatic bile duct obstruction, 601–603
    gallbladder mucocele, 600–601, 600*f*
  obstruction of, acute pancreatitis and, 633
Bilious vomiting syndrome, 470
Bilirubin, in urine, 665
Bilirubinuria, 525–527, 526*f*–527*f*
Binaural eartubes, of stethoscope, 7, 7*f*
Biomarkers, cardiac, 13–14
Biopsy
  chronic pancreatitis, 636
  endoscopic, 429–430
  fine-needle aspiration, 429
  full-thickness, 430
  liver, 553–559, 554*f*
    indications for, 554
    techniques for, 554–555, 555*f*–558*f*
  muscle, 1073
  nasal
    complications of, 255
    hemorrhage caused by, 255
    indications for, 253–255
    nasal flush, 254
    nasal swabs, 254
    pinch biopsy, 254–255, 254*f*
    techniques for, 253–255
    turbinectomy, 255
  nerve, 1073
  pancreatic, 558–559
  pinch, 254–255, 254*f*
  renal, 672–673, 690
  splenic, 1416–1417
  synovial membrane, 1193
  testicular, 1003–1004
Biosol. *see* Neomycin
Bipyridine phosphodiesterase inhibitors, 63–65
Bisacodyl, 445*t*, 515*t*–517*t*
Bismuth subsalicylate, 441, 515*t*–517*t*
Bisphosphonates, 927
Bitch
  artificial insemination of, 947, 947*f*
  breeding management of, 944–945
  breeding soundness consultations in, 935–936
  cystic endometrial hyperplasia/pyometra complex, 985–988, 986*f*–987*f*, 987*t*
  estrous cycle in
    abnormalities of, 954–958
    description of, 937–940, 938*t*
    variations of, 953–954
  exaggerated pseudocyesis in, 957
  infertility/subfertility in, 984, 984*b*
    microbiology and, 984–985, 985*b*
  labor in, 968
  later than typical puberty in, 953
  metabolic disorders in, 966–967
    gestational diabetes, 967, 967*f*
    hyperemesis gravidarum, 966–967
    pregnancy edema, 967, 968*f*
    pregnancy thrombosis, 967, 967*f*
    pregnancy toxemia, 967
    vasculitides, 967
Bitch *(Continued)*
  ovariohysterectomized, reproductive tract disorders in
    chronic vestibulovaginitis, 980–982, 980*f*–982*f*
    ovarian remnant syndrome, 982–983, 983*f*
  ovulation timing in, 940–945
  pregnancy in. *see also* Pregnancy
    brucellosis, 963–965
    pregnancy loss, 962
    semen peritonitis, 961–962
  pseudopregnancy in, 957
  silent heat cycle in, 953
  split heat cycle in, 953–954
  vagina of
    hyperplasia of, 957–958, 958*f*
    illustration of, 941*f*
  vestibule of, 941*f*
Biventricular failure, heart, 1
Bladder
  overactive, 736–737
  transitional cell carcinoma of, 736
    metastasis of, 1290*t*
Bladder tumor antigen test, 662
"Bland" diets, 434, 434*b*
Blast crisis, 1311
Blast transformation, 1311
Blastomyces dermatitidis, 1502, 1503*f*, 1503*t*, 1505
Blastomycosis, 1502–1505
  antifungal drugs for, 1504*t*
  clinical features of, 1502
  cytologic appearance, 1503*f*, 1503*t*
  diagnosis of, 1502–1504, 1503*f*
  epidemiology of, 1502
  etiology of, 1502
  lymphadenopathy and, 1502
  ocular manifestation of, 1502
  prevention of, 1505
  relapse of, 1505
  treatment of, 1504–1505, 1504*t*
  zoonotic aspects of, 1505
Bleeding
  clinical manifestations of, 1388–1389, 1388*b*, 1391*f*
  clinicopathologic evaluation of, 1389–1393, 1390*f*
  delayed postoperative, 1389
  management of, 1393–1394
  spontaneous, 1388–1389, 1391*f*
β-Blockers
  antiarrhythmic effects of, 93–95
  characteristics of, 94*t*
  electrocardiographic changes associated with, 49*b*
  in heart failure, 73
  hypertension treated with, 217*t*
  nonselective, 93
  pulmonic stenosis treated with, 108–109
  subaortic stenosis treated with, 107
Blood cultures, 133–134
Blood gas analysis, 313–318
  acid-base status, 318
  alveolar-arterial gradient, 317–318, 317*t*, 318*b*
  dorsal pedal artery, 314, 315*f*
  femoral artery, 314, 315*f*
  indications for, 313
  oxygen content, delivery, and utilization, 318
  partial pressure of carbon dioxide ($PaCO_2$), 315–317, 316*b*
  partial pressure of oxygen (PaO_2), 315–317, 316*b*
  results of, 315–318, 315*t*
  techniques of, 313–314, 315*f*
  ventilation/perfusion ratio, 316
Blood glucose
  for diabetes mellitus monitoring in dogs, 818
  measurement of
    in cats, 838*f*
    methods for, 821
Blood glucose *(Continued)*
  serial curves of
    in cats, 837
    in dogs, 819–822, 820*f*–821*f*, 823*f*–824*f*
Blood groups, 1356–1357
Blood loss anemia, 1345–1346, 1345*t*
Blood pressure
  abnormal, 131
  classification of, 211
  control agents, chronic kidney disease, 702
  Doppler ultrasonic measurement of, 215
  elevated levels of. *see* Hypertension
  indirect measurement of, 214–215
  measurement of, 214–217
  oscillometric measurement method for, 215
  pathophysiology of, 212
  regulation of, 212
Blood pressure cuffs, 214
Blood transfusion
  description of, 1356
  immune-mediated hemolytic anemia treated with, 1237
Blood typing, 1357
Blood urea nitrogen, 658
Blood vessels, intrathoracic, 16–18
Body condition scoring, 901, 902*f*–903*f*, 907
Body surface area, 1271, 1271*t*–1272*t*
Body temperature, of neonates, 1010*b*
Body weight conversions to body surface area
  in cats, 1272*t*
  in dogs, 1271, 1271*t*
Body weight measurements, 901
Boehringer Ingelheim. *see* Cabergoline
Bone marrow aplasia-hypoplasia, 1353–1354, 1384–1385
Bone marrow disorders, 1353–1354, 1355*b*
Bone marrow suppression, 735
Bone metastases, 1290
Border Collie collapse (BCC), 1107, 1183–1184
Bordetella spp.
  B. bronchiseptica, 259, 321, 322*f*, 1453, 1455, 1533*t*–1535*t*, 1542
  prevention of, 324
  respiratory epithelium affected by, 321
Borrelia burgdorferi, 153, 1128, 1194, 1440*t*, 1469, 1533*t*–1535*t*. *see also* Lyme disease
Botulism, 1167*t*, 1169
Boxers
  arrhythmogenic right ventricular cardiomyopathy in, 148, 1363
  cardiac tamponade in, 178*f*
  paroxysmal ventricular tachycardia in, 149*f*
Brachial plexus avulsion, 1158*t*, 1159*f*
Brachycephalic airway syndrome, 279–280, 279*f*, 380–381
Bradyarrhythmias, 86–88
  algorithm for, 86*f*
  atrial standstill, 87
  atrioventricular conduction block, 87–88
  sick sinus syndrome, 86–87, 87*f*
  sinus bradycardia. *see* Sinus bradycardia
  treatment of, 86*f*
Bradycardia, 37
Bradycardia-tachycardia syndrome, 86, 87*f*
Bradyzoites, 1520
Brain
  anatomy of, 1037–1039, 1038*f*
  cerebellum, 1038–1039
  degenerative disorders of, 1080
  forebrain, 1037
  infective endocarditis effects on, 134*b*
  medulla, 1037–1038
  pons, 1037–1038
Brain natriuretic peptide, 13
  dilated cardiomyopathy and, 144
  synthesis of, 58
Brain tumors, 1081
Brainstem
  anatomy of, 1037
  lesions of, 1038*b*
Brainstem auditory evoked response, 1072
Breathing
  open-mouth, 4, 4*f*
  rate of, 4
Breathing pattern
  in laryngeal diseases, 271
  in respiratory distress, 284
Breeding husbandry
  artificial insemination
    intrauterine, 947–948, 947*f*–948*f*
    transcervical, 947–948, 948*f*
    vaginal, 947
  semen analysis, 946–947, 946*f*
  semen collection, 945–946, 945*b*
Breeding management
  of bitch, 944–945
  of queen, 944–945
Brethine. *see* Terbutaline; Terbutaline sulfate
Bromocriptine, 955
Bronchi
  bronchoscopy of, 314*t*
  disorders of, 283*b*
Bronchial asthma, 330*b*
Bronchial pattern, 290, 290*f*–291*f*, 290*b*, 293*f*
Bronchiectasis, 290, 325, 325*f*
Bronchitis
  allergic, 329*t*, 337
  canine chronic. *see* Canine chronic bronchitis
  feline. *see* Feline bronchitis
  mycoplasmal, 329*t*
Bronchoalveolar lavage
  advantages and disadvantages of, 299*t*
  canine chronic bronchitis evaluations, 326
  diagnostic yield, 310, 310*f*
  heartworm disease evaluations, 206
  interpretation of results, 309–310
  pulmonary neoplasia findings, 352*f*
  recovery from, 308–309
  specimen handling, 309
Bronchodilators
  aspiration pneumonia treated with, 347–348
  bacterial pneumonia treated with, 343
  feline bronchitis treated with, 332
  idiopathic pulmonary fibrosis treated with, 351
  pulmonary parenchymal disorders treated with, 381–382
Bronchoscopy, 309*t*, 312
  airway collapse evaluations of, 335
  aspiration pneumonia evaluations, 347
  canine chronic bronchitis evaluations, 326
  indications for, 312
  Oslerus osleri on, 338*f*
  technique for, 312, 313*f*
Brucella canis, 963–964, 1441*t*, 1446, 1533*t*–1535*t*, 1543
Brucellosis, 963–965, 1000
Bubonic plague, 1541
Buccal mucosa bleeding time, 1389, 1391*b*
Budesonide, 441, 515*t*–517*t*
Bulbourethral reflex, 1049*t*, 1050
Bulk laxatives, 445
Bulking agents, 445*t*
Bundle branch block
  left, 44, 46*b*
  patterns, 45–46
  right, 44, 45*f*, 46*b*
Buprenorphine, 19–20, 629*t*–630*t*, 1268*t*
  analgesic uses of, 227*b*
  dosage of, 1134*t*
  stress relief using, 380*t*

Buspirone, 728*b*
Butorphanol, 19–20, 62*b*, 386*t*–388*t*, 515*t*–517*t*
  analgesic uses of, 227*b*
  canine infectious tracheobronchitis treated with, 323
  dosage of, 1134*t*
  stress relief using, 380*t*

C

Cabergoline, 955, 960, 1034*t*–1036*t*
Calcitonin, 759*t*, 926–927, 934*t*
Calcitriol, 695–696, 702
Calcium, 934*t*
  balance, 695–697
  dietary deficiency of, 758
  hormones that affect metabolism of, 759*t*
  hypercalcemia, 48, 49*b*, 761*t*, 923–927, 925*f*, 1268, 1298
  hypocalcemia, 48, 49*b*, 765*t*, 927–929, 928*b*
  supplementation of, 765
  treatment uses of, 896*t*–897*t*
Calcium channel blockers, 96–97
  adverse effects of, 96
  contraindications for, 96
  diltiazem. *see* Diltiazem
  hypertension treated with, 217*t*
  mechanism of action, 96
Calcium gluconate, 765, 928, 934*t*, 969–972, 1034*t*–1036*t*, 1185*t*–1186*t*
Calcium oxalate calculi, 714
Calcium oxalate dihydrate crystals, 670*f*
Calcium oxalate monohydrate crystals, 670*f*
Calcium oxalate urolithiasis
  dietary modifications for, 717–718, 718*b*
  drug therapy for, 718
  management of, 717*b*
  prevention of, 717–718
Calcium phosphate calculi, 721
Calculi
  apatite-containing, 721
  calcium oxalate, 714
  calcium phosphate, 721
  dried solidified blood, 722, 722*f*
  renal, 715*f*
  ureteral, 715*f*, 716–719
Calicivirus
  polyarthritis caused by, 1201, 1201*f*
  stomatitis caused by, 1496
  vaccine for, 1453
Caloric distribution, 904
Calories, weight loss and, 902–903
Campylobacter spp., 1427–1428, 1440*t*, 1533*t*–1535*t*, 1539
Campylobacteriosis, 480–481
Cancer. *see also* Carcinoma; Neoplasia; Neoplasm(s); *specific cancer*
  bone metastases, 1290
  metastatic, 1289–1290, 1290*t*
  remission of, 1267
  solitary mass, 1288–1289, 1289*f*
  treatment of
    chemotherapy. *see* Chemotherapy
    curative, 1267
    family-related factors, 1265–1266
    general considerations for, 1265
    options for, 1266*b*
    palliative, 1267
    patient-related factors, 1265
    treatment-related factors, 1265–1268
    tumor response criteria, 1267*b*
Cancer cachexia syndrome, 471
Canine acidophil cell hepatitis virus, 586
Canine adenovirus
  type of, 1454–1455
  vaccination for, 1454–1455
Canine bartonellosis, 1457–1458
Canine brucellosis, 963–965
Canine chronic bronchitis, 324–328
  antibiotics for, 328
  breeds commonly affected, 324
Canine chronic bronchitis *(Continued)*
  bronchoalveolar lavage of, 326
  bronchoscopy of, 326
  clinical features of, 324–325
  complications of, 325
  definition of, 324
  diagnosis of, 325–326, 325*b*, 326*f*
  doxycycline for, 328
  drug therapies for, 327–328, 327*b*
  etiology of, 324
  exacerbating factors, 326
  prognosis for, 328
  tracheal wash of, 326
  treatment of, 325*b*, 326
  vaccines, 324
Canine chronic rhinitis, 249*b*
Canine copulatory lock, 940*f*
Canine coronaviral enteritis, 479
Canine distemper virus, 1485–1487
  clinical features of, 1485–1486, 1486*t*
  diagnosis of, 1125, 1486–1487
  etiology of, 1485
  medallion lesions from, 1486*f*
  myocarditis in puppies caused by, 153
  pathogenesis of, 1485
  prevention of, 1487
  signs of, 1124
  treatment of, 1487
  vaccination for, 1454–1455
  zoonotic aspects of, 1487
Canine eosinophilic gastritis, 463
Canine eosinophilic meningitis/meningoencephalitis, 1122
Canine epileptoid cramping syndrome, 1106
Canine erection, 995, 995*f*
Canine granulocytotropic anaplasmosis, 1469–1471
Canine granulocytotropic ehrlichiosis, 1478–1479
Canine herpes virus (CHV), 1022
Canine idiopathic polymyositis, 1176
Canine infectious respiratory disease, 1441*t*
Canine Infectious Respiratory Disease Complex (CIRDC), 322*b*
Canine infectious tracheobronchitis
  client communication challenges associated with, 321
  clinical features of, 322
  cough suppressants for, 323, 323*t*
  diagnosis of, 322–323
  etiology of, 321–322, 322*b*
  prevention of, 323–324
  prognosis for, 323
  treatment of, 323, 323*t*
  uncomplicated, 323
Canine influenza, 340, 1455
Canine leptospirosis, 1462
Canine lymphoplasmacytic rhinitis, 249*b*
Canine monocytotropic ehrlichiosis, 1473–1477
  clinical features of, 1474, 1474*t*
  diagnosis of, 1474–1476, 1475*f*, 1475*t*
  epidemiology of, 1473–1474
  etiology of, 1473–1474
  hypoalbuminemia and, 1475
  prevention of, 1477
  treatment of, 1476–1477
  zoonotic aspects of, 1477
Canine nasal polyps, 264
Canine pancreatic lipase immunoreactivity (cPLI), 512
Canine parvoviral enteritis, 476–478, 477*b*
Canine parvovirus
  -1, 476
  -2, 476
  vaccination for, 1454–1455
Canine rheumatoid-like polyarthritis, 1206–1208, 1206*f*–1207*f*
Canine steroid-responsive tremor syndrome, 1122
Canine thrombocytotropic anaplasmosis, 1472–1473
Canine thyroid neoplasia, 800–804
  aural, 1114
  cervical ultrasonography of, 801–802
  chemotherapy for, 803
  clinical features of, 800–802, 800*f*
  cytologic diagnosis of, 1260*f*
  diagnosis of, 802
  etiology of, 800
  external beam radiation for, 803
  feline leukemia virus-associated, 1495–1496
  lymph nodes, 1264
  oral antithyroid drugs for, 803–804
  peripheral vestibular disease caused by, 1114
  prognosis for, 804
  radioactive iodine for, 803
  signs associated with, 801*f*–802*f*, 801*b*
  surgery for, 803
  thrombocytopenia caused by, 1241*t*
  treatment of, 802–804, 802*f*
Canine toxoplasmosis, 1525
Canine viral-associated pregnancy loss, 966
Canine X-linked muscular dystrophy, 1179
Canned pumpkin pie filling, 445*t*
Capillaria spp.
  C. aerophila
    lower respiratory tract diseases caused by, 296, 297*f*, 297*t*
    pulmonary parenchymal disease caused by, 344
  C. boehmi, 263–264
  C. plica, 651*f*, 669–670
Capillariasis, 263–264
Capillary refill time (CRT), 4–5, 1341
Capnocytophaga canimorsus, 1533*t*–1535*t*
Capsule endoscopy, 429
Captopril
  chronic heart failure treated with, 64*t*, 68
  hypertension treated with, 217*t*
Capture beat, 41
Carafate. *see* Sucralfate
Carbamates, 1099*b*
Carbapenems, 1437*t*–1438*t*
Carbimazole, 796*t*, 797, 896*t*–897*t*
Carboplatin, 1327*b*
Carcinoma, 329*t*
  cytologic findings, 1260, 1261*f*
  parathyroid, 758–759
  squamous cell
    metastasis of, 1290*t*
    oral cavity, 448*t*
  thyroid, 800
Cardiac arrhythmias, 77–99
Cardiac auscultation, 7–8, 7*f*
Cardiac biochemical markers, 13–14
Cardiac cachexia, 72–73
Cardiac catheterization, 52
Cardiac chamber enlargement
  electrocardiography of, 45–46, 46*f*, 46*b*–47*b*
  radiography of, 15–16, 16*f*
Cardiac computed tomography, 18
Cardiac conduction system, 34*f*
Cardiac cycle, 7–8, 8*f*
Cardiac disease
  clinical manifestations of, 1–12
  signs of, 1
Cardiac murmurs. *see also* Murmurs
  auscultation of, 9–11, 10*f*
  characteristics of, 7
  continuous (machinery), 9–11, 10*f*
  decrescendo, 9–10, 10*f*
  in degenerative atrioventricular valve disease, 122
  diastolic, 9, 11
  ejection, 9–10
  functional, 9–11
  grading, 10*t*
  holosystolic, 9–10, 10*f*, 114
  innocent, 9
  "musical," 9
Cardiac murmurs *(Continued)*
  nonpathologic, 9–11
  phonocardiographic configuration of, 9–10, 10*f*
  physiologic, 10–11
  presystolic, 9
  in pulmonary hypertension, 115
  "regurgitant," 9–10
  systolic, 9–11
  systolic ejection, 11
  to-and-fro, 11
Cardiac output
  low, 1, 2*b*, 121*b*
  poor, 80
Cardiac remodeling, 55
Cardiac silhouette, in pericardial effusion, 178–179, 179*f*
Cardiac tamponade
  clinical features of, 178*f*
  echocardiographic findings, 180*f*
  heart sounds in, 177–178
  pathophysiology of, 177–178
  pericardial fluid accumulation as cause of, 177
  treatment of, 188
Cardiac troponins, 13
Cardiac tumors, 174–189
  chemodectomas, 176, 185
  clinical features of, 186–187
  diagnosis of, 187–188
  in dogs, 186*t*
  echocardiographic findings, 187, 187*f*
  electrocardiographic findings, 187
  etiology of, 185–188
  hemangiosarcoma, 176, 178, 185
  lymphoma, 186
  mesothelioma, 186
  pathophysiology of, 185–188
  pericardial fluid analysis for, 187–188
  prognosis for, 188
  radiographic findings, 187
  surgical resection of, 188
  treatment of, 188
Cardiogenic pulmonary edema
  cough caused by, 3
  in dogs, 18
Cardiomegaly, 6
  cardiac radiography of, 15, 15*b*
  hypertension as cause of, 213
Cardiomyopathy
  arrhythmogenic right ventricular
    in boxers, 141
    in cats, 171
    in dogs, 141
  dilated. *see* Dilated cardiomyopathy
  hypertrophic. *see* Hypertrophic cardiomyopathy
  restrictive. *see* Restrictive cardiomyopathy
  tachycardia-induced, 152
  thyrotoxic, 790
Cardiotoxicity
  chemotherapy-related, 1283–1284
  doxorubicin-induced, 150, 170, 1283–1284
Cardiovascular disorders, 1023
Cardiovascular examination, 3–11
  of arterial pulses, 5–6, 6*b*
  auscultation and, 7–11, 7*f*–8*f*
  for fluid accumulation, 6
  of jugular veins, 5, 6*b*
  medical history in, 3–4, 3*b*
  of mucous membranes, 4–5, 5*b*
  of precordium, 6
  of respiratory patterns, 4, 4*f*
Cardiovascular system, diagnostic tests for, 13–54
Carina, 314*t*
Carnassial tooth root abscess, 245–246
Carprofen, 629*t*–630*t*, 1197*t*, 1209*t*–1210*t*, 1268*t*
Carpus, arthrocentesis method in, 1191*f*
Carvedilol, 94*t*, 95
Casts, in urinary sediment, 667–668, 667*f*–668*f*
Cat bites, 1539–1542

Cat scratch disease, 1540
Cataracts
  diabetes mellitus as cause of, 809–810, 810*f*, 828–829
  in dogs, 809–810, 810*f*, 828–829
Cathartics, 443–446, 445*t*, 1100*b*
Catheters
  nasal, 383–384, 384*f*
  for thoracocentesis, 367
  transtracheal, 383*t*, 384
Cauda equina compression, 1054
Cauda equina syndrome, 1149–1151, 1149*f*–1151*f*
Caudal agenesis, 1155
Caudal aortic thromboembolism, 1162–1163
Caudal nasopharynx, evaluation of, 276
Caudal stomatitis, 1439*f*
Caudal vena cava, 17
Caudate cells, 666–667
Caval syndrome
  clinicopathologic findings, 202
  deaths caused by, 202
  description of, 196
  heartworm disease as cause of, 202–203
  signs of, 202
Cavalier King Charles Spaniels, 1395
  episodic falling in, 1106
Cavitary lesions, 294, 295*f*
Cefadroxil, 1437*t*–1438*t*
Cefazolin, 386*t*–388*t*, 515*t*–517*t*, 1437*t*–1438*t*
Cefotaxime, 1185*t*–1186*t*, 1209*t*–1210*t*, 1437*t*–1438*t*
Cefovecin, 1437*t*–1438*t*
Cefoxitin, 515*t*–517*t*, 1437*t*–1438*t*
Cefpodoxime, 1437*t*–1438*t*
Ceftiofur, 1437*t*–1438*t*
Ceftriaxone, 1185*t*–1186*t*, 1209*t*–1210*t*
Cell cycle, 1269, 1270*f*
Cell-mediated immunity, 1451
Cellulitis, 979*f*
Central cord syndrome, 1041
Central diabetes insipidus, 654*t*–655*t*, 742, 742*b*, 1033
Central nervous system
  brain. *see* Brain
  feline infectious peritonitis, nonseptic exudate and, 363
  infections of, 1440*t*, 1442
  inflammation of, 1117
  lymphoma of, 1081, 1307–1309, 1308*f*
  spinal cord. *see* Spinal cord
Central nervous system diseases
  ancillary tests for, 1118*t*
  bacterial meningoencephalomyelitis, 1123–1124
  canine distemper virus, 1124–1125
  canine eosinophilic meningitis/meningoencephalitis, 1122
  canine steroid-responsive tremor syndrome, 1122
  diagnosis of, 1117
  feline immunodeficiency virus encephalopathy, 1123
  feline infectious peritonitis
    ancillary tests for, 1118*t*
    signs of, 1126
  feline polioencephalitis, 1122–1123
  granulomatous meningoencephalitis, 1087–1088, 1120–1121, 1121*b*
  infectious, 1123–1129
  Lyme disease, 1128
  mycotic infections, 1128
  neck pain associated with, 1117–1119
  necrotizing leukoencephalitis, 1122
  necrotizing meningoencephalomyelitis, 1121–1122
  neosporosis, 1118*t*, 1127–1128, 1127*f*
  noninfectious, 1119–1123
  rabies, 1125–1126
  rickettsial diseases, 1128–1129
  steroid-responsive meningitis-arteritis, 1118*f*, 1119, 1119*b*
  toxoplasmosis, 1126
Central venous pressure (CVP)
  acute kidney injury, 690
  in constrictive pericardial disease, 185
  heart failure and, 65
  measurement of, 52
  overhydration assessments, 433
  pericardial effusion levels of, 181
Central vestibular disease
  cerebrovascular disease causing, 1115–1116
  clinical findings of, 1110*b*
  disorders that cause, 1115–1116
  inflammatory diseases causing, 1115
  intracranial neoplasms causing, 1115
  lesion localization, 1110–1111
  thiamine deficiency causing, 1115
Centrine. *see* Aminopentamide
Centronuclear myopathy, 1179–1180, 1180*f*
Cephalexin, 386*t*–388*t*, 1185*t*–1186*t*
  bacterial infections treated with, 1437*t*–1438*t*
  joint disease treated with, 1209*t*–1210*t*
Cephalosporins. *see also specific drug*
  bacterial meningoencephalomyelitis treated with, 1123–1124
  diskospondylitis treated with, 1144
  infective endocarditis treated with, 136–137
  types of, 1437*t*–1438*t*
Cephulac. *see* Lactulose
Cerebellar ataxia, 1046*b*
Cerebellar cortical degeneration, 1080–1081
Cerebellomedullary angle, 1111
Cerebellomedullary cistern, 1070*f*
Cerebellum
  anatomy of, 1038–1039
  lesions of, 1038*b*
Cerebral cortex, 1037
Cerebral meningiomas, 1081
Cerebrospinal fluid
  analysis of, 1071, 1072*b*
  bacterial meningoencephalomyelitis findings, 1123
  canine distemper virus findings, 1486
  collection of
    at cerebellomedullary cistern, 1070*f*
    cisternal puncture for, 1069–1070, 1070*f*
    contraindications for, 1068–1069
    indications for, 1067–1068
    lumbar puncture for, 1070, 1071*f*
    technique for, 1069–1070
  granulomatous meningoencephalitis findings, 1120–1121
  protein concentration in, 1071
  syringomyelia, 1155
  white blood cells in, 1071
Cerenia. *see* Maropitant
Cervical disk extrusion, 1136, 1138*t*, 1139
Cervical intumescence, 1039, 1039*f*, 1041*b*
Cervical spondylomyelopathy, 1151–1153, 1152*f*–1153*f*
Cervical trachea, 287
Cervical ultrasound, 794, 795*f*
Cesarean section, 972–974, 974*f*
Cestex. *see* Epsiprantel
Cestodes, 1537
Cetirizine, 386*t*–388*t*
Chagas disease, 153–154
Chédiak-Higashi syndrome, 1372
Chemodectomas, 176, 185
Chemotherapy, 1269–1275. *see also* Anticancer drugs
  acute leukemia treated with, 1317*b*
  body weight conversions to body surface area, 1271, 1271*t*
  brain tumors treated with, 1082
  canine thyroid neoplasia treated with, 803
  cell kinetics, 1269, 1270*f*
  chronic leukemia treated with, 1319*b*
  combination, 1270–1271
Chemotherapy *(Continued)*
  complications of, 1276–1287
    acute tumor lysis syndrome, 1286, 1286*f*
    alopecia, 1282–1283, 1283*f*
    anemia, 1278
    anorexia, 1281
    cardiotoxicity, 1283–1284
    dermatologic toxicity, 1282–1283, 1282*f*
    feline susceptibility to, 1276
    gastroenterocolitis, 1281
    gastrointestinal toxicity, 1280–1281
    general considerations, 1276
    hematologic toxicity, 1276–1280
    hepatotoxicity, 1285
    hypersensitivity reactions, 1281
    myelosuppression, 1280
    nausea, 1280
    nephrotoxicity, 1284
    neurotoxicity, 1285
    neutropenia, 1278, 1279*f*
    pancreatitis, 1283
    pulmonary toxicity, 1285–1286
    sterile hemorrhagic cystitis, 1284
    thrombocytopenia, 1278
    urotoxicity, 1284–1285
    vomiting, 1280
  contraindications for, 1272
  dosage calculations, 1271
  feline leukemia virus-associated neoplasia treated with, 1497
  hematologic monitoring during, 1279
  indications for, 1272
  local tissue reactions, 1283*b*
  lymphoma treated with, 1302
  metronomic, 1273–1274
  nasal tumors treated with, 265
  osteosarcoma treated with, 1327, 1327*b*
  principles of, 1270–1271
  protocols for, 1337*b*–1339*b*
  toxicities associated with, 1277*t*–1278*t*
  tumor kinetics, 1269–1275, 1270*f*
Chest, auscultation for, 7–8, 8*f*
Chest tubes
  placement of, 367–369, 368*f*–369*f*
  pneumothorax complications, 367
  thoracic radiographs of, 369
Cheyletiella spp., 1430
Chief cells, 758
Chinese Shar-Peis
  enteropathy in, 497
  familial fever in, 1205, 1245*t*
  glomerular disease in, 680
  granulomatous meningoencephalitis in, 1120*f*
Chitosan, 913
Chlamydia felis, 1453, 1533*t*–1535*t*, 1542
Chlamydophila spp.
  C. felis, 1427
  infection caused by, 258
Chlorambucil, 442, 515*t*–517*t*
  dosage of, 1225*t*
  immune-mediated diseases treated with, 1224, 1225*t*, 1255*t*–1256*t*
  immune-mediated polyarthritis treated with, 1204*t*
  joint disease treated with, 1209*t*–1210*t*
Chloramphenicol, 386*t*–388*t*, 1437*t*–1438*t*, 1479
Chlorinated hydrocarbons, 1099*b*
Chlorothiazide, 64*t*, 67, 896*t*–897*t*
Chlorpheniramine, 266, 386*t*–388*t*
Chlorpromazine, 438*t*, 1185*t*–1186*t*
Chlorpropamide, 896*t*–897*t*
Cholangitis, 567–573, 599–600
  chronic neutrophilic, 568*t*
  liver fluke infestation and, 568*t*, 572–573, 573*b*
  lymphocytic, 570–572, 571*f*
  neutrophilic, 568*t*, 569*f*
  sclerosing, 572
Cholecystitis, 569, 573, 599–600
Cholehtiths, 573
Choleretics, 590
Cholestyramine, 913–914
Chondroitin sulfate, 1196, 1197*t*, 1209*t*–1210*t*
Chondroprotective agents, 1196, 1197*t*, 1207
Chondrosarcomas, 1260–1261
Chordae tendineae rupture, 124*f*, 130
Chorioretinitis, 242*f*, 1488
  punctate, 1522*f*
Chronic airway disease, 131
Chronic bronchitis, canine, 324–328, 330*b*
  antibiotics for, 328
  breeds commonly affected, 324
  client communication challenges associated with, 321
  clinical features of, 322, 324–325
  complications of, 325, 328
  cough suppressants for, 323, 323*t*
  diagnosis of, 322–323
  doxycycline for, 328
  drug therapies for, 327–328, 327*b*
  etiology of, 321–322, 322*b*, 324
  exacerbating factors, 326
  prevention of, 323–324
  prognosis for, 323, 328
  treatment of, 323, 323*t*, 326
  uncomplicated, 323
  vaccines, 324
Chronic enteropathy, 493–495
Chronic gastritis, 463–464
Chronic heart failure, 127*b*. *see also* Congestive heart failure; Heart failure
  amlodipine for, 71
  angiotensin-converting enzyme inhibitors for, 67–68
  benazepril for, 68
  captopril for, 64*t*, 68
  client education about, 73–74
  dietary considerations for, 72–73
  digoxin for, 69–70
  diuretics for, 66–67
  drug therapy for, 64*t*
  enalapril for, 68
  furosemide for, 64*t*, 66, 128
  general considerations for, 66
  hydralazine for, 71
  hyponatremia in, 74
  loop diuretics for, 66–67
  monitoring of, 73–74, 74*b*
  nitrates for, 71–72
  pimobendan for, 69, 128
  prazosin for, 71
  reevaluations, 73–74
  refractory, 74–75, 127*b*, 129–130
  salt restriction for, 72, 128–129
  spironolactone for, 67
  thiazide diuretics for, 67
Chronic hepatitis, canine, 584–598
  antibiotics for, 593
  antifibrotics for, 593
  antioxidants for, 590–591
  breed and, 585*b*
  choleretics for, 590
  clinical features of, 588–589, 589*f*
  diagnosis of, 589
  diet for, 590, 591*t*
  drugs for, 590–595
  glucocorticoids for, 592, 592*f*
  idiopathic, 586–595
  immune-mediated, 587
  immunosuppressive drugs for, 592–593
  lobular dissecting, 587
  shared pathogenesis of, 588
  toxic causes of, 587–588
  treatment of, 589–595
Chronic idiopathic polyneuropathy, 1165–1166
Chronic inflammatory demyelinating polyneuropathy (CIDP), 1165, 1166*f*
Chronic kidney disease (CKD), 692–702
  acid-base balance, 697
  acute kidney injury *versus*, 687*t*
  anemia in, 697

Chronic kidney disease (CKD) *(Continued)*
cardiovascular complications of, 698
in cats, 692*b*, 693*t*
causes of, 692*b*
clinical findings of, 698
clinicopathologic findings of, 698–702
course of, 702
in dogs, 692*b*, 693*t*
external solute balance, 694–695, 695*f*
familial, 693*b*
gastrointestinal disturbances in, 697–698
hemostatic defects in, 697
hypertension in, 698
hyperthyroidism and, 696*f*, 698, 790–791
imaging of, 698–702
metabolic acidosis of, 697
metabolic complications of, 698
pathophysiology of, 693–698, 693*b*
prognosis for, 702
progression of, 698–699
proteinuria in, 681, 681*b*
staging of, 692
supportive care for, 702
treatment of, 699–702, 699*b*
anabolic steroids, 702
angiotensin receptor blockers, 701
angiotensin-converting enzyme inhibitors, 701
antiemetics, 701
blood pressure control agents, 702
calcitriol, 702
dietary management, 699–702
endocrine replacement therapy, 701–702
erythropoietin, 701–702
general principles, 699
H_2 receptor antagonists, 701
phosphorus restriction, 700–701
Chronic leukemias
in cats, 1320–1321, 1321*f*
in dogs, 1316–1319
chemotherapy for, 1319*b*
clinical features of, 1317
diagnosis of, 1318–1319
hematologic features of, 1317–1318, 1317*f*–1318*f*
prevalence of, 1316
treatment of, 1319
Chronic lymphocytic leukemia, 1312*t*
blood smear findings, 1321*f*
differential diagnosis of, 1379
Chronic myeloid leukemia, 1312*t*
Chronic neutrophilic cholangitis, 568*t*
Chronic pancreatitis
acute pancreatitis *versus*, 623*t*
autoimmune, 634
biopsy of, 636
clinical features of, 635
definition of, 633
description of, 620
diagnosis of, 635–636
etiology of, 633–634
idiopathic, 634, 634*f*
pathogenesis of, 633–634
prognosis for, 636
signs of, 635
treatment of, 636
Chronic renal disease, 654*t*–655*t*
Chronic vestibulovaginitis, 980–982, 980*f*–982*f*
Chyle, 362*f*, 363, 374
Chylomicron test, 910–911
Chylomicrons, 908, 911–912
Chylothorax, 363, 374–375, 375*b*
Chylous pleural effusions, 361*t*, 362*f*, 363
Chymase, 120
Ciba. *see* Terbutaline
Cicatrix
description of, 424–425
esophageal, 459–460
Ciliary dyskinesia, 326
Ciliates, 1538–1539
Cimetidine, 439
Cinefluoroscopy, 451
Circling, 1046, 1046*f*
Circulating neutrophil pool, 1372
Cisapride, 440–441, 455–456, 515*t*–517*t*
Cisternal puncture, for cerebrospinal fluid collection, 1069–1070, 1070*f*
Citrate intoxication, 1358
Clavamox. *see* Amoxicillin-clavulanate
Cleansing enemas, 445
Cleft palate, 1015*f*–1017*f*
Clindamycin, 386*t*–388*t*, 515*t*–517*t*, 1127–1128, 1185*t*–1186*t*, 1437*t*–1438*t*, 1443, 1521
Clomipramine, 728*b*
Clopidogrel
for arterial thromboembolism
in cats, 226–228, 227*b*
in dogs, 232
immune-mediated diseases treated with, 1255*t*–1256*t*
Cloprostenol, 955–956, 960, 1034*t*–1036*t*
Clostridial colitis, 494
Clostridial disease, 482, 482*f*
Clostridium spp., 1427–1428
acute hemorrhagic diarrheal syndrome and, 462
C. botulinum, 1169
C. perfringens, 1427–1428, 1440*t*, 1442
C. tetani, 1181
Clotrimazole
complications of, 263
nasal aspergillosis treated with, 261–263, 262*f*
Clotting factors
defects of, 1393*b*
deficiency of, 1356, 1399–1400
description of, 1387
Cluster seizures, 1095
Coagulation cascade, 222, 1387–1388, 1391*f*
Coagulation tests, 543
Coagulopathies, 527–529, 529*b*
treatment of, 594–595
Coarse wheat bran, 445*t*
Cobalamin, 423–424, 1364, 1364*f*
Coccidians, 1537–1538, 1537*f*
Coccidioides immitis, 1505, 1506*f*
Coccidioides spp., 1503*t*
Coccidioidomycosis, 1505–1507
Coccidiosis, 488, 1028
Codman triangle, 1326
Colace. *see* Dioctyl sodium sulfosuccinate
Colchicine
joint disease treated with, 1209*t*–1210*t*
serum amyloid A protein release affected by, 683–684
Collapse, 1–2
disorders causing, 1183–1184
exercise-induced, 1183–1184
Collapsing trachea. *see* Trachea, collapse of
Colloids, 433
Colonoscopy, 405, 427, 429*f*
Color flow mapping, 31–32, 31*f*–32*f*
Coma, 1043
Combined cytopenias, 1381–1386
bone marrow aplasia-hypoplasia, 1384–1385
classification of, 1381
clinicopathologic features of, 1381–1386
definition of, 1381–1386
Community-acquired pneumonia, 340, 1441*t*
Compazine. *see* Prochlorperazine
Complete blood count, 538
alimentary tract disease, 405–406, 412
hemoglobin assessment using, 318
Computed tomography (CT)
cardiac, 18
larynx and pharynx, 273
lower respiratory tract disorders, 295–296
nasal imaging using, 250, 250*f*
neuromuscular system, 1066, 1067*f*
Computed tomography pulmonary angiography, 355–356
Concentric myocardial hypertrophy, 105
Conduction disturbances
within atrioventricular mode, 43–44, 44*f*
electrocardiography of, 42–45
intraventricular, 44
left bundle branch block, 44
right bundle branch block, 44, 45*f*
ventricular preexcitation, 44–45, 45*f*
Congenital ductal plate abnormalities, 611
Congenital esophageal weakness, 452–454, 453*f*
Congenital heart disease, 100–118
atrioventricular septal defect, 100
atrioventricular valve malformation, 112–113
in cats, 100
cor triatriatum, 117
in dogs, 102*t*
endocardial fibroelastosis, 100, 117
extracardiac arteriovenous shunt, 101–105
general considerations, 100
intracardiac shunt, 109–112
mitral dysplasia, 102*t*–103*t*, 112
murmurs caused by, 100
noninvasive testing for, 100
patent ductus arteriosus. *see* Patent ductus arteriosus
pulmonary hypertension with shunt reversal, 114–116, 115*f*
pulmonic stenosis. *see* Pulmonic stenosis
radiographic findings, 103*t*
subaortic stenosis. *see* Subaortic stenosis
tetralogy of Fallot. *see* Tetralogy of Fallot
tricuspid dysplasia, 102*t*–103*t*, 112–113
vascular ring anomalies, 116–117
ventricular outflow obstruction, 105–109
ventricular septal defect. *see* Ventricular septal defect
Congenital hypothyroidism, 1032–1033, 1033*f*
Congenital infertility, 1005
Congenital portosystemic shunt, 603–609
clinical features of, 604, 604*f*
diagnosis of, 604–605, 604*f*
etiology and pathogenesis of, 603
hepatic encephalopathy in, 606–608, 607*b*
prognosis for, 605–606, 605*f*
treatment for, 605–606
Congenital portosystemic shunts, 577–579, 578*f*
Congenital vascular disorders, 603–612
Congenital vestibular syndromes, 1114
Congestive heart failure (CHF). *see also* Heart failure
acute, 65, 129–130, 145
amlodipine for, 71
angiotensin-converting enzyme inhibitors for, 67–68
arterial thromboembolism as cause of, 225
benazepril for, 68
captopril for, 64*t*, 68
in cats, 164–167, 166*b*
causes of, 59*t*
corticosteroid-associated, 171–172
decompensated, 62*b*, 129
dietary considerations for, 72–73
digoxin for, 69–70
dilated cardiomyopathy as cause of, 146*b*
diuretics for, 66–67
in dogs, 3, 285
drug therapy for, 64*t*
enalapril for, 68
Congestive heart failure (CHF) *(Continued)*
fulminant, 61
furosemide for, 64*t*, 66–67, 128
general considerations for, 66
hydralazine for, 71
hyponatremia in, 74
infective endocarditis as cause of, 132
inotropic support, 63–65
left-sided, 1, 110
description of, 1, 110
edema caused by, 291
loop diuretics for, 66–67
mild to moderate, 128–129
monitoring of, 73–74, 74*b*
nitrates for, 71–72
noncardiac conditions of, 3
pericardial effusion associated with, 176
pimobendan for, 63, 64*t*, 69, 128
prazosin for, 71
reevaluations, 73–74
refractory, 74–75, 127*b*, 129–130, 147, 167
right-sided, 142, 171, 181, 186–187
fluid accumulation in, 6
heartworm disease as cause of, 202–203, 206
jugular vein distention and, 5, 5*f*
salt restriction for, 72, 128–129
severe, 129
spironolactone for, 67
supplemental oxygen for, 61
thiazide diuretics for, 67
treatment of, 61–66, 129, 146*b*
vasodilators for, 61–63, 64*t*, 129
Congestive signs, of heart failure, 1, 2*b*
Congestive splenomegaly, 1412*t*
Conn's syndrome, 892–893
Consciousness, disorders of, 1043*t*
Constant-rate infusion, 88*b*
Constipation, 404–405, 404*b*, 506–507
dietary indiscretion leading to, 507
Constrictive pericardial disease, 184–185
Continuous glucose-monitoring systems, 821, 822*f*
Continuous (machinery) murmurs, 9–11
Continuous wave Doppler echocardiography, 30, 31*f*
Contrast echocardiography, 27, 28*f*
Contrast-enhanced gastrograms, 422
"Convulsive syncope," 1–2
Coombs test, 1216, 1216*b*
Coonhound paralysis, 1166
Copper storage disease, 595–598
clinical features of, 595–596, 596*f*
diagnosis of, 596–597, 596*f*
etiology of, 595
feline, 576
pathogenesis of, 595
treatment of, 597–598, 597*b*
Copulatory lock, 940*f*
Cor triatriatum, 117
Corneal ulcers, 258
Coronary artery thromboembolism, 231
Coronaviral enteritis
canine, 479
feline, 479
Coronavirus, feline, 1488–1491
clinical features of, 1488–1489
diagnosis of, 1489–1490
enteric, 1488
epidemiology of, 1488
etiology of, 1488
prevention of, 1491
treatment of, 1490–1491
zoonotic aspects of, 1491
Corticosteroid(s)
congestive heart failure secondary to, 171–172
fever of unknown origin treated with, 1426
hemolytic anemia treated with, 1349
idiopathic pulmonary fibrosis treated with, 351

Corticosteroid(s) *(Continued)*
immune-mediated disorders treated with, 1222, 1222*b*
immune-mediated thrombocytopenia treated with, 1243
neutrophilia induced by, 1376
pulmonary parenchymal disorders treated with, 381
Corticosteroid-responsive neutropenia, 1375, 1375*f*
Cortisol, 867–868
Cortisol-secreting adrenal tumors, 875–876
Cortisone, 1222*t*
Costochondral junction, 6
Cough
cardiogenic pulmonary edema from, 3
causes of, 289*b*
in dogs, 283*b*
in laryngeal diseases, 271
in lower respiratory tract disorders, 282–283
nonproductive, 282
productive, 282, 283*b*
Cough suppressants
canine infectious tracheobronchitis treated with, 323, 323*t*
in tracheal collapse, 336
Cough syncope, 3
"Cough-drop,", 3
Coumadin. *see* Warfarin
Coxiella burnetii, 1481, 1533*t*–1535*t*, 1542–1543
Coxofemoral joint, arthrocentesis method in, 1191*f*
Crackles, 285–286
Cranial abdominal pain, 625*f*–626*f*
Cranial nerves. *see also specific nerve*
examination of, 1054–1060
function of, 1057*t*
optic nerve, 1055, 1056*t*
regional assessment of, 1056*t*
Cranial-caudal diameter, 21–22
C-reactive protein, 1217–1218, 1425
Creatinine
glomerular function, diagnostic tests for, 658
in Greyhounds, 1362
serum, 658–659
Creatinine clearance, 660–661, 661*t*
Crenosoma vulpis
lower respiratory tract diseases caused by, 296, 297*f*, 297*t*
pulmonary parenchymal diseases caused by, 346
Cretinism, 772–773, 772*b*, 773*f*
Cricopharyngeal achalasia/dysfunction, 451–452
Cricothyroid ligament, 300, 301*f*
Crossed extensor reflex, 1049–1050
Cross-matching, 1357
Crotalus atrox toxoid vaccine, 1455
Cryopoor plasma, 1355–1356
Cryoprecipitate, 1356
Cryptococcal antigen latex agglutination serology, 1128
Cryptococcosis, 1507–1510
ancillary tests for, 1118*t*
central nervous system signs of, 1508
chorioretinitis caused by, 242*f*
clinical features of, 1507–1508, 1508*f*
cytologic diagnosis of, 1509, 1509*f*
description of, 260
diagnosis of, 1508–1509, 1509*f*
epidemiology of, 1507
etiology of, 1507
facial deformity caused by, 242*f*, 245–246
prevention of, 1510
radiographic signs of, 249*b*
treatment of, 1509–1510
zoonotic aspects of, 1510
Cryptococcus spp., 1503*t*
C. gattii, 1128, 1507
C. neoformans, 260, 1128, 1507, 1509*f*
Cryptorchidism, 990–991, 991*f*
Cryptosporidia, 488–489
Cryptosporidiosis, 965–966
Cryptosporidium spp., 488, 1533*t*–1535*t*, 1537
C. canis, 965–966
C. felis, 965–966
C. parvum, 1428*f*, 1432, 1537, 1537*f*
Crystalloid solutions, 916
Crystalluria, 669*t*
Ctenocephalides felis, 1481, 1540, 1540*f*
Culture
fecal, bacterial, 414
infectious disease evaluations, 1431–1432
nasal, 255–256
Cutaneous lymphoma, 1295–1296, 1296*f*, 1309
Cutaneous mast cell tumors, 1333
Cutaneous T-cell lymphoma, 1295–1296
Cutaneous toxoplasmosis, 1522
Cutaneous trunci reflex, 1049*t*, 1050–1051, 1051*f*
Cutaneous xanthomas, 910
Cyanosis
cardiac anomalies that cause, 113–116
definition of, 284
hypoxemia and, 284
Cyanotic mucous membranes, 5*b*
Cyclooxygenase-2 (COX-2) inhibitors, for acute pancreatitis, 628–631
Cyclophosphamide, 386*t*–388*t*, 1204*t*, 1209*t*–1210*t*
Cyclosporin A, 1227*t*
Cyclosporine, 442, 515*t*–517*t*, 592–593, 1224–1226
granulomatous meningoencephalitis treated with, 1121*b*
immune-mediated diseases treated with, 1255*t*–1256*t*
description of, 1225*t*–1226*t*
hemolytic anemia, 1236
polyarthritis, 1204*t*
joint disease treated with, 1209*t*–1210*t*
myasthenia gravis treated with, 1251*t*
neurologic disorders treated with, 1185*t*–1186*t*
Cylindrical bronchiectasis, 290
Cyproheptadine, 386*t*–388*t*, 515*t*–517*t*
Cyst(s)
biliary, 575
follicular, 954, 954*f*
luteal ovarian, 955*f*
ovarian, 955–956, 955*f*–956*f*
pericardial, 175–176
rete ovarii, 956
spinal articular, 1147
Cystatin C, 659
Cystic benign prostatic hyperplasia, 1001–1003, 1002*f*
Cystic endometrial hyperplasia, 985–988, 986*f*–987*f*, 987*t*
Cystic meningioma, 1067*f*
Cystine urolithiasis, 721–722
Cystitis
feline idiopathic. *see* Feline idiopathic cystitis
hemorrhagic, 1284
Cystocentesis, 650–651, 664
Cystoliths, 713*f*
Cystometrography, 672, 732*b*
Cystourethrography, 707–708
Cystourethroscopes, 947
Cytauxzoon felis, 1430, 1516, 1516*f*
Cytauxzoonosis, 1516–1517
Cytochrome P450 enzymes, 89
Cytology, 1257–1264
bacterial diseases, 1429–1430
blastomycosis findings, 1503*f*, 1503*t*
canine monocytotropic ehrlichiosis, 1475–1476, 1475*f*
carcinomas, 1260, 1261*f*
cryptococcosis, 1509, 1509*f*
epithelial tissue, 1258–1259
fine-needle aspiration, 1257–1258
fungal diseases, 1430
general considerations for, 1257
Cytology *(Continued)*
hematopoietic tissue, 1259
hyperplastic processes, 1259
immune-mediated polyarthritis findings, 1246, 1246*f*
impression smears, 1258
infectious diseases, 1429–1430
inflammatory processes, 1259, 1259*f*
lymph nodes, 1263–1264, 1264*f*
lymphoma, 1262*f*, 1299, 1300*f*
malignant cells, 1259–1263, 1260*b*
mesenchymal tissue, 1259
neoplasia, 1260*f*
rickettsial diseases, 1430
round cell tumors, 1261–1263, 1262*f*
sarcomas, 1260–1261, 1261*f*
specimens
interpretation of, 1258–1264
staining of, 1258
Cytoprotective agents, 439–440, 439*t*
Cytosine arabinoside (Cytosar), 1121*b*, 1185*t*–1186*t*, 1320
Cytotec. *see* Misoprostol
Cytoxan. *see* Cyclophosphamide

D

Dacryocytosis, 1386
Dalteparin sodium
arterial thromboembolism in cats treated with, 227*b*
dosage of, 229
Dazzle reflex, 1085–1086
DDAVP. *see* Desmopressin
D-dimers, 355
Decerebrate rigidity, 1044, 1044*f*
Decompensated congestive heart failure, 62*b*, 129
Decompressive cystocentesis, 726*f*
Decrescendo murmurs, 9–10
Deep pain, 1052*f*
Degenerative joint disease, 1195–1196, 1196*f*, 1197*t*
Degenerative myelopathy, 1148–1149
Degenerative valvular disease, heart sounds and, 9
Delayed puberty, 953
DeLee mucous trap, 1009*f*
Demerol. *see* Meperidine
Depo-Medrol. *see* Methylprednisolone acetate
Deracoxib (Deramaxx), 1209*t*–1210*t*, 1268*t*, 1327*b*
Dermacentor variabilis, 1169, 1473, 1479
Dermatologic disorders, 1031–1032, 1032*f*
Dermatomyositis, 1177, 1177*f*, 1253
Dermatophytes, 1533*t*–1535*t*
Dermoepidermal mass, 1263*f*
Dermoepidermal mast cell tumors, 1329*f*, 1333
Deslorelin, 1034*t*–1036*t*
Desmopressin, 663
diabetes insipidus, 744
indications for, 896*t*–897*t*
von Willebrand disease, 1399
Desoxycorticosterone pivalate, 876, 896*t*–897*t*
Desquamative dermatopathy, 1296*f*
Dexamethasone, 386*t*–388*t*, 441, 515*t*–517*t*, 1034*t*–1036*t*
immune-mediated diseases treated with, 1222–1223, 1255*t*–1256*t*
pregnancy termination using, 960
properties of, 1222*t*
Dexamethasone sodium phosphate, 896*t*–897*t*
Dexamethasone suppression test
in cats, 881–882, 881*t*, 882*f*
high-dose, 864–865, 866*t*, 871
low-dose, 864–865, 866*t*, 867–868, 869*f*
oral, 866*t*, 870
Dexrazoxane, 1284
Dextrocardia, 326
Dextromethorphan, 323, 323*t*, 386*t*–388*t*
Dextrose, 1185*t*–1186*t*
Diabetes insipidus, 741–746
arginine vasopressin in, 741–742, 745*f*
central, 654*t*–655*t*, 741*t*, 742, 742*b*
clinical features of, 742–743
clinical signs of, 742–743
desmopressin acetate and, 744
diagnosis of, 743–745
etiology of, 741–742
modified water deprivation test for, 744, 744*t*
nephrogenic, 654*t*–655*t*, 742, 742*b*
physical examination of, 743
prognosis for, 746
random plasma osmolality measurements for, 744–745
signalment, 742
treatment of, 745–746, 745*b*
urine specific gravity in, 743*f*
Diabetes mellitus, 654*t*–655*t*
in cats, 830–840
classification of, 830–832
clinical features of, 832–833
diagnosis of, 833–834
etiology of, 830–832
history in, 832
monitoring techniques for, 835–836
non-insulin-dependent diabetes mellitus, 830, 831*f*
obesity, 834
physical examination of, 833
plantigrade posture associated with, 832, 833*f*
prognosis for, 840
remission of, 830–832, 832*b*, 836–837
risk factors of, 832
sequence of events in, 832*f*
signalment, 832
treatment of, 834–840
diet, 834–835
glipizide, 835
insulin, 834–836
oral hypoglycemic drugs, 835–837
sulfonylureas, 835
in dogs, 809–830
breeds commonly affected, 809, 810*t*
cataracts secondary to, 809–810, 810*f*, 828–829
classification of, 809
clinical features of, 809–810
clinicopathologic abnormalities in, 811*b*
complications of, 812*b*, 828–830
concurrent diseases, 810, 817
diabetic nephropathy caused by, 829
diabetic neuropathy caused by, 829
diagnosis of, 811
etiology of, 809
history in, 809–810, 818
insulin-dependent diabetes mellitus, 809
lens-induced uveitis caused by, 829
monitoring techniques for, 818–830
blood glucose concentrations, 818
continuous glucose-monitoring systems, 821
objective of, 818
serial blood glucose curves, 819–822, 820*f*, 823*f*–824*f*
serum fructosamine concentrations, 818–819
urine glucose, 819
physical examination of, 810, 818
prognosis for, 830
signalment for, 809, 810*t*
systemic hypertension and, 830
treatment of, 811–818
diet, 816, 816*b*
exercise, 816–817
goal for, 811, 812*t*
insulin, 812–814, 813*t*, 814–816, 815*f*, 815*t*
weight loss, 816
endocrine alopecia caused by, 748*t*

Diabetes mellitus *(Continued)*
hyperadrenocorticism and, 874–875
hypertension and, 830
insulin-dependent
in cats, 830
in dogs, 809
insulin-resistant, 753, 830
non-insulin-dependent, 809
Diabetic ketoacidosis, 840–847
bicarbonate therapy for, 842*b*, 844–845
clinical features of, 840–841
clinicopathologic abnormalities associated with, 843*b*
complications of, 847
concurrent illness for, 846
diagnosis of, 841
etiology of, 840
fluid therapy for, 842–845, 842*b*
insulin therapy for, 842*b*, 845–846
magnesium supplementation for, 844
phosphate supplementation for, 843–844
potassium supplementation for, 843
treatment of, 841–846
Diabetic nephropathy, 829
Diabetic neuropathy
in cats, 839–840
in dogs, 829
Diabetic polyneuropathy, 1164, 1165*f*
Diabinese. *see* Chlorpropamide
Dialysis, for acute kidney injury, 692
Diaphragm, of stethoscope, 7
Diaphragmatic hernia
peritoneopericardial, 174–175, 175*f*–176*f*
traumatic causes of, 362–363
Diarrhea
acute, 398–399, 398*b*, 474–476
acute enteritis, 474–475
dietary-induced, 475–476
enterotoxemia and, 475
chronic, 399, 399*t*
definition of, 398–402
dietary-responsive large intestinal, 494
endoparasitism and, 1028
fiber-enriched diets for, 435
fiber-responsive large bowel, 494
infectious, 476–480
canine coronaviral enteritis, 479
canine parvoviral enteritis, 476–478, 477*b*
elokomin fluke fever, 480
feline coronaviral enteritis, 479
feline immunodeficiency virus-associated diarrhea, 480
feline leukemia virus-panleukopenia-like syndrome, 479–480
feline parvoviral enteritis, 478–479
salmon poisoning, 480
large intestinal, 399*t*, 401*b*
motility modifiers for, 440–441, 440*t*
small intestinal, 399*t*, 400*f*
Diastole, 8
Diastolic dysfunction
chronic, 73
heart failure caused by, 65
Diastolic murmurs, 9, 11
Diazepam, 62*b*, 386*t*–388*t*, 1104, 1185*t*–1186*t*
Diazoxide therapy, 850*b*, 852
Dibenzyline. *see* Phenoxybenzamine
Diestrus, 938*t*, 939–940, 940*f*, 949, 955–956
Diet, 434
bland, 434, 434*b*
for calcium oxalate urolithiasis, 717–718, 718*b*
chronic heart failure managed through, 72–73
for chronic hepatitis, in dogs, 590, 591*t*
for chronic kidney disease, 699–702
diabetes mellitus managed with
in cats, 834–835
in dogs, 816, 816*b*
Diet *(Continued)*
elemental, 437
elimination, 434
enteral, 436*t*
for enteral support, 437
fiber-enriched, 435
hypertriglyceridemia managed with, 912*t*
hypoallergenic, 434*b*
iodine-restricted, 796*t*, 797–798
management, 434–437
parenteral nutrition, 437
partially hydrolyzed, 435
ultra-low-fat, 435
veterinary therapeutic, 904, 904*t*–906*t*
weight loss through, 904*t*–906*t*
Dietary options, 903
Dietary supplements, 73
Dietary-induced acute diarrhea, 475–476
Dietary-responsive large intestinal diarrhea, 494
Dietary-responsive small intestinal diarrhea, 491–492
Diethylstilbestrol (DES), 732–735, 733*t*–734*t*, 959, 982
Diffuse splenomegaly, 1409–1410
Diffuse thickening of the laryngeal mucosa, 276
Digestion
diagnostic tests for, 423
fecal tests for evaluating, 399, 413–414
Digestive enzyme supplementation, 440
Digoxin, 62*b*
antiarrhythmic effects of, 69
atrial fibrillation treated with, 85
chronic heart failure treated with, 64*t*, 69–70
contraindications, 69
dilated cardiomyopathy treated with, 145
electrocardiographic changes associated with, 49*b*
heart rate control using, 129
pharmacokinetics of, 72
serum concentrations of, 69–70
toxicity caused by, 70, 147
Digoxin-immune Fab, 70
1,25-Dihydroxycholecalciferol, 695–696
1,25-Dihydroxy-vitamin D_3 (calcitriol), 765–766
Dilated cardiomyopathy, 141–148
in cats, 169–171
chronic therapy for, 170
in dogs
atrial fibrillation associated with, 141
breeds commonly affected, 141
cardiac chamber dilation associated with, 142
clinical findings of, 142
clinicopathologic findings, 144–145
diagnosis of, 142–144, 143*f*
echocardiographic findings, 144, 144*f*
electrocardiographic findings, 142–144
etiology of, 141–142
idiopathic, 141
long term therapy for, 146–147, 146*b*
monitoring of, 147
pathophysiology of, 141–142
primary, 141
prognosis of, 147–148
radiographic findings, 142, 143*f*
sudden death caused by, 147–148
treatment of, 145
ventricular premature complexes and, 142
echocardiographic findings, 170
occult, 145
pimobendan for, 145
taurine deficiency and, 73, 170
treatment of, 145, 170–171
Diltiazem, 73
adverse effects of, 96
atrial fibrillation treated with, 84–85
Diltiazem *(Continued)*
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
heart rate control using, 129
for left ventricular outflow tract obstruction, 167
pharmacokinetics of, 96
Dimethyl sulfoxide (DMSO), 683
Dioctophyma renale, 669–670
Dioctyl sodium sulfosuccinate, 445*t*, 515*t*–517*t*
Dipentum. *see* Olsalazine
Diphenhydramine, 386*t*–388*t*, 515*t*–517*t*, 1185*t*–1186*t*
Diphenoxylate, 440, 440*t*
2,3-Diphosphoglycerate, 1353–1354, 1360
Dipylidium caninum, 1537
Direct antiglobulin test, 1216, 1216*b*
Direct Coombs test, 1233–1234, 1349–1350
Direct current cardioversion, for ventricular tachyarrhythmias, 84
Dirofilaria immitis, 1249
Dirofilaria immitis
life cycle of, 193
lung disease caused by, 344
microfilaria identification tests, 195–196
in urine sediment, 669–670
Disappearing bile duct syndrome, 598–599
Discospondylitis, 1440*t*
Disinfection protocols, 1450
Diskospondylitis, 1143–1144, 1143*f*–1144*f*
Disseminated intravascular coagulation
clinical features of, 1401–1402
complications of, 1404
definition of, 1400–1401
diagnosis of, 1402–1403, 1403*t*
heartworm disease as cause of, 197
hemostatic abnormalities associated with, 1402, 1402*t*
heparin for, 1403
intravascular coagulation cessation, 1403–1404
parenchymal organ perfusion in, 1404
pathogenesis of, 1404
primary disorders associated with, 1400–1404, 1402*t*
prognosis for, 1404
splenic torsion as cause of, 1413
symptomatic, 1401
thrombocytopenia caused by, 1241*t*
treatment of, 1403–1404, 1403*b*
Disseminated toxoplasmosis, 1522
Distemper meningoencephalitis, 1125
Distemper virus, canine, 1485–1487
clinical features of, 1485–1486, 1486*t*
diagnosis of, 1125, 1486–1487
etiology of, 1485
medallion lesions from, 1486*f*
myocarditis in puppies caused by, 153
pathogenesis of, 1485
prevention of, 1487
signs of, 1124
treatment of, 1487
vaccination for, 1454–1455
zoonotic aspects of, 1487
Ditropan. *see* Oxybutynin
Diuresis, for heart failure, 61
Diuretics
acute kidney injury treated with, 691
chronic congestive heart failure treated with, 66–67
loop
acute kidney injury treated with, 691
chronic heart failure treated with, 66–67
pulmonary edema caused by, 382
thiazide, 67
Diuril. *see* Chlorothiazide
Doberman Pinschers
chronic hepatitis in, 584–586
dilated cardiomyopathy in, 141–142
wobbler syndrome in, 1153*f*
Dobutamine, 62*b*
Docosahexaenoic acid, 72–73
DOCP, 887–888
Dofetilide, 96
Dog
clinical conditions of, 990–1006
balanoposthitis in, 992–993, 993*f*
cryptorchidism in, 990–991, 991*f*
paraphimosis in, 993–996, 994*f*
persistent penile frenulum in, 992, 992*f*
phimosis in, 993–996
priapism in, 993–996, 994*f*–996*f*
scrotal dermatitis in, 992, 992*f*
testicular neoplasia in, 996–997, 996*f*–997*f*
testicular torsion in, 991, 991*f*
urethral prolapse in, 992
liver diseases in, 585*t*
myocardial diseases in, 141–157
Dog bites, 1539–1542
Dog erythrocyte antigen (DEA), 1351, 1360–1361
Dolasetron, 438
Dopamine, for atrioventricular conduction block, 88
Dopamine agonists, 955
Dopaminergic compounds, for pregnancy termination, 960
Dopaminergic receptors, 691
Doppler echocardiography, 27–32
color flow mapping, 31–32, 31*f*–32*f*
continuous wave, 30, 31*f*
hypertrophic cardiomyopathy, 152, 164*f*
infective endocarditis, 136, 136*f*
pressure gradient estimation, 30–31
pulsed wave, 28–30, 29*f*–30*f*
Doppler tissue imaging, 32, 32*f*
Dorsal vulvar hooding, 982*f*
Dorsoventral bands, 936–937
Dorsoventral view, 14
Dostinex. *see* Cabergoline
Doubling time, 1269
Doxorubicin
cardiotoxicity induced by, 150, 170, 1283–1284
dosage of, 1327*b*
enterocolitis induced by, 1281
tissue necrosis caused by, 1282*f*
Doxycycline, 386*t*–388*t*, 515*t*–517*t*
acute bacterial upper respiratory infection treated with, 1444
bacterial infections treated with, 1437*t*–1438*t*
bartonellosis treated with, 1457–1458
canine chronic bronchitis treated with, 328
canine monocytotropic ehrlichiosis treated with, 1476
feline bronchitis treated with, 332–333
rickettsial polyarthritis treated with, 1200
Rocky Mountain spotted fever treated with, 1480
toxicity caused by, 1439*t*
Wolbachia pipientis treated with, 198
Dried solidified blood calculi, 722, 722*f*
Droncit. *see* Praziquantel
Drontal Plus. *see* Pyrantel/febantel/praziquantel
Drooling, 389–391, 390*b*
Drug toxicities, electrocardiographic changes associated with, 47–48, 49*b*
Drugs. *see also specific drug*
for cardiovascular disorders, 235*t*–239*t*
for chronic hepatitis, in dogs, 590–595
for electrolyte disorders, 934*t*
for endocrine disorders, 896*t*–897*t*
for hepatobiliary and pancreatic disorders, 643*t*–648*t*

Drugs *(Continued)*
for joint diseases, 1209*t*–1210*t*
for metabolic disorders, 934*t*
for neurologic disorders, 1185*t*–1186*t*
obesity and, 901
for reproductive disorders, 1034*t*–1036*t*
for respiratory disorders, 386*t*–388*t*
therapy, in pediatric dogs and cats, 1013
thrombocytopenia caused by, 1395
tremors induced by, 1183
for urinary tract disorders, 737*t*–739*t*
Ductal plate abnormalities, in cats, 574–575
Dulcolax. *see* Bisacodyl
Dwarfism, pituitary, 753–757
in cats, 786*f*
clinical features of, 754
clinical pathology of, 754
clinical signs of, 754, 754*b*, 755*f*
diagnosis of, 754–755, 756*f*, 756*b*
endocrine alopecia caused by, 748*t*
etiology of, 753–754
growth hormone therapy for, 755–757
lanugo retention associated with, 754
prognosis for, 757
signalment, 754
treatment of, 755–757
Dynamin-associated exercise-induced collapse (dEIC), 1106–1107, 1107*f*, 1183–1184
Dysautonomia, 456, 1172–1173
Dyskinesias, 1181, 1183
Dysphagia, 389–391
causes of, 390*b*
cricopharyngeal achalasia/dysfunction, 451–452
halitosis and, 389–391
masticatory muscle myositis, 451
neurogenic, 391
pharyngeal, 452
in pharyngeal diseases, 271–272
regurgitation and, 391–392
Dyspnea
in cats, 4, 4*f*
in dogs, 4, 4*f*
Dystocia, 969, 1034*t*–1036*t*
causes of, 969
cesarean section for, 972–974, 974*f*
definition of, 969
fetal anomalies as cause of, 969, 970*f*–971*f*
fetal factors associated with, 969
flowchart for, 970*f*
medical therapy for, 969–972
obstructive, 971*f*
Dysuria, 652–653, 653*b*

E

Ebstein anomaly, 112–113
Ecchymotic hemorrhages, 1242*f*
Echinococcus granulosa, 1533*t*–1535*t*, 1537
Echinococcus multilocularis, 1533*t*–1535*t*, 1537
Echinocytosis, 1345*t*
Echocardiography, 18
arterial thromboembolism
in cats, 225
in dogs, 231
atrial septal defect findings, 111
atrioventricular valve disease findings, 123–126, 124*f*
cardiac tamponade findings, 180*f*
cardiac tumors on, 187, 187*f*
in cats, 26*t*
constrictive pericardial disease findings, 185
contrast, 27, 28*f*
dilated cardiomyopathy findings, 144*f*, 170
in dogs, 26*t*
Doppler, 27–32
color flow mapping, 31–32, 31*f*–32*f*
continuous wave, 30, 31*f*
Echocardiography *(Continued)*
infective endocarditis, 136, 136*f*
pressure gradient estimation, 30–31
pulsed wave, 28–30, 29*f*–30*f*
tissue imaging, 32, 32*f*
heartworm disease findings
in cats, 206
in dogs, 197, 197*f*
hypertension findings, 213–214
hypertrophic cardiomyopathy findings
in cats, 160–162, 163*f*–164*f*
infective endocarditis, 136, 136*f*
mitral dysplasia findings, 112
mitral regurgitation findings, 125*f*–126*f*, 144*f*
M-mode, 22–27
atrial fibrillation on, 81*f*
dilated cardiomyopathy on, 144*f*
measurements on, 23–27
mitral valve motion, 26, 27*f*
normal values for, 23–27, 25*t*
patent ductus arteriosus findings, 103–104, 105*f*
pericardial effusion findings, 179–180, 179*f*
views on, 23, 24*f*
pericardiocentesis monitoring using, 183
principles of, 19–20
pulmonary hypertension findings, 192, 192*f*
with shunt reversal, 115–116
pulmonic stenosis findings, 108, 110*f*
restraints for, 19–20
subaortic stenosis, 106–107, 106*f*
tetralogy of Fallot findings, 114
three-dimensional, 33
transesophageal, 32–33, 33*f*
tricuspid dysplasia findings, 112–113, 113*f*
two-dimensional, 20–22
long-axis views, 21*f*, 23*f*
in parasternal position, 20*f*–23*f*
short-axis views, 20*f*, 22*f*
speckle tracking, 32
views on, 20–22
ventricular septal defect findings, 110–111, 110*f*
Echogenicity, 19
Eclampsia, 975–976
Ectopic rhythms
electrocardiography of, 38–42, 41*f*–42*f*
supraventricular premature complexes, 39
supraventricular tachycardias, 39
Ectopic ureters, 730–732, 731*f*, 1026
Edema
pregnancy, 967, 968*f*
pulmonary. *see* Pulmonary edema
scrotal, 1001*f*
Edrophonium chloride, 1170–1171
adverse effects of, 98
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
neurologic disorders treated with, 1185*t*–1186*t*
Effusion
abdominal, 519
feline infectious peritonitis, 1490, 1490*f*
pericardial. *see* Pericardial effusion
pleural. *see* Pleural effusion
Ehrlichia spp., 1533*t*–1535*t*
E. canis, 1241–1242, 1432–1433, 1440*t*, 1470*t*, 1473, 1475*f*, 1477
E. chaffeensis, 1470*t*, 1473, 1477
E. ewingii, 1440*t*, 1470*t*, 1478
Ehrlichiosis
canine granulocytotropic, 1478–1479
canine monocytotropic, 1473–1477
clinical features of, 1474, 1474*t*
diagnosis of, 1474–1476, 1475*f*, 1475*t*
epidemiology of, 1473–1474
etiology of, 1473–1474
Ehrlichiosis *(Continued)*
hypoalbuminemia and, 1475
prevention of, 1477
treatment of, 1476–1477
zoonotic aspects of, 1477
chronic, 1474–1475
description of, 1118*t*
feline monocytotropic, 1477–1478
Eicosapentaenoic acid, 72–73
Eisenmenger syndrome, 114
Ejaculation, obstructive disorders of, 1004–1005
Ejection murmurs, 9–10
Elbow, arthrocentesis method in, 1191*f*
Electrical alternans, 46, 181*f*
Electrocardiography, 34–51
accelerated idioventricular rhythm, 41
ambulatory, 49–51
Holter monitoring, 49–50
intermittent event recording, 50–51
artifacts, 48, 51*f*
atrial fibrillation, 40, 43*f*
atrial flutter, 39
bundle branch block patterns, 45–46
cardiac tumors on, 187
in cats, 38*t*
chamber enlargement, 45–46, 46*f*, 46*b*–47*b*
conduction disturbances, 42–45
dilated cardiomyopathy findings, 142–144
in dogs, 35*t*
drug toxicities, 47–48, 49*b*
ectopic rhythms, 38–42, 41*f*–42*f*
electrolyte imbalance, 47–48, 49*b*
escape complexes, 41–42
heart rate variability, 48
heart rhythm, 37
heartworm disease
in cats, 206–207
in dogs, 197
hyperkalemia, 690–691, 919–920, 920*b*
hypertrophic cardiomyopathy findings, 160–163, 162*f*
interpretation of, 35–37, 78*b*
lead systems, 35, 36*f*, 36*b*
mean electrical axis, 45
normal waveforms, 26*t*, 34–35, 35*f*
pericardial effusion findings, 181–183
pulmonary hypertension findings, 192
QRS abnormalities, 46
QT interval, 47
sick sinus syndrome, 86
sinus arrhythmia, 40*f*
sinus bradycardia, 40*f*
sinus rhythms, 37, 40*f*
ST-T abnormalities, 46–47, 48*b*
supraventricular premature complexes, 39
supraventricular tachycardias, 39
ventricular fibrillation, 41, 43*f*
ventricular premature complexes, 40
ventricular septal defect findings, 110
ventricular tachycardia, 41
Wolff-Parkinson-White preexcitation, 44–45
Electroencephalography, 1072
Electrolyte imbalances, 915–933
electrocardiographic changes associated with, 47–48, 49*b*
hypercalcemia, 48, 49*b*, 761*t*, 923–927, 1268, 1298
hyperkalemia, 47–48, 49*b*, 50*f*, 690–691, 919–921, 920*b*, 921*t*
hypermagnesemia, 933
hypernatremia, 915–917, 916*b*, 917*t*
hyperphosphatemia, 691, 929–930, 929*b*
hypocalcemia, 48, 49*b*, 765*t*, 927–929, 928*b*
hypokalemia, 47, 49*b*, 921–923, 922*b*, 923*t*
hypomagnesemia, 844, 931–933, 932*b*
hyponatremia, 74, 917–919, 918*b*
hypophosphatemia, 843–844, 930–931, 930*b*
Electrolytes
fractional clearance of, 664
in Greyhounds, 1362, 1362*t*
Electromyography, 1071–1072, 1174–1175
Electron microscopy, 415, 1433
Electrophoretograms, 1421, 1421*f*
Electroretinography, 1072
Elemental diets, 437
Elimination diets, 434
ELISA. *see* Enzyme-linked immunosorbent assay
Elliptocytosis, 1345*t*, 1386
Elokomin fluke fever, 480
Emesis, 1100*b*
Emphysema, 330*b*
Enalapril, 64*t*, 68, 217*t*, 1255*t*–1256*t*
Enalaprilat, 217*t*
Encephalitis, 1080, 1117, 1129
Encephalomyelitis, 1122–1123, 1520
Endocardial fibroelastosis, 100, 117
Endocarditis
bacterial, 1440–1442
infective
antibiotics for, 136–137
antimicrobial prophylaxis for, 138
bacteremia, 132
blood culture testing for, 133–134
in cats, 132
cephalosporins for, 136–137
clinical features of, 133
congestive heart failure secondary to, 132
diagnosis of, 133–136, 135*b*
in dogs, 132
Doppler imaging of, 136, 136*f*
echocardiography of, 133–134, 136*f*
etiology of, 132–133
immune-mediated disease *versus*, 133
laboratory tests for, 134
microorganisms associated with, 132
neutrophilia associated with, 134
nonregenerative anemia associated with, 134
pathophysiology of, 132–133
prognosis for, 136–138
prophylactic antibiotics for, 138
sequelae of, 134*b*
signs of, 133
systemic effects of, 134*b*
thromboemboli caused by, 133
treatment of, 136–138
valves commonly affected by, 132
vegetations associated with, 132
Endocrine alopecia, 747–749, 747*f*, 748*t*–749*t*, 750*f*
Endocrine replacement therapy, chronic kidney disease, 701–702
Endometrial hyperplasia, 956*f*
Endometritis, postpartum, 977–978, 977*f*
Endomyocardial biopsy, 52
Endoscopy, 436
alimentary tract disease evaluations, 424–429, 425*f*
biopsy use of, 426
capsule, 429
flexible, 424
hematemesis evaluation, 399–401
removal of foreign objects, 467
rigid, 424, 426
Endothelin, physiologic effects of, 58
Endotracheal technique, for tracheal wash, 300–303
Endotracheal tubes, 384
End-systolic volume index (ESVI), 26, 120
Enema, 443–446
barium contrast, 423
cleansing, 445
hypertonic, 445
retention, 445
Enilconazole, 261

Enoxaparin
  arterial thromboembolism in cats treated with, 227*b*
  dosage of, 229
Enrofloxacin, 386*t*–388*t*, 515*t*–517*t*
  bacterial infections treated with, 1437*t*–1438*t*
  brucellosis treated with, 965
  joint disease treated with, 1209*t*–1210*t*
  neurologic disorders treated with, 1185*t*–1186*t*
Entamoeba histolytica, 1533*t*–1535*t*
Enteral diet, 436*t*
Enteric duplication, 1014
Enteric zoonoses, 1532–1539, 1533*t*–1535*t*
Enteritis
  canine coronaviral, 479
  canine parvoviral, 476–478, 477*b*
  feline coronaviral, 479
  feline parvoviral, 478–479
Enterococcus, 443
Enterocolitis, 1281
Enteropathy
  in Chinese Shar-Peis, 497
  immunoproliferative, of Basenjis, 497
  intestinal lymphangiectasia, 495–497, 496*f*
  protein-losing, 495–498
  in Shiba dogs, 497–498
Enterostomy tubes, 437
Enterotoxemia, 475
Entocort. *see* Budesonide
Environment
  feline bronchitis caused by, 337
  feline idiopathic cystitis, modifications for, 727–728, 728*b*
Enzyme-linked immunosorbent assay
  alimentary tract disease evaluations, 414
  cryptosporidial antigens, 414
  feline leukemia virus detection, 1497
Eosinopenia, 1376
Eosinophilia, 1377, 1377*b*, 1426*t*
Eosinophilic gastritis, 463
Eosinophilic granulomas, 201
Eosinophilic inflammation, 305
Eosinophilic lung disease, 348–349
Eosinophilic pneumonitis, 201
Eosinophilic pulmonary granulomatosis, 348
Eosinophilic splenitis, 1412*t*
Ephedrine, 1034*t*–1036*t*
Epididymal abscess, 1001*f*
Epididymis, 1000–1001, 1000*f*–1001*f*
Epigastric pain, 635
Epilepsy
  definition of, 1093
  idiopathic, 1094, 1105
  scar tissue-related acquired, 1096–1097
Epimastigotes, 1526
Epistaxis, 240, 241*b*
Epithelial cells, 666–667, 667*f*
Epithelial tissue, 1258–1259
Epitheliotropic intestinal lymphoma, 1296*f*, 1309
Epsilon-aminocaproic acid, 1394
Epsiprantel, 444*t*, 515*t*–517*t*
Epulides, 447
Epulis, 448*t*
Equine chorionic gonadotropin, 959
Erection, canine, 995, 995*f*
Erosive immune mediated polyarthritis, 1208
Erosive polyarthritis, 1189, 1208, 1245*t*
Erythrocytes, in Greyhounds, 1360–1361
Erythrocytosis, 1368–1370
  classification of, 1368–1370, 1369*b*
  clinicopathologic findings, 1368–1369
  definition of, 1368–1370
  diagnosis of, 1369–1370, 1370*f*
  hydroxyurea for, 116
  phlebotomy for, 116, 1369
  primary, 1368, 1369*b*
Erythrocytosis *(Continued)*
  in pulmonary hypertension, 116
  relative, 1368, 1369*b*
  secondary, 1368, 1369*b*
  in tetralogy of Fallot, 114
  treatment of, 1369–1370
  tumor-associated, 1368
Erythromycin, 515*t*–517*t*, 1437*t*–1438*t*
Erythropoietin, 1353
  chronic kidney disease, 701–702
Escape complexes, 41–42
Escherichia coli, 1533*t*–1535*t*
Esmolol
  in cats, 90*t*–91*t*
  characteristics of, 94, 94*t*
  in dogs, 90*t*–91*t*
  dosage of, 90*t*–91*t*
  hypertension treated with, 217*t*
Esomeprazole, 439*t*, 515*t*–517*t*
Esophageal regurgitation, 392
Esophageal sphincter
  endoscopy of, 426*f*
  lower, 426*f*
Esophageal weakness, 418*f*
  acquired, 454
  congenital, 452–454, 453*f*
  description of, 393, 393*b*
Esophagitis, 455–456
  clinical features of, 455
  diagnosis of, 455
  endoscopy of, 425*f*
  etiology of, 455
  prognosis for, 456
  treatment of, 455–456
Esophagoscopy, 393, 424–425, 424*f*
Esophagostomy tubes, 436
Esophagrams, 416, 417*f*, 459*f*
Esophagus
  cicatrix of, 459–460
  dysmotility, regurgitation caused by, 346
  foreign objects in, 416–417, 418*f*, 458–459, 458*f*
  imaging of, 416–419
    indications for, 416–419
  neoplasms of, 460, 460*f*
  obstruction of
    description of, 392–393, 393*b*
    foreign objects as cause of, 458–459, 458*f*
    vascular ring anomalies as cause of, 456, 457*f*
  perforation of, 416–417
  sarcomas of, 460
Estriol, 733*t*–734*t*
Estrogen
  ovulation and, 940–942
  pregnancy termination using, 959
Estrous cycle
  in bitch
    abnormalities of, 954–958
    description of, 937–940, 938*t*
    variations of, 953–954
  feline, 948–949
  identification of, 940–945
  manipulation of, 958–960
  prevention of, 958
  in queen, 948–949
Estrumate. *see* Cloprostenol
Estrus
  canine
    description of, 937–939, 938*t*, 939*f*–940*f*
    induction of, 958–959
    prolonged, 954–955, 954*f*
  dopamine agonists for inducement of, 958–959
  feline
    description of, 944, 945*f*
    induction of, 959
  suppression, 1034*t*–1036*t*
Ethyl alcohol, myocardial depression caused by, 150–151
Ethylene glycol intoxication/poisoning, 671, 690, 1099*b*
Etodolac (Etogesic), 1197*t*, 1209*t*–1210*t*
Eucoleus aerophila. *see Capillaria* spp., *C. aerophila*
Euthyroid sick syndrome, 779–780, 780*f*
Eutocia, 968–969
Evans syndrome, 1243–1244
Event recording, intermittent, 50–51
Exacerbating event, in laryngeal diseases, 271
Exaggerated pseudocyesis, 957
Excretory urography, 671
Exercise
  diabetes mellitus in dogs managed with, 816–817
  heart failure effects on, 58
Exercise intolerance
  causes of, 1183–1184, 1184*b*
  heart failure and, 1
  lower respiratory tract disorders as cause of, 283–284
Exercise-induced collapse, 1183–1184
  disorders, 1106–1107
Exocrine pancreas, 620–643
Exocrine pancreatic insufficiency, 491, 636–641
  in cats, 638
  clinical features of, 638
  description of, 399, 413, 620, 622*t*, 636–641
  diet for, 640–641
  drugs for, 640
  folate concentration in, 640
  pancreatic enzymes and, 639
  pathogenesis of, 636–638, 637*f*–638*f*
  prognosis of, 641
  treatment of, 640–641
Exocrine pancreatic neoplasia, 641
Exophthalmos, 1175–1176
Expectorants, 343
Expectoration, regurgitation *versus*, 391–392
Exploratory thoracotomy, 373–374
Extracellular fluid, 844*f*, 915–916
Extrahepatic bile duct obstruction, 526, 573–574, 573*b*, 601–603, 601*f*
  in cats, 573–574, 573*b*
  clinical features of, 574, 601–602
  diagnosis of, 574, 574*f*, 602
  etiology of, 573, 573*b*
  pathogenesis of, 573
  prognosis of, 602–603
  treatment of, 574, 602–603
  ultrasonography of, 574*f*
Extramedullary hematopoiesis, 1413
Extranodal lymphoma, 1294, 1296*t*, 1307
Extraocular muscles, 1058*f*, 1086
Extraocular myositis, 1175–1176, 1175*f*
Extrathoracic airway obstruction, 271, 272*f*, 380–381, 381*f*
Extravascular hemolysis, 1231, 1346–1348
Extrinsic pathway, of coagulation cascade, 221–222, 1387
Exudate, pathogenesis of, 522
Exudative pericardial effusion, 177
Eye(s)
  blastomycosis and, 1502
  hypertension effects on, 212, 213*b*
  lymphoma of, 1296, 1309

F

Facial deformity, 245–246, 245*f*
Facial nerves
  description of, 1056*t*, 1060*f*
  evaluation of, 1059, 1060*f*
  paralysis of, 1160, 1160*f*–1161*f*
Factor Xa inhibitors, 229
Factor XII, 1387
Fading neonates, 1021–1022, 1021*f*–1022*f*
Fading puppy syndrome, 1399
False pregnancy, 1034*t*–1036*t*
Familial Chinese Shar-Pei fever, 1205, 1245*t*
Familial Mediterranean fever (FMF), 683–684
Familial polyarthritis, 1205
Familial reflex myoclonus, 1182
Famotidine, 439, 439*t*, 515*t*–517*t*, 1255*t*–1256*t*
Fasciohumoral muscular dystrophy, 151
Fat, in veterinary therapeutic diets, 904*t*–906*t*
Fear-induced aggression, 975
Febantel/praziquantel/pyrantel, 1538–1539
Febrile neutropenia, 1279–1280
Fecal culture, bacterial, 414
Fecal digestion tests, 413–414
Fecal examination
  Baermann technique, 1428
  direct smear, 1427
  stained smear, 1427–1428, 1428*f*
Fecal fat analysis, 413
Fecal flotation, 413, 1428
Fecal incontinence, 405
Fecal sedimentation, 413
Fecal transplantation, 443
Feces
  cytologic evaluation of, 415
  leukocytes in, 415
  preservation of, 1429
Feeding tubes
  enterostomy, 437
  gastrostomy, 436
  jejunostomy, 437
  nasoesophageal, 435
    feeding uses of, 437
    placement of, 567*f*, 567*b*
  orogastric, 435
  pharyngostomy, 436
Felbamate (Felbatol), 1104, 1185*t*–1186*t*
Feldene. *see* Piroxicam
Felimazole. *see* Methimazole
Feline acromegaly, 749–753
  clinical features of, 750–751, 751*f*
  clinical pathology of, 751–752
  clinical signs of, 750*b*
  diagnosis of, 752, 752*f*
  etiology of, 749–750
  hyperadrenocorticism *versus*, 752
  insulin-resistant diabetes mellitus management in, 753
  magnetic resonance imaging of, 750*f*
  prognosis for, 753
  radiation therapy for, 753
  treatment of, 753
Feline bartonellosis, 1458–1460, 1458*f*, 1540–1541
Feline biliary tract disease, 567–573
  biliary cysts, 575
  cholangitis, 567–573
    neutrophilic, 568*t*, 569*f*
    sclerosing, 572
  cholecystitis, 573
Feline bronchitis, 328–333
  bronchodilators for, 332
  classification of, 330*b*
  clinical features of, 330
  diagnosis of, 330–331
  differential diagnosis of, 329*t*
  doxycycline for, 332–333
  emergency stabilization of, 331
  environmental considerations, 331
  etiology of, 328–330
  failure to respond to therapy, 333, 333*b*
  glucocorticoids for, 331–332
  metered-dose inhaler for drug administration in, 327–328, 332*f*
  physical examination of, 330
  prognosis of, 333
  small airway obstruction in, 328–330, 329*b*
  thoracic radiographs in, 330
Feline calicivirus (FCV), 1453
  description of, 257
  vaccines for, 258–259
Feline chronic progressive polyarthritis, 1245*t*
Feline chronic rhinosinusitis, 266–268
  antibiotics for, 267–268
  clinical features of, 267

Feline chronic rhinosinusitis *(Continued)*
diagnosis of, 267
etiology of, 266–267
radiographic signs of, 249*b*
treatment of, 267–268, 267*b*
Feline coronaviral enteritis, 479
Feline coronavirus, 1488–1491
clinical features of, 1488–1489
diagnosis of, 1489–1490
enteric, 1488
epidemiology of, 1488
etiology of, 1488
prevention of, 1491
treatment of, 1490–1491
zoonotic aspects of, 1491
Feline eosinophilic granuloma, 449–450
Feline fragile skin syndrome, 752, 894*f*
Feline granulocytotropic anaplasmosis, 1471–1472, 1472*f*
Feline hepatic lipidosis, 561–567
Feline hepatocytes, 564*f*
Feline herpesvirus
clinical features of, 257
corneal ulcers caused by, 258
description of, 257
treatment of, 258
vaccines for, 258–259, 1453
Feline hippocampal necrosis, 1077–1078
Feline hypertriglyceridemia, 912*t*
Feline hypokalemic polymyopathy, 1178–1179, 1178*f*
Feline idiopathic cystitis (FIC), 724–729
bladder abnormalities associated with, 724
chronic management of, 727–729
drug therapy for, 728–729, 728*b*
environmental alterations for, 727–728
histopathology of, 724
infectious agents that cause, 724–725
multimodal environmental modifications for, 727–728, 728*b*
nonobstructive, 727
nonulcerative, 724
obstructive, 726–727, 726*f*–727*f*
pathophysiology of, 724–725
pheromones for, 728
systemic abnormalities associated with, 725
treatment of, 726–729
ulcerative, 724
Feline idiopathic polymyositis, 1176–1177
Feline idiopathic vestibular syndrome, 1114
Feline immune-mediated thrombocytopenia, 1244
Feline immunodeficiency virus, 1491–1494
clinical features of, 1492
diagnosis of, 1492–1493
diarrhea associated with, 480
encephalopathy, 1123
epidemiology of, 1491–1492
etiology of, 1491–1492
lymphoma risks, 1294
pregnancy loss and, 966
prevention of, 1494
primary, 1492
syndromes associated with, 1492, 1493*t*
tests for, 243
transmission of, 1491–1492
treatment of, 1493–1494
vaccine for, 1454
zoonotic aspects of, 1494
Feline infectious peritonitis, 514
ancillary tests for, 1118*t*
clinical findings of, 1489*b*
description of, 1488
effusive, 1488, 1490*f*
nonseptic exudate and, 363
pregnancy loss and, 966
signs of, 1126
vaccine for, 1454
Feline ischemic encephalopathy, 1077
Feline leukemia virus, 1494–1498. *see also* Leukemias
clinical features of, 1495–1496
diagnosis of, 1496–1497
enzyme-linked immunosorbent assay detection of, 1497
epidemiology of, 1494–1495
erythropoiesis and, 1353
etiology of, 1494–1495
leukemia caused by, 1319
lymphoma secondary to, 1294, 1295*t*
neoplasia caused by, 1495–1496
outcomes of, 1495*t*
panleukopenia and, 479–480
pregnancy loss and, 966
prevention of, 1497–1498
replication of, 1495
screening for, 1497
tests for, 243
transmission of, 1494–1495
treatment of, 1497
vaccine for, 1453–1454
zoonotic aspects of, 1497–1498
Feline leukemia virus-panleukopenia-like syndrome, 479–480
Feline lower urinary tract disease (FLUTD), 724
Feline lymphocytic-plasmacytic gingivitis, 450–451
Feline mammary fibroadenomatous hyperplasia, 979, 979*f*
Feline monocytotropic ehrlichiosis, 1477–1478
Feline nasopharyngeal polyps, 264, 264*f*
Feline panleukopenia virus, 1453
pregnancy loss and, 966
Feline parvoviral enteritis, 478–479
Feline periosteal proliferative polyarthritis, 1208, 1208*t*
Feline plague, 1460–1462, 1461*f*, 1461*b*, 1541
Feline polioencephalitis, 1122–1123
Feline rheumatoid-like arthritis, 1208–1209
Feline syncytium-forming virus, 1208
Feline toxoplasmosis, 1521–1525
Feline viral-associated pregnancy loss, 966
Feminization, 997
Femoral nerve, 1158*t*
Femoral pulses, 5
Fenbendazole, 386*t*–388*t*, 515*t*–517*t*
Aelurostrongylus abstrusus treated with, 345
Capillaria aerophila treated with, 344
dosage of, 444*t*
nasal capillariasis treated with, 263–264
Paragonimus kellicotti treated with, 345
Fenoldopam, 691–692
Fentanyl citrate, analgesic uses of, 227*b*
Fentanyl patch, 629*t*–630*t*
Fetal heart rate monitoring, 973*f*
Fetus
age determination of, 950–951, 951*f*, 951*b*
dystocia caused by anomalies of, 969, 970*f*–971*f*
Fever
description of, 1423
familial Chinese Shar-Pei, 1205, 1245*t*
of undetermined origin, 1423
causes of, 1424*t*
clinicopathologic evaluation of, 1425–1426
diagnostic approach to, 1424–1426, 1425*b*
disorders associated with, 1423–1424
history and physical examination of, 1425
treatment of, 1426, 1426*t*
Fiber
description of, 445
diabetes mellitus in dogs managed with, 816
Fiber-responsive large bowel diarrhea, 494
Fiber-supplemented diets, 435
Fibric acid derivatives, 913
Fibrin, 1388
Fibrin degradation products, 222, 231, 1388
Fibrinogen, 221–222
Fibrinolysis
activation of, 1388
defective, 223
Fibrinolytic agents, 356
Fibroblast growth factor receptor, 1273
Fibroblast growth factor-23 (FGF-23), 659–660, 695–696
Fibrocartilaginous embolism, 1141–1142
Fibromatous epulis, 448*t*
Fibrosarcoma, 448*t*, 1334
Fibrosing pleuritis, 374
Film digestion tests, 399
Finasteride, 1001–1002, 1034*t*–1036*t*
Fine-needle aspiration
anterior mediastinal masses, 1291
description of, 429, 1257–1258
feline hepatic lipidosis, 562–564
hemangiosarcoma, 1323
lymphoma, 1299
Firocoxib, 1197*t*, 1209*t*–1210*t*, 1268*t*
First heart sound, 5
First-degree atrioventricular block, 43–44, 44*f*, 88
First-order neurons, 1089–1090
Flaccid paralysis, 1438–1439
Flagellates, 1538–1539
Flagyl. *see* Metronidazole
Flecainide
description of, 93
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Flexible endoscopy, 424
Flomax. *see* Tamsulosin
Florfenicol, 1437*t*–1438*t*
Florinef. *see* Fludrocortisone acetate
Fluconazole, 1128, 1504*t*, 1509
Flucytosine, 1504*t*, 1509
Fludrocortisone acetate, 888, 896*t*–897*t*
Fluid
extracellular, 844*f*
intracellular, 844*f*
Fluid accumulation, 6
Fluid therapy, 432–434
colloids, 433
diabetic ketoacidosis treated with, 842–845, 842*b*
fluid calculations, 434
hyperkalemia treated with, 921
hypertonic saline solution, 432–433
in hypoproteinemic animals, 434
leptospirosis treated with, 1464
overhydration, 433
in protein-losing enteropathy, 434
Flumethasone, 1222*t*
Fluorescence in situ hybridization, 1431
Fluoroscopy
idiopathic gastric hypomotility, 469
larynx and pharynx, 273
pharyngeal dysphagia evaluations, 452
tracheal collapse evaluations, 335
Fluoxetine, 728*b*
Flush, nasal, 254
Fluticasone propionate, 331
Focal gastritis, 427*f*
Focal hepatic lesions, 612–615
abscesses, 612–613, 612*f*
neoplasia, 613–615, 613*f*, 614*t*
nodular hyperplasia, 613
Focal neuropathies, 1157–1163
facial nerve paralysis, 1160, 1160*f*–1161*f*
hyperchylomicronemia, 1162
ischemic neuromyopathy, 1162–1163, 1163*f*
traumatic neuropathies, 1157, 1158*t*, 1159*f*
trigeminal nerve paralysis, 1161–1162, 1162*f*
Folate, 423–424, 1364
Follicular cysts, 954, 954*f*
Follicular ovarian cysts, 1034*t*–1036*t*
Forebrain
anatomy of, 1037
lesions of, 1038*b*
Foreign objects
esophageal, 417, 418*f*, 428*f*, 458–459, 458*f*
gastric, 466–467
nasal, 240, 249*b*
Forelimb hopping, 1048*f*
Formalin-ether sedimentation technique, 573*b*
Fort dodge. *see* Deslorelin
Fossa ovalis, 111
Fourth heart sound, 9
"Foxtail" grass, 241*f*
Fractional clearance of electrolytes, 664
Fractional shortening, 25
Fragile skin syndrome, 752, 894*f*
Francisella tularensis, 1533*t*–1535*t*, 1541
Frank-Starling mechanism, 55
Free fatty acids, 840
Free radicals, 151
Frequency-domain analysis, 48
Frontal sinus
exploration of, 252
radiographic imaging of, 247, 248*f*
Fructosamines, 818–819, 819*t*, 822, 837
Full-thickness biopsy, 430
Fulminant congestive heart failure, 61
Fundic examination, 242
Fungal arthritis, 1201
Fungal diseases. *see* Mycotic infections
Fungal pneumonia, 344
Fungi, 1541
Fungizone. *see* Amphotericin B
Furosemide, 386*t*–388*t*, 691, 934*t*
adverse effects of, 146–147
chronic heart failure treated with, 64*t*, 66, 73
congestive heart failure treated with, 164
dilated cardiomyopathy treated with, 145
heart failure treated with, 61, 128
neurologic disorders treated with, 1185*t*–1186*t*
pulmonary edema and, 358, 382
respiratory distress treated with, 166

G

Gabapentin, 1034*t*–1036*t*, 1103–1104, 1185*t*–1186*t*, 1197*t*, 1209*t*–1210*t*
Gag reflex, 1056*t*
Gagging, in laryngeal diseases, 271
Gait
evaluation of, 1045–1046
hypermetric, 1038–1039, 1074–1075
Galactostasis, 978, 978*f*
Galastop. *see* Cabergoline
Gallbladder mucocele, 600–601, 600*f*
Gallop rhythm, 9
Gallop sounds, 9
Gastric acid secretion inhibitors, 439*t*
Gastric antral mucosal hypertrophy, 465, 466*f*
Gastric dilation/volvulus, 419, 467–468
clinical features of, 467
diagnosis of, 467, 468*f*
etiology of, 467
prognosis of, 468
treatment of, 407–408, 467–468
Gastric emptying, 422
Gastric foreign objects, 466–467
Gastric lavage, 1100*b*
Gastric lymphoma, 463, 471
Gastric neoplasms, gastrointestinal ulceration/erosion from, 470
Gastric outflow obstruction/gastric stasis, 419*f*, 465–470
benign muscular pyloric hypertrophy and, 465
bilious vomiting syndrome in, 470
diagnosis of, 465

Gastric outflow obstruction/gastric stasis *(Continued)*
gastric antral mucosal hypertrophy and, 465, 466*f*
gastric dilation/volvulus, 467–468, 468*f*
gastric foreign objects in, 466–467
iatrogenic, 467
idiopathic gastric hypomotility in, 469–470
partial or intermittent chronic gastric volvulus, 469, 469*f*
Gastric ulcer, 426*f*
Gastrin, 424
Gastrinomas, 853, 853*b*
gastrointestinal ulceration/erosion from, 470
Gastrin-secreting neoplasia, 853–854, 853*b*
Gastritis, 462–465
acute, 462
atrophic, 463
canine eosinophilic, 463
chronic, 463–464
Helicobacter-associated disease, 464, 464*f*
hemorrhagic gastroenteritis and, 462–463
lymphocytic-plasmacytic, 463
Gastroduodenal ulceration and erosion, 397–398
Gastroduodenoscopy
gastrin-secreting neoplasia evaluations, 853
indications for, 426, 426*f*
technique for, 426
Gastroduodenostomy, 472
Gastroenteritis
causes of, 1539
hemorrhagic, 462–463, 1368
Gastroenterocolitis, 1281
Gastroesophageal reflux, 455
Gastrograms, contrast-enhanced, 422
Gastrointestinal abnormalities, 1013–1014
Gastrointestinal disorders, 1027–1029, 1029*f*–1030*f*
abdominal distention, 408–411, 410*b*
abdominal effusion, 407
abdominal enlargement, 408–411, 410*b*
abdominal pain, 408, 410*b*
acute abdomen, 407–408, 408*b*, 409*f*
anorexia, 407, 407*b*
clinical manifestations of, 389–411
constipation, 404–405, 404*b*
diarrhea. *see* Diarrhea
drooling associated with, 389–391
drugs used in, 515*t*–517*t*
dysphagia associated with, 389–391
fecal incontinence, 405
halitosis associated with, 389–391
hematemesis. *see* Hematemesis
hematochezia, 402, 402*b*
hyporexia, 407, 407*b*
melena, 402–403, 403*b*
tenesmus, 403–404, 403*b*
vomiting. *see* Vomiting
weight loss, 405–407, 405*b*, 406*f*
Gastrointestinal ulceration/erosion (GUE), 470–471
clinical features of, 470
diagnosis of, 470–471, 471*f*
etiology of, 470
nonsteroidal anti-inflammatory drugs and, 470–471
prognosis of, 471
treatment of, 471
Gastropexy, 468
Gastrostomy tubes
enteral feedings using, 436
esophageal bypass using, 454
Geigy. *see* Terbutaline
General proprioceptive sensory tracts, 1045
Generalized lymphadenopathy, 1314*f*, 1417
Genetic variability screening, 936*b*
Genital tract zoonoses, 1542–1543
Gentamicin, 1437*t*–1438*t*
Geriatric canine vestibular disease, 1113–1114, 1113*f*
Gestation, 949. *see also* Pregnancy
Gestational age, 950–951, 951*f*, 951*b*
Gestational diabetes, 967, 967*f*
Giardia spp., 1533*t*–1535*t*, 1538
antigen tests for, 1432
enzyme-linked immunosorbent assays for detecting, 414
fecal flotation for, 1428, 1429*f*
treatment of, 1443
Giardiasis, 489–490, 489*f*
Giemsa stain, 1258
Gingiva, 448*t*
Gingivitis
description of, 450
feline lymphocytic-plasmacytic, 450–451
Glipizide, 835
Glomerular disease, 675–685
clinical findings of, 680–681
complications of, 684–685
history-taking, 680
hyperlipidemia in, 685
hypertension in, 685
hypoalbuminemia in, 684
immune injury mechanisms, 677, 678*b*
laboratory findings of, 680–681, 681*b*
management of, 681–684, 682*b*–683*b*
pathogenesis of, 676–677, 676*f*–677*f*
physical examination of, 680
prognosis of, 685
progression of, 677–678
sodium retention in, 684
thromboembolism in, 684–685
Glomerular filtration rate, 658, 661, 688*f*, 772
Glomerular function, diagnostic tests for, 658–662
bladder tumor antigen test, 662
blood urea nitrogen, 658, 659*f*
creatinine clearance, 660–661, 661*t*
cystatin C, 659
fibroblast growth factor-23 (FGF-23), 659–660
γ-Glutamyl transferase (GGT), 660
iohexol clearance, 661
kidney injury molecule-1 (KIM-1), 660
microalbuminuria, 662
N-acetyl-β-D-glucosaminidase (NAG), 660
neutrophil gelatinase-associated lipocalin (NGAL), 660
radioisotopes, 661
serum creatinine, 658–659
symmetric dimethylarginine, 659
urine protein-to-creatinine ratio, 661–662
Glomerulonephritis
clinical features of, 1249
diagnosis of, 1248*t*, 1249–1250
etiology of, 1249
histopathologic lesions of, 678–679
immune-complex, 676–677, 676*f*
immune-mediated, 676, 678*b*, 1249–1250
membranoproliferative, 678, 693*b*
membranous, 678
pathogenesis of, 1249*b*
proliferative, 678
treatment of, 1249–1250
Glomerulotubular balance, 694–695, 695*f*
Glomerulus
filtration barrier of, 675
mesangial cells, 675, 676*f*
structure of, 675, 676*f*
Glossopharyngeal nerve, 1056*t*, 1059–1060
Glucagon, 896*t*–897*t*
Glucocorticoid(s), 441. *see also* Corticosteroid(s); *specific drug*
acute addisonian crisis treated with, 886–887, 887*b*
adverse effects of, 1223, 1223*f*
aspiration pneumonia treated with, 348
canine chronic bronchitis treated with, 331–332
chronic hepatitis treated with, 592, 592*f*
endogenous
deficiency of, 883
excess of, 1178
eosinophilic lung disease treated with, 349
feline bronchitis treated with, 331
gastrointestinal ulceration/erosion from, 470
granulomatous meningoencephalitis treated with, 1121, 1121*b*
hemolysis treated with, 1235–1236
immune-mediated disorders treated with, 1221–1223, 1222*t*
immune-mediated hemolytic anemia treated with, 1235–1236
immune-mediated polyarthritis treated with, 1203–1204, 1204*t*, 1204*b*
insulin-secreting β-cell neoplasia treated with, 852
laryngeal paralysis treated with, 278
lymphocytic-plasmacytic gastritis treated with, 463
masticatory muscle myositis treated with, 1175
optic neuritis treated with, 1088
pulmonary edema caused by, 382
steroid-responsive meningitis-arteritis treated with, 1119
thyroid gland function tests affected by, 781
Glucocorticoid resistance, 1222
Glucosamine, 1197*t*, 1209*t*–1210*t*
Glucose
blood
continuous monitoring systems for, 821, 822*f*
for diabetes mellitus monitoring
in cats, 835–836, 836–837, 836*f*
in dogs, 818
measurement of
in cats, 838*f*
methods for, 821
serial curves of, 819–822, 820*f*–821*f*, 823*f*–824*f*, 837
stress hyperglycemia effects on, 837–839
toxicity, 831–832
urine, 665
diabetes mellitus monitoring in dogs using, 819
α-Glucosidase inhibitors, 835
Glucotrol. *see* Glipizide
γ-Glutamyl transferase (GGT), 660
Glutaraldehyde-containing fixatives, 1433
Glycolysis, 806–807
Glycophorins, 1231
Glycopyrrolate, 97, 386*t*–388*t*
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Glycosuria, 811
Golden Retriever muscular dystrophy, 1179
Gonadotropin-releasing hormone, 954–955, 1034*t*–1036*t*
Gonadotropin-releasing hormone agonists, 958
Gradual water deprivation, 664
Granular casts, 667–668, 667*f*
Granulocyte colony-stimulating factor, 1280, 1375
Granulocyte-macrophage colony-stimulating factor, 1280
Granulocytotropic anaplasmosis
canine, 1469–1471
feline, 1471–1472, 1472*f*
Granulomatous meningoencephalomyelitis, 1064, 1087–1088, 1120–1121
Granulomatous splenitis, 1412*t*
Granulomatous ulcerative colitis, 495
Granulosa-theca cell tumors, 954
Great vessels, 16–17
Greyhounds, 1360–1367
acid-base balance in, 1362, 1362*t*
cardiac troponins in, 1363–1364
clinical chemistry parameters in, 1361–1364
clinical pathology in, 1364–1365
creatinine levels in, 1362
dog erythrocyte antigen in, 1360–1361
electrolytes in, 1362, 1362*t*
erosive polyarthritis in, 1208, 1245*t*
erythrocytes in, 1360–1361
hematology in, 1360–1361, 1365*t*
hemostasis in, 1361, 1366*t*
hypoglobulinemia in, 1362–1363
leukocytes in, 1361
liver enzymes in, 1362
platelets in, 1361, 1395
protein levels in, 1362–1363
serum chemistry reference intervals in, 1365, 1366*t*
thyroid hormones in, 1363
Growth fraction, 1269
Growth hormone
anabolic effects of, 749–750
catabolic effects of, 749–750
congenital deficiency of. *see* Pituitary dwarfism
endocrine disorders treated with, 896*t*–897*t*
excessive secretion of. *see* Acromegaly
pituitary dwarfism treated with, 755–757

H

Haemobartonella canis, 1429–1430
Haemobartonella felis, 1429–1430
Halitosis, 389–391
causes of, 390*b*
dysphagia and, 389–391
Halothane, 49*b*
Haw syndrome, 1091
Head bobbing, 1106
Head tilt, 1109–1116
central vestibular disease as cause of, 1111*f*, 1112*b*. *see also* Central vestibular disease
description of, 1043–1044, 1055–1057
general considerations in, 1109
illustration of, 1044*f*, 1056*f*–1058*f*
lesion localization, 1109–1111, 1110*b*
nystagmus, 1109
peripheral vestibular disease as cause of, 1111*f*. *see also* Peripheral vestibular disease
Head trauma, 1075–1076
Heart
conduction system, 34*f*
infective endocarditis effects on, 134*b*
Heart base tumors, 182, 185
Heart block
atrioventricular, 87–88
first-degree, 43–44, 44*f*
second-degree, 43–44, 44*f*
third-degree, 43–44, 44*f*
idiopathic, 87–88
Heart disease, signs of, 1
Heart failure, 1. *see also* Congestive heart failure
acute therapy for, 65
atrioventricular valve disease as cause of, 119
β-blockers in, 73
biventricular, 1
cardiac responses to, 55–56
causes of, 58–59, 59*t*
characteristics of, 58–59

Heart failure *(Continued)*
chronic
amlodipine for, 71
angiotensin-converting enzyme inhibitors for, 67–68
benazepril for, 68
captopril for, 64*t*, 68
client education about, 73–74
dietary considerations for, 72–73
digoxin for, 69–70
drug therapy for, 64*t*
enalapril for, 68
furosemide for, 64*t*, 66
general considerations for, 66
hydralazine for, 71
hyponatremia in, 74
loop diuretics for, 66–67
monitoring of, 73–74, 74*b*
nitrates for, 71–72
pimobendan for, 69
prazosin for, 71
reevaluations, 73–74
refractory, 74–75
salt restriction for, 72
spironolactone for, 67
thiazide diuretics for, 67
cough and, 3, 282
definition of, 55
diastolic dysfunction as cause of, 65
diuresis for, 61
diuretics for, 66–67
drug therapy, 61–65
exercise capacity reductions secondary to, 58
exercise intolerance and, 1
follow-up for, 65–66
inotropic support for, 63–65
management of, 55–76
monitoring of, 65–66
neurohormonal responses to, 56–58, 57*f*
New York Heart Association classification scheme for, 59–60
other respiratory signs of, 3
pressure overload associated with, 59*t*
renal effects of, 58
severity of, 59–60, 60*t*
signs of, 1–3, 2*b*
supplemental oxygen for, 61
syncope and, 1–3
systemic responses to, 56–58
treatment of, 61–66, 129
vasodilation for, 61–63, 64*t*
volume-flow overload associated with, 59*t*
weakness and, 1
Heart rate variability, 48
Heart rhythm, 37
Heart sounds
auscultation of, 7–8
in cardiac tamponade, 177–178
classification of, 7
first, 5, 8
fourth, 9
gallop sounds as, 9
in heartworm disease in dogs, 196
second, 8
third, 9
transient, 7–9
Heartguard. *see* Ivermectin
Heartworm disease, 190–210
in cats
adulticide therapy for, 206
antibody tests for, 206
antigen tests for, 205–206
clinical features of, 204–206
description of, 203
diagnosis of, 204–206
echocardiographic findings, 206
electrocardiographic findings, 206–207
pathophysiology of, 204–206
radiographic findings, 205*f*, 206
serologic tests for, 205
surgical treatment of, 207
treatment of, 207
Heartworm disease *(Continued)*
Dirofilaria immitis
life cycle of, 193
microfilaria identification tests, 195–196
in dogs
adulticides, 199*b*, 200–201
antigen tests for, 195
caval syndrome secondary to, 202–203
clinical features of, 196–197
clinicopathologic findings, 197–201
diagnosis of, 197
echocardiographic findings, 197, 197*f*
electrocardiographic findings, 197
heart sounds associated with, 196
ivermectin prophylaxis, 198
management protocol for, 199*b*
melarsomine dihydrochloride for, 199, 199*b*
microfilaria identification tests, 195–196, 195*t*
microfilaricide therapy, 207–208
pathophysiology of, 194–195
physical examination of, 196
preadulticide evaluation, 197–199
prevention of, 198, 203–207
pulmonary arterial disease associated with, 201
pulmonary complications, 201
pulmonary thromboembolic complications, 201–203
radiographic findings, 196
renal amyloidosis, 194
right-sided congestive heart failure secondary to, 202–203
serologic tests for, 195
severity classifications, 196*t*
treatment of, 197–199
villous proliferations associated with, 194
echocardiographic findings, 197, 197*f*, 206
electrocardiographic findings, 197, 206–207
geographic distribution of, 193
idiopathic feline bronchitis *versus*, 329*t*
microfilaria
tests for identifying, 195–196, 195*t*
treatment for, 200
pulmonary arteries, endothelial injury, 222
pulmonary hypertension caused by, 193, 287
radiographic findings, 196, 205*f*, 206
serologic tests for, 195
severity of, 196*t*
Wolbachia pipientis, 193
Heat cycle
silent, 953
split, 953–954
Heinz bodies, 1345*t*
Helicobacter spp., 1533*t*–1535*t*, 1539
antibiotics for, 1440*t*
chronic gastritis caused by, 463
gastritis caused by, 443
H. pylori, 464, 464*f*
Hemangiomas, 1413–1414
Hemangiosarcoma
abdominal, 513
canine, 1323*f*
clinical features of, 1322
clinicopathologic features of, 1322
description of, 176, 178, 185, 1322, 1413
diagnosis of, 1323
fine-needle aspiration of, 1323
intraabdominal, 1323*f*
primary splenic, 1325*f*
prognosis for, 1324–1325
treatment of, 1324–1325, 1324*f*
Hematemesis, 396*f*, 397–398
acute vomiting without, 394–395
causes of, 397*b*
Hematemesis *(Continued)*
diagnostic approach to, 400*f*
gastroduodenal ulceration and erosion as cause of, 397–398
Hematochezia, 402, 402*b*
Hematocrit, 1340
Hematologic system
chemotherapy complications of, 1276–1280
monitoring of, during chemotherapy, 1279
Hematopoietic tissue, 1259
Hematuria, 650–652, 650*f*–651*f*, 651*b*, 664, 666, 666*b*
Hemi-inattention syndrome, 1043, 1074
Hemiparesis, 1045*t*
Hemiplegia, 1045*t*
Hemoglobin
complete blood count assessment of, 318
oxygen saturation of, 318
Hemolysis
extravascular, 1231
peracute, 1354
prevention of, 1235–1237
Hemolytic anemia
causes of, 1347*t*
congenital, 1348
corticosteroids for, 1349
description of, 843–844, 930, 1346–1351, 1348*f*
diagnosis of, 1248*t*
immune-mediated
blood smear findings, 1234*f*
blood transfusion for, 1237
bone marrow evaluation in, 1235
clinical features of, 1232
cytologic findings, 1232*f*
definition of, 1231
description of, 1348*f*, 1349–1351, 1350*f*
diagnosis of, 1215–1216, 1232–1235
dog breeds at risk for, 1232*b*
etiology of, 1231
genetic predisposition of, 1231
glucocorticoids for, 1235–1236
hemolysis prevention in, 1235–1237
history-taking, 1233*b*
infectious diseases that cause, 1232*b*
laboratory tests, 1232–1233, 1233*b*, 1234*f*, 1234*t*
myelofibrosis in, 1235
nonregenerative, 1239*t*
physical examination of, 1233*b*
prednisone for, 1350
prognosis for, 1237–1238
regenerative, 1239*t*
secondary, 1231, 1234, 1235*t*
spherocytes in, 1233, 1234*t*
supportive care for, 1237
thromboembolism prevention in, 1237
thrombosis associated with, 223
treatment of, 1235–1237
vaccinations and, 1231
nonspherocytic, 1347*t*
spherocytic, 1396
Hemophilia A, 1399
Hemophilia B, 1399
Hemoplasmas, 1432–1433
Hemoptysis, 282
Hemorrhagic cystitis, 1284
Hemorrhagic effusions
pericardial, 176–177, 182–183
pleural, 361*t*, 362*f*, 363–364
Hemorrhagic gastroenteritis, 462–463, 1368
Hemostasis
cage-side tests for, 1390
disorders of, 1387–1406
in Greyhounds, 1361, 1366*t*
laboratory evaluation of, 1392, 1392*t*
physiology of, 1387–1388
point-of-care tests for, 1389, 1389*t*
Hemostatic defects
buccal mucosa bleeding time test for, 1391–1392, 1391*b*
clinical manifestations of, 1388–1389, 1388*b*, 1391*f*
clinicopathologic evaluation of, 1389–1393, 1390*f*
disseminated intravascular coagulation. *see* Disseminated intravascular coagulation
mixed (combined), 1400–1404
overview of, 1387
point-of-care tests for, 1389, 1389*t*
primary
description of, 1388*b*, 1389
platelet dysfunction, 1397–1399, 1397*b*
von Willebrand disease, 1398–1399, 1398*t*
screening tests for, 1392*t*
secondary, 1399–1400
congenital clotting factor deficiencies, 1399–1400
description of, 1388*b*, 1389
evaluation of, 1399
vitamin K deficiency, 1400
thrombocytopenia. *see* Thrombocytopenia
thrombosis, 1405, 1405*f*
Hemostatic plugs, 1401
Hemothorax, 382
Heparin
arterial thromboembolism in cats treated with, 227*b*, 228
disseminated intravascular coagulation treated with, 1403
immune-mediated diseases treated with, 1255*t*–1256*t*
low-molecular-weight
arterial thromboembolism uses of, 228, 230
dosage of, 229
pregnancy thrombosis treated with, 967
monitoring of, 228
unfractionated, 228
Hepatic amyloidosis, 575–576
Hepatic biopsy. *see* Liver biopsy
Hepatic congestion, 617
Hepatic cystadenoma, 575*f*
Hepatic encephalopathy, 522–524, 522*f*–523*f*, 523*b*
clinical signs of, 524, 524*f*, 524*b*
management of, 606–608, 607*b*, 609*b*
acute, 606*f*, 608–609, 609*b*
pathogenesis of, 522–524, 522*f*–523*f*
precipitating factors for, 523*b*
treatment of, 1440*t*
Hepatic lipidosis
feline, 561–567
primary, 561
secondary, 561–567
Hepatitis
acute, 598–599, 598*b*
chronic. *see* Chronic hepatitis, canine
Hepatobiliary disease, 518–530
abdominal pain in, 519
bilirubinuria and, 525–527, 526*f*–527*f*
in cats, 561–583
biliary tract diseases. *see* Feline biliary tract disease
characteristics of, 563*t*
clinical features of, 562
diagnosis of, 562–565, 564*f*
extrahepatic bile duct obstruction, 573–574, 573*b*
general considerations for, 561
hepatic amyloidosis, 575–576
hepatic lipidosis, 561–567
hepatobiliary manifestations, of systemic disease, 582
neoplasia, 576–577
prognosis for, 565–567
treatment of, 565–567, 565*f*, 566*b*–567*b*
types of, 562*t*

Hepatobiliary disease *(Continued)*
change in fecal color and, 525–527
change in liver size and, 524–525, 525*t*
coagulopathies in, 527–529
in dogs, 584–619
characteristics of, 563*t*
chronic hepatitis. *see* Chronic hepatitis, canine
congenital vascular disorders, 603–612
copper storage disease, 595–598
general considerations for, 584
drugs used in, 643*t*–648*t*
gastrointestinal signs with, 518–519, 519*b*
hepatic encephalopathy in, 522–524
jaundice in, 525–527, 526*f*, 528*f*
polyuria and polydipsia in, 519–522
protein-calorie malnutrition, 529–530, 529*f*
Hepatobiliary infections, in cats, 579–580, 580*b*
Hepatobiliary system
diagnostic approach for, 531–545
diagnostic tests for, 531–560
abdominocentesis, 543–544, 544*t*
coagulation tests, 543
complete blood count, 538
computed tomography, 553, 553*f*
fecal evaluation, 545
liver cytology, 553, 554*f*
magnetic resonance imaging, 553
plasma ammonia concentration, 536–537
plasma protein C activity, 537
scintigraphy, 553
serum albumin concentration, 537–538
serum bile acid concentration, 535–536, 535*b*
serum bilirubin concentration, 534–535
serum biochemistry, 541–542, 541*t*–542*t*
serum cholesterol concentration, 538
serum liver enzyme activities, 532–534
serum urea nitrogen concentration, 538
status of, 532–534, 533*t*
survey radiography, 545–549, 546*f*–549*f*
ultrasonography, 549–553, 549*f*, 550*t*–551*t*, 551*f*–552*f*
urinalysis, 544–545
urinary bile acid concentration, 536
Hepatocutaneous syndrome, 615–616, 616*f*
Hepatocyte vacuolation, 616–617, 617*f*
Hepatocytes, feline, 564*f*
Hepatojugular (abdominojugular) reflux, 5–6
Hepatomegaly, 1342*t*
Hepatosplenomegaly, 1314*f*
Hepatoxicity, chemotherapy-induced, 1285
Hepatozoon americanum, 154, 1430, 1440*t*, 1517
Hepatozoon canis, 1517
Hepatozoonosis, 1517–1518
Heritable teratospermia, 1005
Hernia
diaphragmatic. *see* Diaphragmatic hernia
hiatal, 416, 456, 457*f*
perineal, 504–505
Herpesvirus
feline. *see* Feline herpesvirus
pregnancy loss and
canine, 966
feline, 966
Hetastarch, 515*t*–517*t*
Heterobilharzia, 491
Hiatal hernia, 416, 456, 457*f*
High portal pressure, disorders associated with, 609–612
High-density lipoproteins, 908
High-dose dexamethasone suppression test, 864–865, 866*t*, 871
Higher-protein diets, 904
High-molecular-weight kininogen, 1387–1388, 1393
Hilar lymphadenopathy, 366*f*, 926
Hindlimb paresis, 225
Histamine-2 (H_2) receptor antagonists, 439, 439*t*, 701
Histiocytic ulcerative colitis, 495
Histoplasma capsulatum, 1503*t*, 1510, 1510*f*
Histoplasmosis, 483–484, 484*f*, 1510–1511
HMG-CoA reductase inhibitors, 913–914
Hock, arthrocentesis method in, 1191*f*
Holmium:YAG laser lithotripsy, 714, 714*f*
Holosystolic murmurs, 9–10, 114
Holosystolic timing, 11
Holter monitoring, 49–50
description of, 78
ventricular ectopy detection using, 143–144
Homocysteine, 1364
Hookworms, 487, 1536
Hormones, 1273, 1273*b*
Horner syndrome, 1089–1091, 1089*f*–1090*f*, 1089*b*, 1111*f*
Howell-Jolly bodies, 1345*t*
Human chorionic gonadotropin (hCG), 1034*t*–1036*t*
Human intravenous immunoglobulin, 1225*t*, 1228, 1236–1237, 1243, 1255*t*–1256*t*
Human toxoplasmosis, 1524*b*
Humidification, 342
Humoral hypercalcemia of malignancy, 760, 924
Hyaline cast, 667–668, 667*f*
Hydralazine, 62*b*, 63
chronic heart failure treated with, 64*t*, 71, 147
dilated cardiomyopathy treated with, 147
hypertension treated with, 217*t*
Hydrocephalus, 1078–1080, 1078*f*–1079*f*
Hydrochlorothiazide, 64*t*, 67, 718
Hydrocodone bitartrate, 386*t*–388*t*
Hydrocortisone, 1222*t*
Hydromorphone, 386*t*–388*t*, 629*t*–630*t*
analgesic uses of, 227*b*
stress relief using, 380*t*
Hydromyelia, 1155
1α-Hydroxylase, 697
17α-Hydroxyprogesterone caproate, 962–963
Hydroxyurea
chronic myelogenous leukemia treated with, 1319
erythrocytosis treated with, 116
polycythemia rubra vera treated with, 1369
Hyoscyamine
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Hypalgesia, 1040–1041
Hyperadrenocorticism
acromegaly *versus*, 752
adrenal-dependent, 863*f*
in cats, 878–883
adrenalectomy for, 883
clinical features of, 879–882, 879*b*
clinical pathology of, 880–881
description of, 878
diagnosis of, 882
etiology of, 878
imaging of, 881
physical examination findings in, 879–880, 879*f*
pituitary-adrenocortical axis tests, 881–882, 881*t*
prognosis for, 883
Hyperadrenocorticism *(Continued)*
signs of, 879–880
treatment of, 882–883
description of, 654*t*–655*t*, 741*t*
diagnosis of, 1249–1250
in dogs, 857–878
abdominal ultrasonography of, 862–864, 862*b*, 863*f*–865*f*
adrenocortical tumors, 857–858, 858*f*
clinical features of, 858–871
clinical pathology of, 861–862, 861*b*
diagnostic evaluation of, 861
etiology of, 857–858
imaging of, 862–864, 862*b*
medical complications of, 860–861, 860*b*
occult hyperadrenocorticism, 878
physical examination of, 860*t*
pituitary macrotumor syndrome, 859–860, 860*f*
pituitary-dependent hyperadrenocorticism, 857, 858*f*–859*f*, 863*f*, 869*f*, 876*f*
prognosis for, 877–878
signalment for, 858
signs of, 858–859, 860*t*
treatment, 871–877
adrenalectomy, 875–876
hypophysectomy, 877
ketoconazole, 875
mitotane, 872–875, 874*b*
pituitary irradiation, 876–877, 876*f*
trilostane, 871–872, 872*f*
endocrine alopecia caused by, 748*t*
hypertriglyceridemia associated with, 910
hypothyroidism *versus*, 783–784
iatrogenic, 858, 870
occult, 878
pituitary-dependent
in cats, 869*f*, 879*f*–880*f*
in dogs, 857, 858*f*–859*f*, 863*f*, 869*f*, 876*f*
Hyperbilirubinemia, 1231, 1489
Hypercalcemia, 48, 49*b*, 761*t*, 923–927, 1268, 1298
Hypercapnia, 385
Hypercholesterolemia, 685, 913
Hyperchylomicronemia, 1162
Hypercoagulability, 223
Hyperechoic, defined, 19
Hyperemesis gravidarum, 966–967
Hypereosinophilic syndrome, 1377
Hyperestrogenism, 747–748, 748*t*, 954, 982–983
Hyperfiltration, 693–694, 694*f*
Hypergastrinemia, 701
Hyperglycemia
clinical features of, 806
etiology of, 806, 807*b*
transient stress-induced, 833
Hyperhomocysteinemia, 223
Hyperkalemia, 47–48, 49*b*, 50*f*, 690–691, 919–921, 920*b*, 921*t*
Hyperkinetic, defined, 5
Hyperlipidemia
causes of, 909*b*
classification of, 909–910
clinical features of, 910
definition of, 908
diagnosis of, 910–911
in glomerular disease, 685
HMG-CoA reductase inhibitors for, 913–914
pathophysiology of, 908–909
postprandial, 909
secondary, 909–910
treatment of, 911–914, 912*t*
Hypermagnesemia, 933
Hypermetria, 1074–1075, 1147*f*
Hypermetric gait, 1038–1039, 1074–1075
Hypernatremia, 915–917, 916*b*, 917*t*
Hyperparathyroidism
classification of, 758
primary, 758–763
clinical signs of, 759, 760*b*
definition of, 758–759
diagnosis of, 760–761, 762*f*
differential diagnosis of, 924, 925*f*
etiology of, 758–760
hypercalcemia caused by, 761*t*
physical examination of, 760
prognosis for, 763
signalment, 759
treatment of, 761–763
secondary, 758
Hyperphosphatemia, 691, 929–930, 929*b*
Hyperpigmentation, 1283
Hyperplasia
benign prostatic, 1001–1003, 1002*f*, 1034*t*–1036*t*
cytologic features of, 1259
Hyperplastic lymphadenopathy, 1263–1264
Hyperplastic splenomegaly, 1411, 1412*t*
Hyperpnea, 4
Hyperprogesteronism, 748*t*
Hyperproteinemia, 1298, 1420–1422
Hypersensitivity reactions, 1281
Hypersthenuria, 663
Hypertension
amlodipine besylate for, 215, 217*t*
angiotensin-converting enzyme inhibitors for, 215, 217*t*
antihypertensive drugs for, 215, 217*t*
cardiomegaly secondary to, 213
in chronic kidney disease, 698
clinical features of, 213
complications of, 213*b*
diabetes mellitus and, 830
diagnosis of, 213–214
dietary salt restriction for, 215–216
diseases associated with, 211–212, 212*b*
echocardiographic findings, 213–214
etiology of, 211–212
general considerations for, 211–219
in glomerular disease, 685
hyperthyroidism and, 791
idiopathic, 211–212
mild, 211
moderate, 211
ocular effects of, 212, 213*b*
organs affected by, 211
pathophysiology of, 212
portal
chronic hepatitis and, 588
congestive splenomegaly caused by, 1413
prognosis for, 215–217
renal disease and, 211–212
severe, 211
treatment of, 215–217, 216*b*, 217*t*
Hypertensive crisis, 217*t*, 219
Hypertensive emergency, 218–219
Hypertensive encephalopathy, 213, 1077
Hyperthyroidism, 654*t*–655*t*
in cats, 167–168, 788–800
carbimazole, 796*t*, 797
cervical ultrasound for, 794, 795*f*
chronic kidney disease with, 790–791
clinical features of, 789
clinical pathology of, 790–791
diagnosis of, 791–794
etiology of, 788–789, 788*f*–789*f*
gastrointestinal tract disorders and, 791
iatrogenic hypothyroidism and, 790–791
iodine-restricted diet for, 796*t*, 797–798
methimazole for, 794, 796*t*
oral antithyroid drugs for, 794–797
physical examination of, 789, 790*t*
radioactive iodine for, 796*t*, 799–800, 799*f*
serum TSH concentration, 793

Hyperthyroidism *(Continued)*
signalment of, 789
signs of, 789, 790*t*
surgery for, 798–799, 798*b*
systemic hypertension and, 791
T3 suppression test for, 793–794, 793*f*
thyroid scintigraphy, 794
thyroidectomy for, 796*t*, 798, 798*b*
thyrotoxic cardiomyopathy, 790
treatment of, 794–800
urinary tract infection with, 791
chronic kidney disease, 696*f*, 698
myocardial hypertrophy and, 162
Hypertonic enemas, 445
Hypertonic saline, 432–433, 934*t*
Hypertriglyceridemia, 909, 910*t*
Hypertrophic cardiomyopathy
in cats
breeds affected by, 158
clinical features of, 159–160
clinicopathologic findings of, 162–163
color flow Doppler imaging of, 164*f*
diagnosis of, 160, 161*f*, 163*f*
echocardiographic findings of, 160–163, 163*f*–164*f*
electrocardiographic findings of, 160, 162*f*
etiology of, 158
myocardial ischemia secondary to, 159
pathophysiology, 158–159
prevalence of, 159–160
prognosis for, 167
radiographic findings of, 160, 161*f*
treatment of, 163–164, 166*b*
color flow Doppler of, 165*f*
description of, 80
in dogs, 152–153
echocardiographic findings, 152
subclinical, 163–164
Hyperventilation, 318, 1076
Hyperviscosity
description of, 113
treatment of, 116
Hypoadrenocorticism, 654*t*–655*t*, 883–889
ACTH stimulation test for, 885–886
acute addisonian crisis, 886–888
atypical, 884, 889
breeds at increased risk for, 884*b*
clinical features of, 884–885
clinical pathology of, 884–885, 885*b*
definition of, 883
diagnosis of, 885–886
electrocardiography for, 885
etiology of, 883–884
glucocorticoid-deficient, 889
imaging of, 885
megaesophagus and, 885
physical examination of, 884
primary, 886*t*
primary adrenal insufficiency, 888–889
secondary, 884, 886*t*
signalment for, 884
signs of, 884, 884*b*
treatment of, 886–889
Hypoalbuminemia
in canine monocytotropic ehrlichiosis, 1475
in dogs, 923
nephrotic syndrome causing, 684
plasma oncotic pressure decreases caused by, 362
pulmonary edema caused by, 358
Hypoallergenic diets, 434*b*
Hypocalcemia, 48, 49*b*, 765*t*, 927–929, 928*b*
Hypochloremic-hypokalemic metabolic alkalosis, 465–466
Hypochromasia, 1345*t*
Hypocobalaminemia, 640
Hypoechoic, defined, 19
Hypogastric nerve, 995
Hypoglobulinemia, 1362–1363
Hypoglossal nerve, 1056*t*, 1059–1060, 1060*f*
Hypoglycemia, 806–809
chronic, 852
clinical features of, 807
diagnostic approach of, 807–808
etiology of, 806–807, 807*b*
iatrogenic, 806
insulin therapy and, 824, 837–838
seizures caused by, 808*b*
signs of, 807
treatment of, 808–809, 808*b*, 815
Hypoglycemic drugs, 808*b*, 835–837
Hypogonadism, 754
Hypokalemia, 47, 49*b*, 921–923, 922*b*, 923*t*
Hypokalemic polymyopathy, 1178–1179, 1178*f*
Hypokinetic, defined, 5
Hypoluteiodism, 962–963
Hypomagnesemia, 844, 931–933, 932*b*
Hypomotility, idiopathic gastric, 469–470
Hyponatremia, 74, 917–919, 918*b*
Hypo-osmolality, 918
Hypoparathyroidism, 798–799
iatrogenic, 764
primary, 763–766
clinical signs of, 764, 764*b*
diagnosis of, 764–765
etiology of, 763–764
hypocalcemia caused by, 765*t*
physical examination of, 764
prognosis for, 766
signalment, 764
treatment of, 765–766
transient, 764
Hypophosphatemia, 843–844, 930–931, 930*b*
Hypoproteinemia, 923
Hyporexia, 407, 407*b*
Hyposthenuria, 663, 742
Hypothalamic-pituitary-thyroid gland complex, 767, 768*f*
Hypothalamus, disorders of, 740–757
Hypothyroid myopathy, 770–771
Hypothyroid polyneuropathy, 1164–1165
Hypothyroidism
in cats, 785–788
congenital, 788
diagnosis of, 786–787, 787*f*
etiology of, 785–786
levothyroxine for, 787
prognosis for, 788
signs of, 786, 786*f*, 786*b*
treatment of, 787
congenital, 767–768
in dogs, 767–785
autoimmune polyendocrine syndromes associated with, 773
behavioral problems associated with, 772
clinical features of, 768–773
clinical manifestations of, 770*b*
clinical pathology of, 773–782
congenital, 767–768
cretinism associated with, 772–773, 772*b*, 773*f*
dermatohistopathologic findings, 773–774
dermatologic signs of, 768–770, 771*f*
diagnosis of, 782–783
estrous cycle affected by, 956
etiology of, 767–768, 768*b*
glomerular filtration rate, 772
histologic findings, 769*f*
levothyroxine, 783–784, 783*b*–784*b*
myopathies associated with, 1178
myxedema coma, 772
neuromuscular signs of, 770–771
prognosis for, 785
reproductive signs of, 771–772
therapeutic monitoring, 784, 785*f*
thyroid-stimulating hormone, 782
treatment of, 783–785, 783*b*
ultrasonographic findings, 774, 774*f*
Hypothyroidism *(Continued)*
endocrine alopecia caused by, 748*t*
etiology of, 767–768
peripheral vestibular disease caused by, 1115
in puppies, 783
secondary, 767, 768*b*
tertiary, 767, 768*b*
Hypoxemia
arterial, 113
cyanosis as sign of, 284

I

Iatrogenic gastric outflow obstruction, 467
Iatrogenic hyperadrenocorticism, 858, 870
Iatrogenic hypoglycemia, 806
Iatrogenic hypoparathyroidism, 764
Ibutilide fumarate, 96
Icteric mucous membranes, 5*b*, 1232*f*
Icterus, 525, 1232*f*
Ictus, 1093
Idiopathic aplastic anemia, 1240
Idiopathic canine chronic rhinitis, 268–269
Idiopathic chronic hepatitis, 586–595
Idiopathic epilepsy, 1094, 1105
Idiopathic feline bronchitis, 329*t*
Idiopathic feline lower urinary tract disease. *see* Feline idiopathic cystitis
Idiopathic gastric hypomotility, 469–470
Idiopathic interstitial pneumonias, 349–352
Idiopathic megacolon, 507
Idiopathic preterm labor, 962–963, 963*f*–964*f*
Idiopathic pulmonary fibrosis, 329*t*, 349–352, 350*f*
Idiopathic renal hematuria, 652, 652*f*
Idiopathic thrombocytopenic purpura
causes of, 1241*t*
classification of, 1240
clinical features of, 1240, 1242*f*
description of, 1216–1217
diagnosis of, 1240–1244
etiology of, 1240
feline, 1244
immunosuppressive drugs for, 1243
physical examination of, 1240, 1242*f*
prognosis for, 1244
supportive care for, 1243–1244
treatment of, 1243
Idioventricular rhythm, accelerated, 41
Ileocolic valve, 429*f*
Ileoscopy, 428–429, 429*f*
Ileus, anatomic, 419
Imidapril, 64*t*
Imidocloprid/moxidectin, 444*t*
Imipenem-cilastatin, 1437*t*–1438*t*
Immiticide. *see* Melarsomine dihydrochloride
Immune-complex glomerulonephritis, 676–677, 676*f*
Immune-mediated disorders
definition of, 1211
dermatomyositis, 1253
diagnostic approach to, 1215
diagnostic tests, 1215–1219
antinuclear antibody test, 1217
antiplatelet antibodies, 1216–1218
autoimmune panels, 1218
Coombs test, 1216, 1216*b*
C-reactive protein, 1217–1218
immunofluorescence, 1218
immunohistochemistry, 1218
lupus erythematosus test, 1217
rheumatoid factor, 1217
slide agglutination test, 1215–1216
examples of, 1212–1213
glomerulonephritis, 676, 678*b*, 1249–1250
hemolytic anemia. *see* Immune-mediated hemolytic anemia
idiopathic aplastic anemia, 1240
Immune-mediated disorders *(Continued)*
immunopathologic mechanisms, 1211–1212, 1212*t*
leukopenia, 1248*t*
myasthenia gravis, 1250–1251, 1251*t*
myositis, 1252–1253, 1253*b*
neutropenia, 1244–1245
pathogenesis of, 1211–1214
polyarthritis, 1119
breed-specific, 1245*t*
clinical features of, 1245–1246, 1246*b*
cytologic findings, 1246, 1246*f*
diagnosis of, 1246, 1246*f*
erosive, 1208, 1245*t*
etiology of, 1245
glucocorticoids for, 1203–1204, 1204*t*, 1204*b*
nonerosive, 1202–1204, 1202*b*, 1204*t*, 1245*t*
primary, 1245
signs of, 1246*b*
treatment of, 1246–1247
polymyositis, 1252–1253, 1253*b*
primary, 1211
pure red cell aplasia, 1238–1240, 1239*t*
secondary, 1211
treatment of, 1220–1230
azathioprine, 1223–1224
chlorambucil, 1224, 1225*t*
corticosteroids, 1222, 1222*b*
cyclosporine, 1224–1226, 1225*t*–1226*t*
glucocorticoids, 1221–1223, 1222*t*
human intravenous immunoglobulin, 1225*t*, 1228
immunosuppressive therapy, 1220–1221
leflunomide, 1225*t*, 1226–1227
mycophenolate mofetil, 1225*t*, 1227–1228
pentoxifylline, 1228–1229
principles of, 1220
splenectomy, 1228
vincristine, 1225*t*, 1229
Immune-mediated hemolytic anemia
blood smear findings, 1234*f*
blood transfusion for, 1237
bone marrow evaluation in, 1235
clinical features of, 1232
cytologic findings, 1232*f*
definition of, 1231
description of, 1348*f*, 1349–1351, 1350*f*
diagnosis of, 1215–1216, 1232–1235
dog breeds at risk for, 1232*b*
etiology of, 1231
genetic predisposition of, 1231
glucocorticoids for, 1235–1236
hemolysis prevention in, 1235–1237
history-taking, 1233*b*
infectious diseases that cause, 1232*b*
laboratory tests, 1232–1233, 1233*b*, 1234*f*, 1234*t*
myelofibrosis in, 1235
nonregenerative, 1239*t*
physical examination of, 1233*b*
prednisone for, 1350
prognosis for, 1237–1238
regenerative, 1239*t*
secondary, 1231, 1234, 1235*t*
spherocytes in, 1233, 1234*t*
supportive care for, 1237
thromboembolism prevention in, 1237
thrombosis associated with, 223
treatment of, 1235–1237
vaccinations and, 1231
Immune-mediated orchitis, 1003–1004, 1004*f*
Immune-mediated thrombocytopenia
causes of, 1241*t*
classification of, 1240
clinical features of, 1240, 1242*f*
description of, 1396–1397
diagnosis of, 1240–1244, 1248*t*
etiology of, 1240

Immune-mediated thrombocytopenia *(Continued)*
feline, 1244
immunosuppressive drugs for, 1243
physical examination of, 1240, 1242*f*
prognosis for, 1244
supportive care for, 1243–1244
treatment of, 1243
Immunodeficiency virus. *see* Feline immunodeficiency virus
Immunofluorescence, 1218
Immunoglobulin G, 1346–1348
Immunohistochemistry, 1218
Immunopathologic mechanisms, 1211–1212, 1212*t*–1213*t*
Immunoproliferative enteropathy of basenjis, 497
Immunosuppressive drugs, 442
chronic hepatitis treated with, 592–593
complications of, 1237
glomerular disease treated with, 682, 683*b*
hemolysis prevention using, 1235
immune-mediated disorders treated with, 1220–1221
immune-mediated hemolytic anemia treated with, 1237
immune-mediated thrombocytopenia treated with, 1243
Imodium. *see* Loperamide
Impression smears, 1258
Imuran. *see* Azathioprine
Inappetence, 72
Incarcerated intestinal obstruction, 498–499, 499*f*
Incidental adrenal mass, 892–893, 893*f*–894*f*
Incurin. *see* Estriol
Infectious agents
description of, 1427
laboratory diagnosis of, fecal examination, 1427–1429
Infectious diarrhea, 476–480
canine coronaviral enteritis, 479
canine parvoviral enteritis, 476–478, 477*b*
elokomin fluke fever, 480
feline coronaviral enteritis, 479
feline immunodeficiency virus-associated diarrhea, 480
feline leukemia virus-panleukopenia-like syndrome, 479–480
feline parvoviral enteritis, 478–479
salmon poisoning, 480
Infectious diseases
antemortem diagnosis of, 1435
antibody detection
in body fluids, 1434–1435
in serum, 1433–1434
biosecurity procedures for small animals hospitals, 1448–1450, 1449*b*
disinfection protocols for, 1450
laboratory diagnosis of, 1427–1435
animal inoculation, 1433
culture techniques, 1431–1432
cytology, 1429–1430
electron microscopy, 1433
immunocytochemistry, 1432
immunologic techniques, 1432
molecular diagnostics, 1432–1433
polymerase chain reaction, 1432–1433, 1432*f*
tissue techniques, 1430–1431
prevention of
in hospitalized patients, 1449–1450
overview of, 1448–1456
patient evaluation, 1449
screening, 936*b*
zoonotic transfer of, 1449
Infectious inflammatory disease, 1142–1143
Infectious orchitis, 1000–1001
Infectious pericarditis, 182
Infectious prostatitis, 1002–1003, 1002*f*
Infective endocarditis
antibiotics for, 136–137
antimicrobial prophylaxis for, 138
bacteremia and, 132
blood culture testing for, 133–134
in cats, 132
cephalosporins for, 136–137
clinical features of, 133
congestive heart failure secondary to, 132
diagnosis of, 133–136, 135*b*
in dogs, 132
Doppler imaging of, 136, 136*f*
echocardiography of, 133–134, 136*f*
etiology of, 132–133
immune-mediated disease *versus*, 133
laboratory tests for, 134
microorganisms associated with, 132
neutrophilia associated with, 134
nonregenerative anemia associated with, 134
pathophysiology of, 132–133
prognosis for, 136–138
prophylactic antibiotics for, 138
sequelae of, 134*b*
signs of, 133
systemic effects of, 134*b*
thromboemboli caused by, 133
treatment of, 136–138
valves commonly affected by, 132
vegetations associated with, 132
Infective myocarditis, 153–154
Infertility
congenital, 1005
male. *see* Male infertility
sexual differentiation disorders, 1005–1006, 1006*f*
Infiltrative diseases
gastric, 471–472
gastrointestinal ulceration/erosion from, 470
Infiltrative splenomegaly, 1412*t*, 1413
Inflammatory bowel disease, 493–495
endoscopy of, 428*f*
Inflammatory myopathies, 1174–1178
Influenza, canine, 340, 1455
Influenza A viral infections, 1542
Injection site sarcomas, 1334–1335, 1335*f*
Innocent murmurs, 9, 100
Inosine monophosphate dehydrogenase, 1227
Inotropic agents, for heart failure, 63–65, 69–70
Insulin
allergic reactions to, 827
antibodies to, 828
complications of, 824–828, 837–839
diabetes mellitus managed with
in cats, 834–836
in dogs, 812–814, 813*t*, 814–816, 815*f*, 815*t*
diabetic ketoacidosis treated with, 842*b*, 845–846
dilution of, 814
disorders causing resistance to, 827–828, 828*b*
dosage of, 934*t*
duration of effect, 826–827, 826*f*–827*f*, 839
endocrine disorders treated with, 896*t*–897*t*
hypoglycemia and, 824, 837–838
inadequate absorption of, 827
initial requirements for, 817–818
initiating of, 846
intermittent intramuscular regimen for, 846
longer-acting, 846
overdosing of, 825–826, 826*f*, 836–837
prolonged duration of effect, 826–827, 827*f*, 839
rapid-acting, 812
recommendations for
in diabetic cats, 834
in diabetic dogs, 814
Insulin *(Continued)*
short duration of effect, 826, 826*f*–827*f*, 839
Somogyi response, 825–826, 826*f*
storage of, 814
subcutaneous technique for, 846
during surgery, 823–824, 837
treatment regimen, 825
types of, 812, 813*t*
underdosing of, 825–826, 839
Insulin aspart, 812
Insulin detemir, 812–814, 813*t*, 837
Insulin glargine, 812–814, 813*t*, 837
Insulin Lente, 813*t*, 846
Insulin lispro, 812, 813*t*, 846
Insulin NPH, 813*t*
Insulin resistance
in cats, 836–837, 839
in dogs, 817, 817*b*, 827–828
ketogenesis and, 840
Insulin-binding antibodies, 828
Insulin-like factor, 990
Insulin-like growth factor, 749–750, 752*f*
Insulinoma polyneuropathy, 1165
Insulin-secreting β-cell neoplasia, 808, 847–853
clinical features of, 848–849
clinical pathology of, 848–849
clinical signs of, 848
diagnosis of, 849–850, 849*f*
etiology of, 847
peripheral neuropathy, 848
physical examination of, 848
signalment for, 848
signs associated with, 848*b*
treatment of, 850–852
diazoxide therapy, 850*b*, 852
feedings, 852
glucocorticoid therapy, 852
overview of, 850
postoperative complications, 851–852, 851*f*
prognosis for, 853
somatostatin therapy, 852
streptozotocin therapy, 852
surgery, 850–851, 850*b*, 851*f*
Interceptor. *see* Milbemycin
Interestrus
definition of, 949
prolonged, 955
shortened, 956–957
Interferon omega, 515*t*–517*t*
Intermittent weakness, 2–3, 2*b*
Internal nares, 251*f*
International normalization ratio, 233
Interstitial pattern, 292–293, 292*f*, 292*b*–293*b*
Intervertebral disk disease
acute
cervical disk extrusion, 1139
clinical features of, 1136, 1136*f*
description of, 1135–1141
diagnostic approach, 1136–1137, 1137*f*–1139*f*
magnetic resonance imaging of, 1137
medical management of, 1139
myelography for, 1137, 1138*f*
treatment of, 1137–1141
type II, 1148
Intervertebral disks, 1135–1136, 1135*f*
Intestinal adenocarcinoma, 503
Intestinal diseases, 474–509
acute enteritis, 474–475
acute hemorrhagic diarrheal syndrome, 482–483
alimentary tract parasites, 485–491
antibiotic-responsive enteropathy, 442
antibiotic-responsive small intestinal enteropathy, 492
campylobacteriosis, 480–481
canine coronaviral enteritis, 479
canine parvoviral enteritis, 476–478, 477*b*
clostridial colitis, 494
clostridial diseases, 482, 482*f*
Intestinal diseases *(Continued)*
coccidiosis, 488
cryptosporidia, 488–489
diarrhea. *see* Diarrhea
dietary-responsive large intestinal diarrhea, 494
dietary-responsive small intestinal diarrhea, 491–492
elokomin fluke fever, 480
enterotoxemia, 475
exocrine pancreatic insufficiency, 413, 491
feline coronaviral enteritis, 479
feline immunodeficiency virus-associated diarrhea, 480
feline leukemia virus-panleukopenia-like syndrome, 479–480
feline parvoviral enteritis, 478–479
giardiasis, 489–490, 489*f*
heterobilharzia, 491
histoplasmosis, 483–484, 484*f*
hookworms, 487
infectious diarrhea, 476–480
inflammatory bowel disease. *see* Inflammatory bowel disease
intussusception. *see* Intussusception
large intestinal inflammatory bowel disease, 494–495
maldigestive disease, 491
miscellaneous bacteria, 483
protothecosis, 484, 485*f*
pythiosis, 484
roundworms, 486–487, 486*f*
salmon poisoning, 480
salmonellosis, 481–482
strongyloidiasis, 488
tapeworms, 487–488
trichomoniasis, 490–491, 490*f*
whipworms, 485–486, 485*f*
Intestinal distention, 420*f*
Intestinal leiomyoma, 503
Intestinal lymphangiectasia, 495–497, 496*f*
Intestinal obstruction, 498–502
cecocolic intussusception, 501–502
description of, 419, 420*f*
incarcerated, 498–499, 499*f*
intussusception, 501, 501*f*
linear foreign objects, 499–501, 500*f*
mesenteric torsion/volvulus, 499
simple, 498
Intestinal "protectants,", 440
Intoxication(s)
citrate, 1358
ethylene glycol, 671, 1099*b*
mentation abnormalities caused by, 1074
seizures caused by, 1099*b*
treatment of, 1100*b*
Intraabdominal lymphoma, 1299
Intracardiac shunt, 109–112
Intracellular fluid, 844*f*
Intracranial disorders, 1074–1083
cerebellar cortical degeneration, 1080–1081
cerebellar hypoplasia, 1080
considerations in, 1074
degenerative disorders of brain, 1080
diagnostic approach to, 1075, 1075*b*
disorders causing, 1075*b*
encephalitis, 1080
feline hippocampal necrosis, 1077–1078
feline ischemic encephalopathy, 1077
head trauma, 1075–1076
hydrocephalus, 1078–1080, 1078*f*–1079*f*
hypermetria, 1074–1075
hypertensive encephalopathy, 1077
intoxications, 1074
lissencephaly, 1080
management of, 1076*b*
mentation abnormalities, 1074
metabolic encephalopathies, 1074
neoplasia, 1081–1082, 1082*f*
neuroaxonal dystrophy, 1080

Intracranial disorders *(Continued)*
thiamine deficiency, 1078
vascular accidents, 1076–1077
Intracranial pressure, increased
signs of, 1069*b*
treatment of, 1069*b*
Intracranial tumors
central vestibular disease caused by, 1115
description of, 742
Intramedullary tumors, 1145
Intranasal catheters, 384*f*
Intranasal lymphoma, 1297*f*, 1308*f*
Intraoral radiography, 248*f*
Intraosseous catheter, in neonate, 1011*f*
Intrathoracic pressure, 385–386
Intrauterine artificial insemination, 947–948, 947*f*–948*f*
Intravascular coagulation, 1403–1404
Intravascular hemolysis, 1348
Intravenous fluids supplementation, 433*t*
Intravenous immunoglobulin, 1350–1351
Intraventricular conduction disturbances, 44
Intrinsic factor, 620
Intrinsic pathway, of coagulation cascade, 221–222, 1387
Intussusception, 1029, 1030*f*
Iodine-restricted diet, 796*t*, 797–798
Iohexol, 661
Ipecac syrup, 1185*t*–1186*t*
Iron deficiency anemia, 471–472, 1354–1355, 1356*f*
Irradiation, pituitary, 876–877, 876*f*
Irritative laxatives, 445
Ischemic myocardial diseases, 151–152
Ischemic neuromyopathy, 1162–1163, 1163*f*
Ischemic priapism, 993
Ischemic stroke, 1076
Islet amyloidosis, 831*f*
Isoproterenol
atrioventricular conduction block treated with, 88
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
indications for, 98
Isosorbide dinitrate, 64*t*
Isosorbide mononitrate, 64*t*
Isosthenuria, 663, 680, 695, 698–699
Itraconazole, 386*t*–388*t*, 515*t*–517*t*
dosage of, 1504*t*
nasal aspergillosis treated with, 261
pythiosis treated with, 472
Ivabradine, 97, 167
Ivermectin, 386*t*–388*t*, 515*t*–517*t*
dosage of, 444*t*
heartworm disease uses
in cats, 207
in dogs, 198, 203
nasal capillariasis treated with, 263–264
Oslerus osleri treated with, 338
Ixodes scapularis, 1471–1472

J

Jaundice, 525–527, 526*f*–528*f*
mucous membrane color abnormalities caused by, 4–5
Jejunostomy tubes, 437
Jen Chung acupressure, 1010*f*
Jerk nystagmus direction, 1109
Joint diseases
breed-specific polyarthritis syndromes, 1205
canine rheumatoid-like polyarthritis, 1206–1208, 1206*f*–1207*f*
classification of, 1188*b*
clinical manifestations of, 1187–1194
degenerative, 1195–1196, 1196*f*, 1197*t*
diagnostic approach to, 1187–1189
diagnostic tests for, 1187–1194
immunologic tests for, 1194
Lyme disease titers, 1194, 1200
minimum database, 1189
Joint diseases *(Continued)*
rheumatoid factor, 1194, 1206
rickettsial titers, 1194
serologic tests, 1194
synovial fluid collection and analysis
arthrocentesis for, 1190, 1190*f*–1192*f*
collection methods, 1190, 1190*f*
description of, 1188–1189, 1189*t*
gross appearance, 1190–1192, 1192*f*
microscopic appearance, 1192, 1192*f*–1193*f*
neutrophils, 1192
radiography, 1193
smear preparation, 1190, 1192*f*
synovial fluid culture, 1193
synovial membrane biopsy, 1193
drugs for, 1209*t*–1210*t*
erosive polyarthritis, 1208
familial Chinese Shar-Pei fever, 1205
feline erosive immune mediated polyarthritis, 1208
feline periosteal proliferative polyarthritis, 1208
feline rheumatoid-like arthritis, 1208–1209
fungal arthritis, 1201
immune-mediated nonerosive polyarthritis, 1187, 1188*f*
infectious inflammatory, 1197–1201
leishmaniasis, 1200–1201
Lyme disease, 1200
lymphoplasmacytic synovitis, 1206
Mycoplasma polyarthritis, 1199
noninflammatory, 1187, 1195–1196
overview of, 1187
physical examination of, 1187
reactive polyarthritis, 1201–1202, 1202*f*
rickettsial polyarthritis, 1199–1200
septic arthritis, 1193, 1197–1201, 1198*f*–1199*f*
viral arthritis, 1201
Joint pain, 1203*f*
J-point, 46–47
Jugular pulsations, 5
Jugular vein
cardiovascular examination of, 5, 6*b*
distention of, 5, 5*f*
Juvenile cellulitis, 1031–1032, 1032*f*
Juvenile diabetes, 1033
Juvenile glomerulopathy, 693*b*
Juxtaglomerular apparatus, 675

K

Kaolin-pectin, 515*t*–517*t*
Kaon Elixir. *see* Potassium gluconate
Kaopectate, 440*t*
Keflex. *see* Bismuth subsalicylate
Kennel cough. *see* Canine infectious tracheobronchitis
Keppra. *see* Levetiracetam
Ketamine, 386*t*–388*t*, 515*t*–517*t*, 629*t*–630*t*
Ketoconazole, 515*t*–517*t*, 875, 896*t*–897*t*, 1504–1505, 1504*t*, 1507
Ketogenesis, 840
Ketone bodies, 840
Ketones, 665
Ki-67, 1329
Kidney injury molecule-1 (KIM-1), 660
Kidneys
acute injury. *see* Acute kidney injury
chronic disease of. *see* Chronic kidney disease
glomerulus of. *see* Glomerulus
infective endocarditis effects on, 134*b*
physical examination of, 650
renomegaly of, 656–657
ultrasonography of, 671
Kit, 1273
Kitten, biochemical parameters, 1019*t*–1020*t*
Knott's centrifugation technique, 195
Knuckling, 1048*f*

L

Labetalol, 94*t*, 217*t*
Labor, normal, 968
Labrador Retrievers, centronuclear myopathy of, 1179–1180, 1180*f*
Lacrimal gland, 1086
Lactescence, 910
Lactobacillus, 443
Lactulose, 445–446, 445*t*, 515*t*–517*t*
Lameness, 1046, 1142*f*, 1187
Lansoprazole, 439
Lanthanum carbonate, 700–701
Lanugo retention, pituitary dwarfism and, 754
Laplace's law, 55–56
Large airway disease, 379–382, 380*t*
Large cell lymphoma, 1299
Large intestinal diarrhea, 399*t*, 401*b*
dietary-responsive, 494
fiber-responsive, 494
Large intestine. *see also specific intestinal entries*
inflammatory bowel disease, 494–495
neoplasms of, 503–504
Laryngeal collapse, 275*f*, 276
Laryngeal diseases
clinical manifestations of, 271–272
clinical signs of, 271
differential diagnosis of, in dogs and cats, 272, 272*b*
Laryngeal neoplasia, 281
Laryngeal paralysis, 271, 275, 277–279
clinical features of, 277
congenital, 277
definition of, 277
diagnosis of, 277–278, 278*b*
etiology of, 277, 278*b*
hypothyroidism and, 770–771
idiopathic, 277
laryngoplasty for, 278
prognosis for, 278–279
traumatic causes of, 277
treatment of, 278
upper airway obstruction caused by, 380–381
Laryngeal paralysis-polyneuropathy complex, 277, 1164
Laryngitis, obstructive, 280
Laryngoplasty, 278
Laryngoscopy, for larynx and pharynx, 273–276, 274*f*–275*f*
Larynx
computed tomography for, 273
diagnostic tests for, 273–276
disorders of, 277–281
fluoroscopy for, 273
laryngoscopy for, 273–276, 274*f*–275*f*
magnetic resonance imaging for, 273
pharyngoscopy for, 273–276, 274*f*
radiography for, 273, 274*f*
ultrasonography for, 273
Lasix. *see* Furosemide
Latex agglutination capsular antigen test, 244
Laxatives, 443–446, 445*t*
L-carnitine, 73, 151
Lead, 1099*b*
Lead systems, for electrocardiography, 35, 36*f*, 36*b*
Lean body mass, 904
Leflunomide, 1185*t*–1186*t*, 1204*t*, 1207–1208, 1209*t*–1210*t*, 1225*t*, 1226–1227
glomerular disease treated with, 682
immune-mediated diseases treated with, 1255*t*–1256*t*
Left anterior fascicular block (LAFB), 44, 46*b*
Left atrium
enlargement of
in arterial thromboembolism, 224
Left atrium *(Continued)*
in degenerative atrioventricular valve disease, 120, 125*f*
description of, 15–16, 17*f*
rupture of, 130–131, 177
Left atrium-to-aortic root ratio, 21–22
Left bundle branch block (LBBB), 44, 46*b*
Left ventricle
dilation, 46*b*
enlargement, 16
Left ventricular hypertrophy
electrocardiography of, 46*b*
in hypertension, 213–214
ventricular systolic pressure and, 168
Left ventricular outflow tract obstruction
in cats, 160
diltiazem in, 167
Left ventricular pressure overload, 106
Left-sided congestive heart failure
description of, 1, 110
edema caused by, 291
Leiomyomas, 424–425, 460
Leiomyosarcomas, 427*f*, 460, 503
Leishmania infantum, 1518
Leishmania spp., 1430, 1518, 1519*f*
Leishmaniasis, 154, 1200–1201, 1421–1422, 1518–1520, 1518*f*
Lens-induced uveitis, 829
Leptospira spp., 1533*t*–1535*t*
antibiotics for, 1441*t*
L. grippotyphosa, 1434
L. interrogans, 1455, 1462
transmission of, 1543
Leptospires, 586–587, 1462
Leptospirosis, 1462–1464
clinical findings of, 1463, 1463*b*
diagnosis of, 1463–1464
epidemiology of, 1462
etiology of, 1462
prevention of, 1464
treatment of, 1464
zoonotic aspects of, 1464
Leukemias, 1311–1321. *see also* Feline leukemia virus
in cats, 1312*t*, 1319–1321
classification of, 1311–1313, 1312*t*
cytochemical stains for, 1312*t*
definition of, 1311–1313
in dogs, 1313–1319
flow cytometric analysis, 1312*f*
Leukeran. *see* Chlorambucil
Leukocyte esterase reaction, 665
Leukocytes
in Greyhounds, 1361
morphology of, 1371–1372
physiology of, 1371–1372
Leukocytosis, 1371–1380
description of, 1317–1318
diagnosis of, 1371
Leukoerythroblastic reaction, 1381
Leukoerythroblastosis, 1381–1386, 1382*b*–1383*b*
Leukogram, 1371
Leukopenia, 1248*t*, 1345*t*
Leukotriene inhibitors, 333
Levamisole, 344
Levetiracetam
neurologic disorders treated with, 1185*t*–1186*t*
seizures treated with, 1103
Levothyroxine, for hypothyroidism, 783–784, 783*b*
Leydig cell tumors, 997
L-form bacteria, 1440*t*
Lidocaine, 89–91
in cats, 90–91, 90*t*–91*t*
constant-rate infusion of, 88*b*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
electrocardiographic changes associated with, 49*b*
half-life of, 89
indications for, 89
infusion of, 629*t*–630*t*
metabolism of, 89

Lidocaine *(Continued)*
seizures induced by, 90–91
toxic effects of, 90–91
ventricular tachycardia treated with, 82
Ligamentum arteriosum, 116–117
Lincomycin, 1437*t*–1438*t*
Lincosamides, 1437*t*–1438*t*
Linear foreign objects, 499–501, 500*f*
Lipemia, 911*t*
Lipoprotein(s)
classes of, 908
description of, 908
high-density, 908
low-density, 908
very-low-density, 908
Lipoprotein electrophoresis, 911
Lipoprotein lipase, 908
Liposomal amphotericin B, pythiosis treated with, 472
Liquid barium sulfate, 422–423
Lisinopril, 64*t*
Lissencephaly, 1080
Lithium carbonate, 1280
Little white shaker syndrome, 1183
Liver. *see also specific hepatic entries*
chemotherapy toxicity to, 1285
enlargement of, 524–525
size of, change in, 524–525, 525*t*
Liver biopsy, 553–559, 554*f*
indications for, 554
techniques for, 554–555, 555*f*–558*f*
Liver disease
breed-related, 586*b*
diagnostic approach to, 531–532, 532*b*
Liver enzymes, 1362
Liver fluke infestation, 568*t*, 572–573, 573*b*
Liver tumors
in cats, 576
clinical features of, 577*t*
Lobular dissecting hepatitis, 587
Lomotil. *see* Diphenoxylate
Lomustine, 587–588, 1285, 1332–1333
Lone atrial fibrillation, 85–86
Loop diuretics
acute kidney injury treated with, 691
chronic heart failure treated with, 66–67
Loperamide, 440, 440*t*, 515*t*–517*t*
Low-density lipoproteins, 908
Low-dose dexamethasone suppression test, 864–865, 866*t*, 867–868, 869*f*
Lower esophageal sphincter, 426*f*, 461*f*
Lower motor neuron (LMN)
paralysis of, 1163*f*, 1164*b*
signs, 1039–1040, 1039*f*, 1040*t*
Lower respiratory tract disorders
arterial blood gas analysis for, 286
clinical manifestations of, 282–286
complete blood count in, 286
cough associated with, 282–283
definition of, 282
diagnostic approach to, 284–286, 284*f*
diagnostic tests for, 287–320
blood gas analysis. *see* Blood gas analysis
bronchoalveolar lavage. *see* Bronchoalveolar lavage
bronchoscopy, 309*t*, 312
computed tomography, 295–296
magnetic resonance imaging, 295–296
nuclear imaging, 296
parasitology, 296–298, 297*f*, 297*t*
polymerase chain reaction, 298
pulse oximetry, 318–319
serology, 298
thoracic radiography, 287–295
thoracoscopy with lung biopsy, 312
thoracotomy, 299*t*, 312
tracheal wash. *see* Tracheal wash
transthoracic lung aspiration and biopsy, 310–311
ultrasonography, 295, 296*f*
urine antigen tests, 298
Lower respiratory tract disorders *(Continued)*
differential diagnosis of, 283*b*, 289*b*
disease-specific testing, 286
exercise intolerance caused by, 283–284
physical examination of, 284–286
pulmonary specimens for, 286
radiographic evaluations, 286
respiratory distress caused by, 283–284
signs of, 282–284
thoracic auscultation of, 285–286
Lower urinary tract, 731*f*
Lower urinary tract signs
abdominal ultrasonogram of, 726*f*
bacterial cystitis, 704
cystoscopic findings, 726*f*
diagnostic tests for, 725–726
Low-molecular-weight heparin
arterial thromboembolism uses of, 228, 230
dosage of, 229
pregnancy thrombosis treated with, 967
Low-profile gastrostomy tubes, 436
Lumbar intumescence, 1039*f*, 1041*b*
Lumbar myelography, 1065
Lumbar puncture, 1070, 1071*f*
Lumbosacral plexus lesions, 1158*t*
Lung(s)
alveolar pattern, 290–292, 291*f*, 291*b*
atelectasis, 294, 294*f*
bronchial pattern, 290, 290*f*–291*f*, 290*b*, 293*f*
infective endocarditis effects on, 134*b*
interstitial patterns, 292–293, 292*f*, 292*b*–293*b*
lobes
consolidation of, 293–294, 294*f*
torsion of, 294–295, 363
neoplasia of
bronchoalveolar lavage findings, 352*f*
clinical features of, 352
diagnosis of, 352–353, 352*f*
metastatic, 1289–1290
prognosis for, 353
treatment of, 353
nodular interstitial pattern, 292, 292*f*, 292*b*
radiographs of, 288–295
vascular patterns of, 288–290, 289*f*, 289*b*
Lung aspiration, transthoracic, 299*t*, 310–312
complications of, 310–311
indications for, 310–311
techniques for, 311–312, 311*f*
Lung sounds
abnormal, 285–286
description of, 285–286
Lung stiffness, 4
Lung ultrasound, 33, 34*f*
Lutalyse. *see* $PGF_{2\alpha}$
Luteal ovarian cysts, 955*f*, 1034*t*–1036*t*
Luteinizing hormone, 942, 949
Lyme disease, 1128
diagnosis of, 1200
diagnostic tests for, 1194, 1200
etiology of, 1200
myocarditis caused by, 153
treatment of, 1200
Lymph nodes
anatomy of, 1407, 1408*f*
aspiration of, 1417
cytologic evaluation of, 1263–1264, 1264*f*
in dogs, 1410*f*
excision of, 1417–1418
functions of, 1407
histology of, 1407
lymphadenitis, 1264
lymphadenopathy. *see* Lymphadenopathy
neoplasia of, 1264
palpation of, 1408, 1410, 1410*f*
Lymphadenitis, 1264, 1408
Lymphadenopathy, 1407–1419
anemia associated with, 1414–1415
approach to, 1414–1418
blastomycosis and, 1502
classification of, 1409*t*
clinical features of, 1408–1411, 1410*f*
clinicopathologic features of, 1414–1415
cytologic evaluation of, 1416, 1417*f*
definition of, 1407–1408
disorders associated with, 1342*t*
distribution of, 1410
etiology of, 1407–1408
generalized, 1314*f*, 1407–1408, 1410*t*, 1417
hilar, 366*f*, 926
imaging of, 1415–1416
infectious, 1410–1411, 1411*f*
infiltrative, 1408, 1409*t*
inflammatory, 1409*t*
lymph node palpation in, 1410–1411, 1410*f*
management of, 1418
mandibular, 1295*f*, 1411*f*
massive, 1410–1411, 1411*f*
mesenteric, 1299*f*
pathogenesis of, 1407–1408
proliferative, 1409*t*
reactive, 1263–1264, 1408
regional, 1407–1408, 1410*t*
signs of, 1410
solitary, 1407–1408, 1410*t*
sublumbar, 1411*f*
Lymphangiectasia, intestinal, 495–497, 496*f*
Lymphocytic cholangitis, 570–572, 571*f*
Lymphocytic myocarditis, 153
Lymphocytic thyroiditis
antibody tests for, 778
description of, 767, 769*f*
serum T_4 concentrations, 775
Lymphocytic-plasmacytic gastritis, treatment of, 463
Lymphocytosis, 1379, 1379*b*, 1426*t*
Lymphoma, 1294–1310
alimentary, 1294, 1309, 1496
in cats, 1296*t*
central nervous system, 1307–1309, 1308*f*
chemotherapy for, 1302
CHOP chemotherapy protocols for, 1305–1306
clinical features of, 1294–1299
COP chemotherapy protocols for, 1302–1305, 1302*b*–1303*b*, 1304*f*
cutaneous, 1295–1296, 1296*f*, 1309
cytologic findings, 1262*f*, 1299, 1300*f*
definition of, 1294
diagnosis of, 1299–1301, 1496–1497
in dogs, 1296*t*
epidemiology of, 1294
epitheliotropic intestinal, 1296*f*, 1309
etiology of, 1294
extranodal, 1294, 1296*t*, 1307
feline leukemia virus and, 1294, 1295*t*
fine-needle aspiration of, 1299
hematologic features of, 1297–1298, 1298*f*
hypercalcemia associated with, 1298
hyperproteinemia associated with, 1298
imaging of, 1298–1299, 1299*f*
immunophenotyping of, 1300
intraabdominal, 1299
intranasal, 1297*f*, 1308*f*
large cell, 1299
with lymphocytic gastritis, 463–464
mediastinal, 1294, 1496
multicentric, 1294, 1295*f*, 1496
nasal, 265
nasopharyngeal, 1296
neural, 1297
ocular, 1296, 1309
physical examination of, 1296*t*
radiographic findings, 1298
Lymphoma *(Continued)*
radiotherapy for, 1301
remission of, 1301
renal, 1296–1297
retroorbital, 1308*f*
serum biochemical features of, 1297–1298
solitary, 1307
spinal, 1145
staging of, 1301
TNM staging of, 1300*t*
treatment of, 1301–1309
Lymphopenia, 1371–1380, 1379*b*
Lymphoplasmacytic rhinitis, 268–269
Lymphoplasmacytic splenitis, 1412–1413, 1412*t*
Lymphoplasmacytic synovitis, 1206
Lymphosarcoma, 656
Lysine, 386*t*–388*t*
Lysodren, 872–873. *see also* o,p'DDD

M

Macroadenoma, 749
Macrocytosis, 1345*t*
α_2-Macroglobulin, 684
Macrolides, 1437*t*–1438*t*
Macrophagic (granulomatous) inflammation, 305
Macrothrombocytosis, 1241*t*
Magnesium
hypermagnesemia, 933
hypomagnesemia, 844, 931–933, 932*b*
supplementation of
diabetic ketoacidosis treated with, 844
dosages, 934*t*
Magnesium hydroxide, 439*t*, 515*t*–517*t*
Magnesium sulfate
hypomagnesemia treated with, 932–933
muscle spasms in tetanus treated with, 1182
ventricular tachyarrhythmias treated with, 84
Magnetic resonance imaging (MRI)
description of, 18
feline acromegaly, 750*f*
intracranial tumors, 1081
larynx and pharynx, 273
lower respiratory tract disorders, 295–296
nasal imaging using, 250, 250*f*
neuromuscular system, 1066–1067, 1067*t*, 1068*f*–1069*f*
peripheral nerve sheath tumors, 1160*f*
Maintenance energy requirement, 898–899
Malabsorptive diseases
causes of, 401*b*
nonprotein-losing, 399
Maldigestive disease, 491
Male infertility
ejaculation disorders, 1004–1005
epididymitis as cause of, 1000–1001, 1000*f*–1001*f*
microbiology and, 997–1001, 998*f*, 999*t*–1000*t*, 1000*f*
orchitis as cause of, 1000–1001
semen evaluation, 1003–1004
spermatogenesis defects, 1005
Malignant melanoma, 448*t*
Mammary disorders
feline fibroadenomatous hyperplasia, 979, 979*f*
mastitis, 978–979, 979*f*, 1441*t*
Mammary hyperplasia, 1034*t*–1036*t*
Mandibular lymphadenopathy, 1295*f*, 1411*f*
Mannitol, 934*t*, 1185*t*–1186*t*
Manx cats, 1155
Marbofloxacin, 386*t*–388*t*, 1437*t*–1438*t*
Marginal neutrophil pool, 1372
Maropitant, 435, 437–438, 438*t*, 515*t*–517*t*
Massive lymphadenopathy, 1410–1411, 1411*f*

Mast cell tumors
biologic behavior of, 1329–1330
in cats, 1333–1334
clinicopathologic findings, 1328–1329
cutaneous, 1333
dermoepidermal, 1329*f*, 1333
description of, 1263*f*, 1290*t*
diagnosis of, 1330–1331, 1331*f*
disseminated, 1332–1333
in dogs, 1328–1333
epidemiology of, 1328
etiology of, 1328
prognosis for, 1331–1333
staging of, 1332*t*
treatment of, 1331–1333, 1332*t*
ulceration and, 470
Masticatory muscle myositis (MMM), 451, 1091*f*, 1174–1175, 1175*f*, 1252
Mastitis, 978–979, 979*f*, 1441*t*
Mastocytoma, 1328
Maternal behavior, inappropriate, 974–975, 975*f*
Maternal bonding, 974–975
Mean electrical axis, 45
Meclizine, 1185*t*–1186*t*
Medetomidine, 49*b*
Median nerve, 1158*t*
Mediastinal lymphomas, 1294, 1496
Mediastinal masses, 377–378, 377*f*
anterior, 1290
approach to, 1290–1293
cytological characteristics of, 1292*f*
description of, 360, 366
fine-needle aspiration of, 1291
radiographic findings, 1291*f*
types of, 1290*t*
Mediastinum, radiography of, 365–366
Medical adrenalectomy, 874
Medical history, 3–4, 3*b*
Medium-chain triglycerides (MCTs), 435
Medulla, 1037–1038
Mefoxin. *see* Cefoxitin
Megaesophagus
acquired, 455
in dysautonomia, 456
hypoadrenocorticism and, 885
regurgitation caused by, 346
upright feeding for animals with, 1171*f*
Megakaryocytes, 1395
Melanoma
cytologic findings, 1262*f*
metastasis of, 1290*t*
Melarsomine dihydrochloride
administration of, 199
heartworm disease treated with, 199, 199*b*
Melatonin, 749, 896*t*–897*t*
Melena, 402–403, 403*b*
Meloxicam, 1197*t*, 1209*t*–1210*t*, 1268*t*
Membranoproliferative glomerulonephritis, 678, 693*b*
Membranous glomerulonephritis, 678
Menace response, 1055, 1056*f*, 1084, 1085*f*, 1085*b*
Meninges, 134*b*
Meningiomas, 1081, 1145
Meningitis, 1117–1129
canine eosinophilic, 1122
general considerations in, 1117
parasitic, 1129
steroid-responsive meningitis-arteritis, 1118*f*, 1119, 1119*b*
Meningoencephalitis
canine eosinophilic, 1122
clotrimazole treatment as cause of, 263
distemper, 1125
parasitic, 1129
Meningoencephalomyelitis
bacterial, 1123–1124
granulomatous, 1064, 1087–1088, 1120–1121, 1121*b*
necrotizing, 1121–1122
toxoplasmosis as cause of, 1126
of unknown etiology, 1119–1120
Mental state, 1043
Mentation, abnormal, 1074
Meperidine, 629*t*–630*t*
Merck. *see* Finasteride
Meropenem, 1437*t*–1438*t*
Mesalamine, 441, 515*t*–517*t*
Mesangial cells, 675, 676*f*
Mesenchymal tissue, 1259
Mesenchymal tumors, 1260–1261
Mesenteric lymphadenopathy, 1299*f*
Mesenteric torsion, 499
Mesothelioma, 186, 513–514
Mestinon. *see* Pyridostigmine
Metabolic acidosis
in acute kidney injury, 691
bicarbonate therapy for, 844–845
in chronic kidney disease, 697
Metabolic alkalosis, hypochloremic-hypokalemic, 465–466
Metabolic encephalopathies, 1074
Metabolic epidermal necrosis, 615
Metabolic myopathies, 1178–1179, 1181
Metabolic storage diseases, 1153–1154
Metabolism disorders
hyperlipidemia. *see* Hyperlipidemia
obesity. *see* Obesity
polyphagia with weight loss, 898–899, 899*t*
Metacam. *see* Meloxicam
Metaldehyde, 1099*b*
Metamucil. *see* Psyllium
Metarubricytosis, 1345*t*
Metastatic cancer, 1289–1290, 1290*t*
Metered-dose inhaler (MDI), 327–328, 332*f*
Methadone, 629*t*–630*t*
Methicillin-resistant *Staphylococcus aureus*, 1539
Methimazole, 794, 796*t*, 896*t*–897*t*
Methocarbamol, 1185*t*–1186*t*
Methotrexate, 1204*t*, 1209*t*–1210*t*, 1305
Methoxyflurane, 49*b*
Methylprednisolone acetate, 386*t*–388*t*, 515*t*–517*t*, 1222*t*
Methylprednisolone sodium succinate, 1133–1134, 1185*t*–1186*t*
Methylxanthines
in cats, 327*b*
in dogs, 327*b*
Metoclopramide, 438, 440–441, 455–456, 515*t*–517*t*
prolactin release controlled using, 978
reproductive uses of, 1034*t*–1036*t*
Metoprolol
in cats, 90*t*–91*t*
characteristics of, 94*t*, 95
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Metronidazole, 444*t*, 515*t*–517*t*
bacterial infections treated with, 1437*t*–1438*t*
joint disease treated with, 1209*t*–1210*t*
toxicity caused by, 1116
Metronomic chemotherapy, 1273–1274
Mexiletine, 83–84
adverse effects of, 92
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
pharmacokinetics of, 92
Microalbuminuria, 662
Microangiopathic hemolysis, 1322
Microbiology, male fertility and, 997–1001, 998*f*, 999*t*–1000*t*, 1000*f*
Microcardia, 885
Microcytosis, 1345*t*
Microfilaricides, for heartworm disease, 207–208
Microthrombosis, 1404
Microvascular dysplasia, 610–611
Micturition
anatomy of, 730, 731*f*
disorders of, 730–737
drugs that affect, 733*t*–734*t*
neurologic control of, 1042–1043
physiology of, 730
Mifepristone, 960
Milbemycin, 386*t*–388*t*, 515*t*–517*t*
description of, 203
dosage of, 444*t*
nasal mites treated with, 263
Milk of Magnesia. *see* Magnesium hydroxide
Milk thistle, 590–591
Mineral oil, 346
Mineralocorticoids, 883–884, 887
Minipress. *see* Prazosin
Minocycline, 1437*t*–1438*t*
Minute virus, pregnancy loss and, 966
Mirtazapine, 515*t*–517*t*
Misoprostol, 439*t*, 440, 515*t*–517*t*, 960
Mites, nasal, 253*f*, 263
Mitotane, 872–875, 874*b*. *see also* o,p'DDD
Mitral dysplasia
description of, 112
dog breeds affected by, 102*t*
radiographic findings, 103*t*
Mitral insufficiency, 11
echocardiographic findings, 124*f*
murmurs associated with, 285
radiographic findings, 123*f*
Mitral regurgitation
in cats, 159
in dogs, 17*f*
echocardiographic findings, 125*f*–126*f*, 144*f*
in restrictive cardiomyopathy, 168
Mitral valve
echocardiography for, 26, 27*f*
enlargement of, 125*f*
Mitral valve motion, 26, 27*f*
M-mode echocardiography, 22–27
atrial fibrillation on, 81*f*
dilated cardiomyopathy on, 144*f*
measurements on, 23–27
mitral valve motion, 26, 27*f*
normal values for, 23–27, 25*t*
patent ductus arteriosus findings, 103–104, 105*f*
pericardial effusion findings, 179–180, 179*f*
views on, 23, 24*f*
Mobitz type I atrioventricular block, 43–44
Mobitz type II atrioventricular block, 43–44
Modified Karnovsky performance score, 1266*t*
Modified transudate pleural fluid, 361–363
Monoclonal gammopathies, 1421–1422, 1421*b*
Monoclonal hyperglobulinemia, 1415
Monocytosis, 1377–1378, 1378*b*, 1426*t*
Mononuclear-phagocytic cells, 1407
Monoparesis, 1045*t*
Morphine, 62*b*, 386*t*–388*t*
for acute pancreatitis, 628–631
analgesic uses of, 227*b*
dosage of, 1134*t*
stress relief using, 380*t*
Motility modifiers, 440–441
Mucopurulent nasal discharge, 240–241, 241*b*, 1444
Mucosal lesions, 389
Mucous membranes, 4–5, 5*b*
color of, 284
Multicat households, obesity and, 906
Multicentric lymphoma, 1294, 1295*f*, 1496
Multidrug-resistant infections, 443
Multimodal environmental modifications, 727–728, 728*b*
Multinodular adenomatous hyperplasia, 788
Multiorgan failure, 621
Multiple myeloma, 654*t*–655*t*
Murmurs
auscultation of, 9–11, 10*f*, 10*t*
characteristics of, 7
Murmurs *(Continued)*
congenital heart disease as cause of, 100
continuous (machinery), 9–11, 10*f*
decrescendo, 9–10, 10*f*
in degenerative atrioventricular valve disease, 122
diastolic, 9, 11
ejection, 9–10
functional, 9–11
grading, 10*t*
holosystolic, 9–10, 10*f*, 114
innocent, 9, 100
in kittens, 101*f*
mitral insufficiency, 285
"musical,", 9
nonpathologic, 9–11
in patent ductus arteriosus, 103
phonocardiographic configuration of, 9–10, 10*f*
physiologic, 10–11
presystolic, 9
in pulmonary hypertension, 115
in puppies, 101*f*
"regurgitant,", 9–10
systolic, 9–11
systolic ejection, 11
to-and-fro, 11
Muscle atrophy, 1047
Muscle biopsy, 1073
Muscle size, 1047
Muscle spasms, in tetanus, 1182
Muscle tone
involuntary alterations in, 1181–1183
in screening neurologic examination, 1047
Muscular dystrophy, 1179
Musculocutaneous nerve, 1158*t*
Musculoskeletal disorders, 1023–1025, 1024*f*
Musculoskeletal system, 134*b*
Myasthenia gravis, 1042, 1169–1172, 1171*f*, 1171*b*, 1250–1251, 1251*t*
Mycobacterium spp.
culture of, 1431
M. avium, 1259*f*, 1429–1430
Mycophenolate mofetil, 1225*t*, 1227–1228, 1251*t*, 1255*t*–1256*t*
Mycoplasma spp., 1440*t*
antibiotics for, 1441*t*, 1446
clinical findings of, 1465
diagnosis of, 1465–1466
epidemiology of, 1464–1465
etiology of, 1464–1465
M. canis, 1465–1466
M. cynos, 321
M. felis, 1465
M. haemofelis, 1211
nasal cultures for, 255
polyarthritis caused by, 1199
prevention of, 1466
treatment of, 1466
zoonotic aspects of, 1466
Mycoplasmal bronchitis, 329*t*
Mycosis fungoides, 1295–1296, 1296*f*
Mycotic infections, 1128
antifungal drugs for, 1504*t*
blastomycosis. *see* Blastomycosis
coccidioidomycosis, 1505–1507
cryptococcosis. *see* Cryptococcosis
histoplasmosis, 1510–1511
nasal. *see* Nasal mycoses
polysystemic, 1502–1513
Mydriasis, 1086
Myelinosis, 919
Myelitis, 1117
Myelodysplastic syndromes, 1312–1313, 1355*b*, 1385–1386
Myelofibrosis, 1355*b*, 1386, 1386*f*
Myelography, 1064–1065, 1065*f*–1066*f*, 1137, 1138*f*
Myelomalacia, 1140–1141
Myelophthisis, 1355*b*, 1385
Myeloproliferative disease, 1311
Myelosuppression, 1280

Myocardial diseases
in cats
arrhythmogenic right ventricular cardiomyopathy, 171
corticosteroid-associated heart failure, 171–172
description of, 158
hypertrophic cardiomyopathy. *see* Hypertrophic cardiomyopathy, in cats
myocarditis, 172
dilated cardiomyopathy, 169–171
in dogs, 141–157
arrhythmogenic right ventricular cardiomyopathy, 148–150
dilated cardiomyopathy. *see* Dilated cardiomyopathy, in dogs
doxorubicin-induced cardiotoxicity, 150
free radicals, 151
hypertrophic cardiomyopathy. *see* Hypertrophic cardiomyopathy, in dogs
ischemic myocardial disease, 151–152
L-carnitine deficiency, 151
secondary causes of, 150–152
tachycardia-induced cardiomyopathy, 152
ischemic, in dogs, 151–152
restrictive cardiomyopathy, 168–169, 169*f*
Myocardial dysfunction, sepsis-induced, 155
Myocardial failure, 58–59. *see also* Heart failure
Myocardial hypertrophy, 105
in cats, 158
as compensatory response, 167
description of, 55–56
hyperthyroidism and, 162
Myocardial ischemia, 159
Myocardial strain, 32
Myocardial thickening, 160–162
Myocarditis
bacterial, 153
in cats, 172
clinical findings of, 154–155
diagnosis of, 154–155
in dogs, 153–155
drug-related, 155
infective, 153–154
Lyme, 153
lymphocytic, 153
noninfective, 154–155
parvoviral, 153
protozoal, 153–154
traumatic, 155
treatment of, 155
viral, 153, 172
Myoclonus, 1181–1183
Myocyte hypertrophy, 55
Myopathies
acquired metabolic, 1178–1179
canine idiopathic polymyositis, 1176
centronuclear, 1179–1180, 1180*f*
dermatomyositis, 1177, 1177*f*
extraocular myositis, 1175–1176, 1175*f*
feline idiopathic polymyositis, 1176–1177
glucocorticoid excess, 1178
hypokalemic polymyopathy, 1178–1179, 1178*f*
hypothyroidism, 1178
inflammatory, 1174–1178
inherited, 1179–1181
masticatory muscle myositis, 451, 1091*f*, 1174–1175, 1175*f*
metabolic, 1178–1179, 1181
muscular dystrophy, 1179
myotonia, 1180–1181
Myositis
atrophic, 451
dermatomyositis, 1177, 1177*f*
extraocular, 1175–1176, 1175*f*
immune-mediated, 1252–1253, 1253*b*
Myositis *(Continued)*
masticatory muscle, 451, 1091*f*, 1174–1175, 1175*f*, 1252
protozoal, 1177–1178
Myotomy, cricopharyngeal, 452
Myotonia, 1180–1181
Myxedema, 769–770
Myxedema coma, 772
Myxomatous degeneration, 119

N

N-acetyl-β-D-glucosaminidase (NAG), 660
N-acetylcysteine, idiopathic pulmonary fibrosis treated with, 351
Nadolol, 94*t*
Nanophyetus salmincola, 413
Nares
rhinoscopy of, 251*f*
stenotic, 279, 279*f*
Nasal aspergillosis
description of, 242, 242*f*
diagnosis of, 256
radiographic signs of, 249*b*, 250*f*
Nasal biopsy
complications of, 255
hemorrhage caused by, 255
indications for, 253–255
nasal flush, 254
nasal swabs, 254
pinch biopsy, 254–255, 254*f*
techniques for, 253–255
turbinectomy, 255
Nasal capillariasis, 263–264
Nasal catheters, 383–384, 384*f*
Nasal cavity, 247–256
Nasal cultures, 255–256
Nasal discharge
after nasal aspergillosis treatment, 260
classification of, 240–241
computed tomography evaluations, 244
diagnostic approach to, 241–244, 242*f*, 243*b*
differential diagnosis of, 241*b*
etiology of, 240–241
mucopurulent, 240–241, 241*b*, 1444
physical examination of, 241
serous, 241*b*
serous or mucopurulent, 257
Nasal disease, clinical manifestations of, 240–246
Nasal flush, 254
Nasal foreign bodies
description of, 240
radiographic signs of, 249*b*
Nasal imaging
computed tomography, 250, 250*f*
frontal sinus exploration, 252
indications for, 247
magnetic resonance imaging, 250, 250*f*
radiography, 247–248, 248*f*–250*f*, 249*b*
rhinoscopy, 250–252, 251*f*–252*f*, 253*b*
Nasal lymphoma, 265
Nasal mites, 253*f*, 263
Nasal mycoses, 260–263
aspergillosis. *see* Aspergillosis, nasal
cryptococcosis, 260
Nasal neoplasia, 249*b*
Nasal polyps, 264
Nasal swabs, 254, 259*f*
Nasal tumors, 265–266
Nasoesophageal tubes
feeding uses of, 435
placement of, 567*f*, 567*b*
Nasopharyngeal lymphoma, 1296
Nasopharyngeal polyps
feline, 264, 264*f*
peripheral vestibular disease caused by, 1114
radiographic signs of, 249*f*, 249*b*
Nasopharynx
caudal, 251–252, 251*f*
rhinoscopy of, 251
Natriuretic peptides
description of, 13
dilated cardiomyopathy and, 144
Nausea, chemotherapy-related, 1280
Nebulization
airway hydration using, 342
oxygen supplementation use of, 383
Nebulizers, 342, 342*f*
Neck pain, 1053, 1053*f*–1054*f*, 1055*b*, 1117–1119, 1118*b*
Necrotizing leukoencephalitis, 1122
Necrotizing meningoencephalomyelitis, 1121–1122
Necrotizing splenitis, 1412–1413, 1412*t*
Nematodes, 1532–1536, 1533*t*–1535*t*
Ollulanus tricuspis, 465
Physaloptera rara, 464–465
Nemex. *see* Pyrantel; Pyrantel pamoate
Neo-Mercazole. *see* Carbimazole
Neomycin, 515*t*–517*t*, 1437*t*–1438*t*
Neonates
exam, anomalies apparent at, 1013–1033, 1013*f*, 1015*f*–1016*f*, 1021*f*
fading, 1021–1022, 1021*f*–1022*f*
orphans' special needs, 1022–1023, 1023*f*
pediatric systemic abnormalities, 1023–1033
resuscitation of, 1007–1013, 1008*f*–1012*f*, 1008*b*–1010*b*, 1014*t*, 1016*t*, 1018*t*–1020*t*
Neonatology, 1007–1034
Neoplasia, 613–615. *see also* Cancer
canine thyroid. *see* Canine thyroid neoplasia
in cats, 576–577
intracranial, 1081–1082, 1082*f*
laryngeal, 281
lung
bronchoalveolar lavage findings, 352*f*
clinical features of, 352
diagnosis of, 352–353, 352*f*
metastatic, 1289–1290
pleural effusion caused by, 364, 366*f*
prognosis for, 353
treatment of, 353
prostatic, 1003, 1003*f*
spinal cord, 1142
clinical features of, 1145
description of, 1145–1147, 1145*f*
diagnosis of, 1145–1146
treatment of, 1146–1147
testicular, 996–997, 996*f*–997*f*
Neoplasm(s), 1322–1337. *see also* Cancer
esophageal, 460, 460*f*
gastric, 471–472
oral cavity
in cats, 449
in dogs, 447–449, 448*t*
Neoplastic effusion, 375–376
Neoplastic lymphocytosis, 1319
Neoplastic pericardial effusions, 182
Neorickettsia helminthoeca, 1481
Neospora caninum, 965–966, 1127, 1127*f*, 1430, 1440*t*, 1520, 1521*f*
Neosporosis, 154, 965–966, 1118*t*, 1127–1128, 1127*f*, 1520–1521
Neostigmine methylsulfate, 1185*t*–1186*t*, 1251*t*, 1255*t*–1256*t*
Nephrectomy, 652
Nephrogenic diabetes insipidus, 654*t*–655*t*, 742, 742*b*
Nephrotic syndrome
definition of, 675
hypercoagulable state of, 684
Nephrotoxicant, 686–687
Nephrotoxicity, chemotherapy-related, 1284
Nerve biopsy, 1073
Nerve conduction velocities, 1072
Nervous system
brain. *see* Brain
diagnostic tests for, 1063–1073
imaging, 1064–1067
routine, 1064
Nervous system *(Continued)*
lesion localization and, 1037–1043, 1038*b*
spinal cord. *see* Spinal cord
Neural lymphoma, 1297
Neuroanatomic regions, 1038*b*
Neuroaxonal dystrophy, 1080
Neurodegenerative disorders, 1116
Neuroendocrine reflex, 974–975
Neuroepithelioma, 1145
Neurogenic dysphagia, 391
Neurogenic keratitis, 1160–1161
Neurologic disorders, 1029–1031, 1031*f*
Neurologic examination, 1063
lesion localization, 1037–1062
screening
ataxia, 1045–1046, 1046*f*, 1046*b*
components of, 1043*b*
consciousness, disorders of, 1043*t*
description of, 1043–1061
gait, 1045–1046
head tilt, 1043–1044, 1044*f*
mental state, 1043
muscle size, 1047
muscle tone, 1047
pain, 1052*f*, 1053–1054
paralysis, 1045, 1045*t*
paresis, 1045, 1045*t*
postural reactions, 1046–1047, 1048*f*
posture, 1043–1045, 1044*f*
sensory evaluation, 1051–1052, 1052*f*
spinal reflexes. *see* Spinal reflexes
urinary tract function, 1054
systemic abnormalities, search for, 1063
Neurologic lesions
diagnostic approach to, 1061, 1061*b*
animal history, 1061
disease onset and progression, 1061
localization of, 1061
Neuromuscular junction (NMJ)
description of, 1041–1042, 1157
disorders of, 1164*b*, 1168–1172
acute fulminating myasthenia gravis, 1167*t*, 1170
botulism, 1167*t*, 1169
myasthenia gravis, 1169–1172, 1171*f*, 1171*b*
tick paralysis, 1167*t*, 1169
Neuromuscular system
diagnostic tests of, 1063–1073
biochemical profile, 1063
brainstem auditory evoked response, 1072
cerebrospinal fluid analysis. *see* Cerebrospinal fluid
computed tomography, 1066, 1067*f*
electrodiagnostic testing, 1071–1072
electroencephalography, 1072
electromyography, 1071–1072
electroretinography, 1072
immunology, 1064
laboratory studies, 1063–1064
magnetic resonance imaging, 1066–1067, 1067*t*, 1068*f*–1069*f*
microbiology, 1064
muscle biopsy, 1073
myelography, 1064–1065, 1065*f*–1066*f*
nerve biopsy, 1073
nerve conduction velocities, 1072
radiographs, 1064
serology, 1064
spinal radiographs, 1064
lesions of, 1042*b*
muscle, 1042
neuromuscular junction, 1041–1042
peripheral nerves, 1041
Neuronal abiotrophies, 1153
Neurontin. *see* Gabapentin
Neuroophthalmologic evaluation, 1084–1086
dazzle reflex, 1085–1086
eyeball position and movement disorders, 1086

Neuroophthalmologic evaluation *(Continued)*
lacrimal gland function, 1086
menace response, 1084, 1085*f*, 1085*b*
pupil size and symmetry, 1086
pupillary light reflex, 1084–1085, 1085*f*, 1086*t*
vision, 1084
Neuroparalytic keratitis, 1160–1161
Neutropenia, 1372–1375
afebrile, 1279–1280, 1375
causes of, 1244*t*, 1373*b*
chemotherapy-related, 1278, 1279*f*
comorbid conditions with, 1373
corticosteroid-responsive, 1375, 1375*f*
definition of, 1372–1373
evaluation of, 1374, 1374*f*
febrile, 1279–1280
fever associated with, 1426*t*
immune-mediated, 1244–1245
parvoviral enteritis with, 1373–1374
pathogenesis of, 1375
signs of, 1373–1374
Neutrophil(s)
description of, 1192
giant, 1372
morphologic abnormalities of, 1371–1372
physiology of, 1372, 1372*f*
pools of, 1372*f*
stimulation of production, 1375
toxic, 1371–1372, 1372*f*
Neutrophil gelatinase-associated lipocalin (NGAL), 660
Neutrophilia, 134, 1375–1376, 1376*b*, 1426*t*
Neutrophilic cholangitis, 568*t*, 569–570, 569*f*
New methylene blue stain, 1258
New York Heart Association heart failure classification scheme, 59–60
Nexium. *see* Esomeprazole
Niacin, 913
Nifurtimox, 1526
Nitazoxanide, 1443
Nitrates, 71–72
Nitric oxide, 58, 221
Nitroglycerin, 63
Nitroimidazoles, 1437*t*–1439*t*
Nitroprusside, 217*t*
Nizatidine, 439–441
Nizoral. *see* Ketoconazole
Nocardia spp., 1429–1430
Nocturia, 649
Nodular hyperplasia, 613
Nonabsorbable aminoglycosides, 442
Nonbronchoscopic bronchoalveolar lavage, 305–310
in cats, 307, 307*f*
complications of, 305–307, 306*f*
in dogs, 307–308, 308*f*
indications for, 305–307, 306*f*
Noncirrhotic portal hypertension, 609*f*, 610–611
Nonerosive immune-mediated polyarthritis, 1187, 1188*f*, 1202–1204, 1202*b*
Noninfectious inflammatory disease, 1143
Noninfective myocarditis, 154–155
Nonischemic priapism, 996
Nonproductive cough, 282
Non-protein-losing malabsorptive disease, 399–401, 491–492
Nonregenerative anemia, 1218*t*–1219*t*, 1351–1355, 1352*b*, 1358*f*, 1426*t*
Nonseptic exudates, 362*f*, 363
Nonspecific reactive hepatitis, 617
Nonsteroidal anti-inflammatory drugs, 629*t*–630*t*
acute kidney injury caused by, 686–687
degenerative joint disease treated with, 1197*t*
gastrointestinal ulceration/erosion treated with, 470–471
Nonthyroidal Illness Syndrome (NTIS), 779–780, 780*f*
NT-proBNP, 13–14, 162–163
Nuclear cardiology, 18
Nuclear hypersegmentation, 1372
Nuclear imaging, 296
Nucleus of Onuf, 730
Nutrition. *see also* Diet
for acute pancreatitis, 631–632, 631*b*, 632*f*
Nutritional supplementation, 435–437
Nutritional therapy
nasoesophageal tube feeding, 435
orogastric tube feeding, 435
Nyquist limit, 28
Nystagmus, 1055–1057, 1058*f*, 1109

O

Obesity, 899–907
adverse effects of, 899*b*
body condition scoring for, 901, 902*f*–903*f*
body weight measurements, 901
definition of, 899
diagnosis of, 901
dietary considerations for, 73
dog breeds commonly affected, 900*b*
drug and, 901
endocrine abnormalities associated with, 901
etiology of, 899–901, 900*b*
nutritional considerations, 903, 904*t*–906*t*
prevention of, 907
treatment of, 901–907, 904*t*–906*t*
Obstetrics. *see* Pregnancy
Obstructive laryngitis, 280
Obturator nerve, 1158*t*
Occult blood, in urine, 665
Occult hyperadrenocorticism, 878
Octreotide, 441. *see also* Somatostatin
Ocular lymphoma, 1296, 1309
Oculocephalic reflex, 1109
Oculomotor nerve, 1055, 1056*t*
Olfactory nerve, 1056*t*
Oliguria, 688*f*
Ollulanus tricuspis, 463, 465
Olsalazine, 441, 515*t*–517*t*
Omega-3 fatty acids, 72–73
Omeprazole, 439*t*, 515*t*–517*t*
immune-mediated diseases treated with, 1255*t*–1256*t*
Omnizole. *see* Thiabendazole
Omphalitis, 1020
Oncogenes, 1269
Oncologic disorders
cancer. *see* Cancer
leukemia. *see* Leukemias
lymphoma. *see* Lymphoma
Ondansetron, 438, 515*t*–517*t*
o,p'DDD, 896*t*–897*t*
Open-mouth breathing, 4, 4*f*
Ophthalmologic disorders, 1031
Opisthotonos, 1181
Optic chiasm lesions, 1088
caudal, 1088–1089, 1089*f*
Optic disk lesions, 1087–1088
Optic nerve
description of, 1055, 1056*t*
lesions of, 1087–1088
Optic neuritis, 1087–1088, 1088*b*
Optic radiation, 1084
Oral cavity
imaging of, 416–419
squamous cell carcinoma of, 448*t*
Oral cavity disorders
atrophic myositis, 451
cricopharyngeal achalasia/dysfunction, 451–452
feline eosinophilic granuloma, 449–450
feline lymphocytic-plasmacytic gingivitis, 450–451
gingivitis, 450
masticatory muscle myositis, 451
periodontitis, 450
Oral cavity disorders *(Continued)*
salivary gland necrosis, 447
sialoadenitis, 447
sialoadenosis, 447
sialocele, 447
stomatitis, 450, 450*b*
Oral cavity neoplasms
in cats, 449
in dogs, 447–449, 448*t*
Oral dexamethasone suppression test, 866*t*, 870
Oral hypoglycemic drugs, 835–837
Oral rehydration therapy, 433–434
Orbax. *see* Orbifloxacin
Orbifloxacin, 386*t*–388*t*, 515*t*–517*t*, 1437*t*–1438*t*
Orchitis, 1003–1004
Organophosphates, 1099*b*
Ormetoprim-sulfadimethoxine, 1437*t*–1438*t*
Orogastric tube feeding, 435
Oropharyngeal disorders
salivary gland necrosis, 447
sialoadenitis, 447
sialoadenosis, 447
sialocele, 447
Orthopnea, 379
Oslerus osleri, 296, 297*t*, 337–338, 338*f*
Osmolality, urine, 662–663
Osmotic diuretics, 691
Osmotic laxatives, 445
Ossifying epulis, 448*t*
Osteoarthritis. *see* Degenerative joint disease
Osteolysis, 1146
Osteomyelitis, 1440*t*, 1443
Osteopetrosis, 1355*b*, 1386
Osteosarcoma
appendicular, 1325–1326
chemotherapy for, 1327*b*
clinical features of, 1325–1326
diagnosis of, 1326
epidemiology of, 1325
etiology of, 1325
metastasis of, 1290*t*
prognosis for, 1327–1328
radiographic findings, 1326, 1326*f*
round cells associated with, 1260–1261
treatment of, 1327–1328
Osteosclerosis, 1355*b*, 1386
Otitis media-interna
facial nerve paralysis caused by, 1161*f*
imaging of, 1112–1113
peripheral vestibular disease caused by, 1112–1113, 1112*f*
treatment of, 1113, 1161, 1440*t*
Ovarian cysts, 955–956, 955*f*–956*f*
Ovarian neoplasias, 954
Ovarian remnant syndrome, 982–983, 983*f*
Ovariohysterectomy, 973–974, 1446
Overactive bladder, 736–737
Overflow incontinence, 735–736
Overhydration, 358, 433
Ovulation
in bitch
estrogen levels, 940–942
luteinizing hormone levels, 942
progesterone levels, 942–943
timing of, 940–945
ultrasonography detection of, 943, 943*f*–944*f*
induction
during estrus, 1034*t*–1036*t*
in queens, 949
Ovuplant. *see* Deslorelin
Oxacillin, 1437*t*–1438*t*
Oxybutynin, 733*t*–734*t*
Oxygen cages, 379, 383*t*, 385
Oxygen hoods, 383, 384*f*
Oxygen masks, 383
Oxygen saturation
of hemoglobin, 318
pulse oximetry evaluation of, 65
Oxygen supplementation
administration of, 383, 383*t*, 384*f*
endotracheal tubes for, 384
flow rates, 383*t*
heart failure treated with, 61
indications for, 383
pulmonary parenchymal disorders treated with, 381
tracheal tubes for, 384–385
Oxyhemoglobin dissociation curve, 315, 316*f*
Oxymetazoline, 386*t*–388*t*
Oxymorphone, 227*b*, 1134*t*
Oxytocin, 969–972, 1034*t*–1036*t*

P

Packed cell volume, 1420
Packed red blood cell transfusion, 1237
Pain
abdominal, 408, 410*b*, 519
assessment of, 1052*f*–1054*f*, 1053–1054
deep, 1052*f*
joint, 1203*f*
neck, 1053, 1053*f*–1054*f*, 1055*b*, 1117–1119, 1118*b*
polyarthritis, 1187
spinal, 1053*f*–1054*f*, 1134*t*
Palpebral reflex, 1056*t*
PAM. *see* Pralidoxime chloride
Pamidronate, 927, 934*t*, 1327*b*
Panacur. *see* Fenbendazole
Pancreas
anatomy of, 620, 622*t*
biopsies, 558–559
exocrine. *see* Exocrine pancreatic insufficiency
function of, 622*t*
normal canine, 621*f*
structure, 622*t*
Pancreatic disease, 518–530
diagnostic approach to, 532
drugs used in, 643*t*–648*t*
gastrointestinal signs with, 518–519, 519*b*
Pancreatic endocrine function, tests of, 540
Pancreatic enzymes, 515*t*–517*t*
assays of, 625–626
in exocrine pancreatic insufficiency, 639
Pancreatic exocrine function, tests of, 540
Pancreatic inflammation, specific tests of, 538–540, 539*t*
Pancreatic lipase immunoreactivity (PLI), 538–539, 625–626
Pancreatic secretory trypsin inhibitor, 621
Pancreatic system
diagnostic approach for, 531–545
diagnostic tests for, 531–560
Pancreatitis, 620–636
acute
analgesia for, 628–631, 629*t*–630*t*
antibiotics for, 633
antiemetics for, 632–633
biliary tract obstruction and, 633
in cats, 624*f*
chronic pancreatitis *versus*, 623*t*
clinical features of, 621–625, 623*t*, 624*f*
description of, 620
diagnosis of, 625–627
diagnostic imaging of, 626–627, 627*f*
etiology of, 621, 623*t*
fluid analysis for, 627
gastroprotectants for, 633
histopathology of, 627
intravenous fluids and electrolytes for, 628
necrotizing, 628
nutrition for, 631–632, 631*b*, 632*f*
pancreatic enzyme assays, 625–626
pathogenesis of, 621, 623*t*

Pancreatitis *(Continued)*
plasma transfusion for, 628
practice for feeding in, 631*b*
prognosis for, 627–633
prognostic factors of, 626
prognostic indicators of, 626
risk factors for, 623*t*
treatment of, 627–633
ultrasonography of, 627*f*
chemotherapy-related, 1283
chronic
acute pancreatitis *versus*, 623*t*
autoimmune, 634
biopsy of, 636
clinical features of, 635
definition of, 633
description of, 620
diagnosis of, 635–636
etiology of, 633–634
idiopathic, 634, 634*f*
pathogenesis of, 633–634
prognosis for, 636
signs of, 635
treatment of, 636
Pancreazyme, 440. *see also* Pancreatic enzymes
Pancytopenia, 1345*t*, 1381, 1382*b*, 1383*f*–1384*f*, 1415
Panting, in dogs, 7
Pantoprazole, 439*t*, 515*t*–517*t*
Papillary muscle hypertrophy, 162
Papilledema, 1088
Papillomatosis, 448*t*
Paracetamol. *see* Acetaminophen
Paradoxic septal motion, 25
Paradoxical breathing, 360, 382
Paradoxical vestibular syndrome, 1111
Paragonimus infections, 376
Paragonimus kellicotti, 296, 297*f*, 344–345, 345*f*
lower respiratory tract diseases caused by, 297*t*
Parainfluenza virus vaccination, 1455
Paralysis, 1045
definition of, 1045
facial nerve, 1160, 1160*f*–1161*f*
laryngeal. *see* Laryngeal paralysis
lower motor neuron, 1163*f*, 1164*b*
tick, 1167*t*, 1169
trigeminal nerve, 1161–1162, 1162*f*
Paranasal sinuses, 240, 247–256
Paraneoplastic polyneuropathy, 1165
Paraneoplastic syndromes, 1291
Paraparesis, 1045*t*
Paraphimosis, 993–996, 994*f*
Paraplegia, 1045*t*
Parasites. *see also specific parasite*
alimentary tract, 485–491
cutaneous diseases caused by, 1430
encephalitis caused by, 1129
fecal evaluation, 413
lower respiratory tract, 296–298, 297*f*, 297*t*
meningitis caused by, 1129
myelitis caused by, 1129
nasal, 263–264
pulmonary parenchymal disorders caused by, 344–346
urinary tract, 651–652
Parasitic granulomas, 292
Parasympathetic preganglionic motor neurons, 730
Parathyroid adenoma, 758–759, 759*f*
Parathyroid carcinoma, 758–759
Parathyroid gland, disorders of, 758–766
Parathyroid hormone, 695–696, 759*t*
secretion of, 758
serum, measurement of, 765
Parathyroid hormone-related peptide, 760, 926
Parathyroid mass, 760
Parenchymal organ perfusion, 1404
Parenteral fluid solutions, 917*t*
Parenteral nutrition, 437
total, for acute pancreatitis, 632
Paresis, 1045, 1045*t*
Paroxysmal AV reciprocating tachycardia, 80–82
Paroxysmal dyskinesias, 1105–1106
Paroxysmal events
nonepileptic, 1093, 1094*b*
seizures and, 1093–1108
Paroxysmal ventricular tachycardia, 2*f*
in Boxers, 149*f*
description of, 149*f*
Partial or intermittent chronic gastric volvulus, 469, 469*f*
Partial pericardiectomy, 182
Partial pressure of carbon dioxide ($PaCO_2$), 313
Partial pressure of oxygen (PaO_2), 313
Partially hydrolyzed diets, 435
Parturient disorders, 968–974
agalactia. *see* Mammary disorders
dystocia. *see* Dystocia
mammary disorders
agalactia, 978
feline fibroadenomatous hyperplasia, 979, 979*f*
galactostasis, 978, 978*f*
mastitis, 978–979, 979*f*
postpartum
eclampsia, 975–976
endometritis, 977–978, 977*f*
inappropriate maternal behavior, 974–975, 975*f*
metabolic, 975–976
overview of, 974–979
placental sites subinvolution, 976–977, 976*f*
uterine, 976–978
Parturition, 968–974
dystocia during. *see* Dystocia
normal, 968–974
Parvoviral enteritis
canine, 476–478, 477*b*
feline, 478–479
neutropenia with, 1373–1374
Parvoviral myocarditis, 153
Parvovirus, 1432
Patellar reflex, 1047, 1049*f*, 1049*t*
Patent ductus arteriosus
clinical features of, 103
compensatory mechanisms for, 102
descending aorta dilation caused by, 16–17
diagnosis of, 103–104
dog breeds affected by, 101–105, 102*t*
echocardiographic findings in, 103–104
etiology of, 101–103
hyperkinetic arterial pulses associated with, 101, 102*f*
murmurs associated with, 11, 103
pathophysiology of, 101–103
prognosis for, 104–105
pulmonary artery pressure changes, 102–103
radiographic findings, 103, 103*t*, 104*f*
treatment of, 104–105
Patent foramen ovale, 111
Pediatric systemic abnormalities, 1023–1033
cardiovascular disorders, 1023
dermatologic disorders, 1031–1032, 1032*f*
endocrinologic, 1032–1033, 1033*f*
gastrointestinal disorders, 1027–1029, 1029*f*–1030*f*
musculoskeletal disorders, 1023–1025, 1024*f*
neurologic disorders, 1029–1031, 1031*f*
ophthalmologic disorders, 1031
respiratory disorders, 1023, 1023*f*–1024*f*
urogenital disorders, 1025–1027, 1025*f*–1027*f*
vaccination, 1033, 1033*f*
Pediatrics, 1007–1034
Pelger-Huët anomaly, 1372
Pelvic fracture, pelvic canal obstruction, 506
Pelvic limb hopping, 1048*f*
Pelvic limb withdrawal reflex, 1047–1049, 1049*f*, 1049*t*
Penicillin G, 1437*t*–1438*t*
Penicillins, 1437*t*–1438*t*
Penicilliosis, 256
Penis
canine, 993–994, 994*f*
mucosa, 995*f*
necrosis of, 993
persistent frenulum of, 992, 992*f*
Pentasa. *see* Mesalamine
Pentobarbital, 1185*t*–1186*t*
Pentosan polysulfate, 728*b*, 1197*t*, 1209*t*–1210*t*
Pentoxifylline, 1228–1229, 1253, 1255*t*–1256*t*
Pepcid. *see* Famotidine
Pepto-Bismol. *see* Bismuth subsalicylate
Peracute hemolysis, 1354
Percutaneous balloon pericardiotomy, 182
Perfusion, 4–5
Perfusion pressure, 212
Periactin. *see* Cyproheptadine
Perianal fistulae, 403–404, 505
Perianal gland tumors, 506
Perianal neoplasms, 506
Pericardial cysts, 175–176
Pericardial disease, 174–189
constrictive, 184–185
description of, 174
pericardial effusion. *see* Pericardial effusion
peritoneopericardial diaphragmatic hernia, 174–175, 175*f*–176*f*
Pericardial effusion
cardiac silhouette associated with, 178–179, 179*f*
cardiac tamponade caused by, 177–178
cardiac tumor as cause of, 187
central venous pressure levels in, 181
clinical features of, 178
clinicopathologic findings, 178
congestive heart failure and, 176
diagnosis of, 178
echocardiographic findings, 179–181, 179*f*–180*f*
electrocardiographic findings, 181–183
etiology of, 176
exudative, 177
fluid types, 176
hemorrhagic, 176–177, 182–183
idiopathic, 176–177, 181–182
neoplastic, 182
pathophysiology of, 177
percutaneous balloon pericardiotomy for, 182
pericardiocentesis for, 183–184
prognosis for, 181
radiographic findings, 178–179, 179*f*
recurrent, 181–182
transudative, 177
treatment of, 181
Pericardiocentesis
complications of, 184
echocardiographic monitoring during, 183
equipment for, 183
pericardial effusion applications of, 183–184
technique for, 183
Pericarditis, infectious, 182
Pericardium
anatomy of, 174
congenital defects of, 176
Perineal hernia, 504–505
Perineal reflex, 1049*t*, 1050, 1051*f*
Perinephric pseudocysts, 656–657, 657*f*
Periodontitis, 450
Periosteal proliferative polyarthritis, 1189
Peripheral nerve sheath tumors (PNSTs), 1157–1161, 1159*f*–1160*f*
Peripheral nerves, 1041
disorders of, 1157–1173, 1164*b*
focal neuropathies in, 1157–1163
general considerations in, 1157
polyneuropathies in, 1163–1168
Peripheral nervous system, 1041
Peripheral neuropathy, 848
Peripheral parenteral nutrition, canine parvoviral enteritis, 478
Peripheral vestibular disease in cats, 1111*f*
causes of
aminoglycoside ototoxicity, 1114–1115
chemical ototoxicity, 1115
congenital vestibular syndromes, 1114
feline idiopathic vestibular syndrome, 1114
geriatric canine vestibular disease, 1113–1114, 1113*f*
hypothyroidism, 1115
nasopharyngeal polyps, 1114
neoplasia, 1114
otitis media-interna, 1112–1113, 1112*f*
trauma, 1114
clinical findings of, 1110*b*
lesion localization, 1109
Peripheral vestibular system, 1110*f*
Peritoneal fluid analysis, 423
Peritoneopericardial diaphragmatic hernia, 174–175, 175*f*–176*f*
Peritoneum, disorders of, 510–514
feline infectious peritonitis, 514
hemoabdomen, 513
septic peritonitis, 510–512
Peritonitis
feline infectious, 514
ancillary tests for, 1118*t*
clinical findings of, 1489*b*
description of, 1488
effusive, 1488, 1490*f*
nonseptic exudate and, 363
pregnancy loss and, 966
signs of, 1126
treatment of, 1490–1491
vaccine for, 1454
nonseptic exudate and, 363
semen, 961–962, 961*f*
septic. *see* Septic peritonitis
Perivulvar dermatitis, 981*f*
Persistent left cranial vena cava, 117
Persistent penile frenulum, 992, 992*f*
Persistent right aortic arch
dog breeds affected by, 102*t*
radiographic findings, 103*t*
Petechiae, in mucous membrane, 4–5
$PGF_{2\alpha}$, 1034*t*–1036*t*
pH, of urine, 664–665
Pharyngeal diseases
clinical manifestations of, 271–272
clinical signs of, 271–272
differential diagnosis of, in dogs and cats, 272, 272*b*
Pharyngeal dysphagia, 452
Pharyngoscopy, 273–276, 274*f*
Pharyngostomy tubes, 436
Pharynx
computed tomography for, 273
diagnostic tests for, 273–276
disorders of, 277–281
fluoroscopy for, 273
imaging of, 416–419
laryngoscopy for, 273–276, 274*f*–275*f*
magnetic resonance imaging for, 273
pharyngoscopy for, 273–276, 274*f*
radiography for, 273, 274*f*
ultrasonography for, 273
Phenobarbital
neurologic disorders treated with, 1185*t*–1186*t*
seizures treated with, 1101–1102
thyroid gland function tests affected by, 781
Phenothiazine derivatives, 438, 438*t*

Phenoxybenzamine, 733*t*–734*t*, 891, 896*t*–897*t*, 1185*t*–1186*t*
Phentolamine, 217*t*
Phenylephrine, 386*t*–388*t*
Phenylephrine hydrochloride
  in cats, 90*t*–91*t*
  description of, 98
  in dogs, 90*t*–91*t*
  dosage of, 90*t*–91*t*
Phenylpropanolamine, 733*t*–734*t*
Phenytoin
  in cats, 90*t*–91*t*
  in dogs, 90*t*–91*t*
  dosage of, 90*t*–91*t*
  toxic effects of, 93
Pheochromocytoma, 889–892
  clinical features of, 889–890
  description of, 862–864
  diagnosis of, 890–891, 891*t*
  etiology of, 889
  hypertensive crisis caused by, 218
  physical examination of, 890*t*
  prognosis for, 892
  signs of, 890*t*
  treatment of, 891–892
Pheromones, 728
Phimosis, 993–996
Phlebotomy, for erythrocytosis, 116, 1369
Phosphate supplementation
  diabetic ketoacidosis treated with, 843–844
  hypophosphatemia treated with, 930–931, 930*b*
Phosphorus
  balance, 695–697
  hormones that affect metabolism of, 759*t*
  hyperphosphatemia, 691, 929–930, 929*b*
  hypophosphatemia, 843–844, 930–931, 930*b*
  restriction, 700–701
Physaloptera rara, 463–465
Physiologic nystagmus, 1109
Physiotherapy, for bacterial pneumonia, 343
Pilocarpine, 1172
Pimobendan
  chronic heart failure treated with, 63, 64*t*, 69, 128
  congestive heart failure treated with, 63, 64*t*, 129, 201–202
  dilated cardiomyopathy treated with, 145, 170
  pulmonary hypertension treated with, 193, 354
Pinch biopsy, 254–255, 254*f*
Pindolol, 94*t*
Piroxicam
  dosage of, 1268*t*
  joint disease treated with, 1209*t*–1210*t*
  nasal tumors treated with, 265
Pituitary dwarfism, 753–757, 1033
  in cats, 786*f*
  clinical features of, 754
  clinical pathology of, 754
  clinical signs of, 754, 754*b*, 755*f*
  diagnosis of, 754–755, 756*f*, 756*b*
  endocrine alopecia caused by, 748*t*
  etiology of, 753–754
  growth hormone therapy for, 755–757
  lanugo retention associated with, 754
  prognosis for, 757
  signalment, 754
  treatment of, 755–757
Pituitary gland, disorders of, 740–757
Pituitary irradiation, 876–877, 876*f*
Pituitary macrotumor syndrome, 859–860, 860*f*
Pituitary tumors, 877
Pituitary-adrenocortical axis, 858*f*
Pituitary-adrenocortical axis tests
  adrenocorticotropic hormone stimulation test, 870, 870*f*
  in cats, 881–882
Pituitary-adrenocortical axis tests *(Continued)*
  description of, 864–871, 866*t*, 867*b*
  high-dose dexamethasone suppression test, 864–865, 866*t*, 871
  low-dose dexamethasone suppression test, 864–865, 866*t*, 867–868, 869*f*
  urine cortisol/creatinine ratio, 866*t*, 867, 867*f*–868*f*, 881, 881*t*
Placental sites subinvolution, 976–977, 976*f*
Plague, feline, 1460–1462, 1461*f*, 1461*b*, 1541
Plant alkaloids, 1273, 1273*b*
Plantigrade posture, 832, 833*f*
Plasma ammonia concentration, 536–537
Plasma cells, 1211
Plasma oncotic pressure, 361
Plasma osmolality, 918
Plasma protein C activity, 537
Plasma protein fraction, 1420
Plasmacytoma, 448*t*
Plasmin, 222
Plasminogen activator inhibitor, 1388, 1405*f*
Platelet(s)
  activation of, 221
  adhesion of, 1387–1388
  aggregability of, 223, 1387–1388
  dysfunction, 1397–1399, 1397*b*
  in Greyhounds, 1361
  hyperaggregability of, 223
Platelet count, 397–398, 412
Platelet-derived growth factor receptor, 1273
Platelet-rich plasma, 1355–1356
Platynosomum concinnum, 573*b*
Plavix. *see* Clopidogrel
Plerixafor, 1494
Pleural cavity
  computed tomography of, 366
  disorder of, 371–378
    chylothorax, 374–375, 375*b*
    mediastinal masses, 377–378, 377*f*
    neoplastic effusion, 375–376
    pneumomediastinum, 378
    pyothorax, 371–374, 372*f*
  disorders of, general considerations for, 360
  radiography of, 364
  ultrasonography of, 366
Pleural effusion
  chylous, 361*t*, 362*f*, 363
  cytologic findings, 371, 373*f*
  diagnostic approach, 360–361, 361*t*, 382
  fluid classification, 360
  hemorrhagic, 361*t*, 362*f*, 363–364
  modified transudates, 361–363, 362*f*
  neoplasia as cause of, 364
  nonseptic exudates, 361*t*, 362*f*, 363
  pulmonary thromboembolism as cause of, 360
  radiographic findings, 360, 364–366, 365*f*
  septic exudates, 361*t*, 362*f*, 363
  thoracentesis for, 360
  thoracic radiographs of, 360
  thoracocentesis for, 167
  transudates, 361–363, 361*t*, 362*f*
  ultrasonography of, 360, 366
Pleural fibrosis, 372*f*
Pleural fissure lines, 364
Pleural fluids
  chylous, 361*t*, 362*f*, 363
  hemorrhagic, 362*f*, 363–364
  modified transudate, 361–363, 362*f*
  nonseptic exudates, 361*t*, 362*f*, 363
  septic exudates, 361*t*, 362*f*, 363
  transudates, 361–363, 361*t*
Pleural space disease, 382
Pleural thickening, 364
Pleuroperitoneal shunts, 375–376
Pleurovenous shunts, 375
Pneumomediastinum, 360, 365, 365*f*, 378
Pneumonia
  aspiration. *see* Aspiration pneumonia
  bacterial. *see* Bacterial pneumonia
  with clinical evidence of sepsis, 1441*t*
  community-acquired, 340, 1441*t*
  definition of, 340
  fungal, 344
  idiopathic interstitial, 349–352
  viral, 340–343
Pneumonic plague, 1541
Pneumonitis
  allergic, 201
  eosinophilic, 201
  heartworm disease as cause of, 201, 206
Pneumonyssoides caninum, 244
Pneumoperitoneum, 419–420
Pneumothorax, 376–377
  characteristics of, 364–365
  chest tubes as cause of, 367
  definition of, 364–365
  radiographic findings of, 364–365, 365*f*
  spontaneous, 364–365, 376–377, 377*f*
  thoracocentesis for, 345
  traumatic, 376
Poikilocytosis, 1345*t*
Point of maximal intensity (PMI), 7–8, 10*f*
Polioencephalitis, 1122–1123
Pollakiuria, 649, 652, 736
Polyarthritis, 1440*t*. *see also* Arthritis
  breed-specific syndromes, 1205
  calicivirus, 1201, 1201*f*
  canine rheumatoid-like, 1206–1208, 1206*f*–1207*f*
  classification of, 1202*b*
  clinical manifestations, 1187
  diagnosis of, 1248*t*
  erosive, 1189, 1208
  familial, 1205
  feline chronic progressive, 1245*t*
  feline periosteal proliferative, 1208, 1208*t*
  immune-mediated
    breed-specific, 1245*t*
    clinical features of, 1245–1246, 1246*b*
    cytologic findings, 1246, 1246*f*
    diagnosis of, 1246, 1246*f*
    erosive, 1208, 1245*t*
    etiology of, 1245
    glucocorticoids for, 1203–1204, 1204*t*, 1204*b*
    nonerosive, 1187, 1188*f*, 1202–1204, 1202*b*, 1204*t*
    noninfectious, 1189
    primary, 1245
    signs of, 1246*b*
    treatment of, 1246–1247
  infectious causes of, 1189*t*
  Mycoplasma, 1199
  noninfectious, 1201–1206
  pain and, 1187
  periosteal proliferative, 1189
  reactive, 1189, 1201–1202, 1202*f*
  rickettsial, 1199–1200
  septic, 1443–1444
  systemic lupus erythematosus-induced, 1204–1205
Polychromasia, 1345*t*
Polyclonal gammopathies, 1421, 1421*b*
Polycystic kidney disease, 693*b*
Polycythemia, 1368
Polycythemia rubra vera, 1368
Polydipsia, 213, 519–522, 649, 653–656, 654*t*–655*t*, 695, 740–741, 741*t*
  psychogenic, 655–656, 741*t*, 746–747
Polymerase chain reaction
  bartonellosis diagnosis using, 1457
  canine monocytotropic ehrlichiosis diagnosis using, 1476
  fecal analysis, 414
  infectious diseases, 1432–1433, 1432*f*
  lower respiratory tract disorders, 298
  lymphoma diagnosis using, 1300
Polymorphic ventricular tachycardia, 41
Polymyositis
  canine idiopathic, 1176
  characteristics of, 1252–1253
  diagnosis of, 1248*t*, 1253
  feline idiopathic, 1176–1177
  immune-mediated, 1252–1253, 1253*b*
  infectious causes of, 1253*b*
Polyneuropathies, 1163–1168
  acquired chronic, 1164–1168
  chronic idiopathic, 1165–1166
  chronic inflammatory demyelinating, 1165, 1166*f*
  congenital/inherited, 1163–1164, 1164*b*
  diabetic, 1164, 1165*f*
  hypothyroid, 1164–1165
  insulinoma, 1165
  paraneoplastic, 1165
Polyphagia with weight loss, 898–899, 899*t*
Polyps
  nasopharyngeal
    feline, 264, 264*f*
    peripheral vestibular disease caused by, 1114
    radiographic signs of, 249*f*, 249*b*
  rectal, 503–504
Polysulfated glycosaminoglycans, 1196, 1197*t*, 1209*t*–1210*t*
Polyuria, 213, 519–522, 649, 653–656, 654*t*–655*t*, 695, 695*b*, 740–741, 741*t*
Pons, 1037–1038
Pontine micturition center (PMC), 730
Portal hypertension
  chronic hepatitis and, 588
    treatment of, 593–594, 594*f*
  noncirrhotic, 609*f*, 610–611
Portal vein, primary hypoplasia of, 610–611
Portal vein thrombosis, 233
Portal venous hypoplasia, 721
Portocaval shunt, congenital, 588*f*
Portosystemic shunt
  acquired, 588*f*
  congenital, 577–579, 578*f*, 603–609
    clinical features of, 604, 604*f*
    diagnosis of, 604–605, 604*f*
    in dogs, 584, 603–609
    etiology and pathogenesis of, 603
    hepatic encephalopathy in, 606–608, 607*b*
    prognosis for, 605–606, 605*f*
    treatment for, 605–606
  description of, 117
Posaconazole, 472, 1504*t*
Positional nystagmus, 1109
Positional ventrolateral strabismus, 1111*f*
Positive inotropic agents
  dilated cardiomyopathy treated with, 169
  heart failure treated with, 69–70
Positive pressure, 385
Postictal period, 1093
Postobstructive diuresis, 654*t*–655*t*
Postpartum disorders, 974–979
  eclampsia, 975–976
  endometritis, 977–978, 977*f*
  inappropriate maternal behavior, 974–975, 975*f*
  metabolic, 975–976
  overview of, 974–979
  placental sites subinvolution, 976–977, 976*f*
  uterine, 976–978
Postpartum metritis, 1034*t*–1036*t*
Postprandial hyperchylomicronemia, 909
Postrenal azotemia, 649
Postural reactions, 1046–1047, 1048*f*
Posture, 1043–1045, 1044*f*
Potassium
  hyperkalemia, 47–48, 49*b*, 50*f*, 690–691, 919–921, 920*b*, 921*t*
  hypokalemia, 47, 49*b*, 921–923, 922*b*, 923*t*
  supplementation of

Potassium *(Continued)*
description of, 66
diabetic ketoacidosis treated with, 843
guidelines for, 917*t*
hypernatremia treated with, 917*t*
Potassium bromide, 1102–1103, 1185*t*–1186*t*
Potassium chloride, 922
Potassium gluconate, 934*t*, 1185*t*–1186*t*
Potentiated sulfas, 1437*t*–1438*t*
PR interval, 26*t*
Pradofloxacin, 386*t*–388*t*, 1437*t*–1438*t*
Pralidoxime chloride, 1185*t*–1186*t*
Praziquantel, 386*t*–388*t*, 444*t*, 515*t*–517*t*
for liver fluke infestation, 573
Prazosin, 733*t*–734*t*
chronic heart failure treated with, 64*t*, 71
hypertension treated with, 217*t*
Prebiotics, 443
Precordial impulse, 6
Precordial thrill, 6
Precordium, 6
Prednisolone, 515*t*–517*t*
administration of, 332
atrophic myositis treated with, 451
eosinophilic gastritis treated with, 463
feline nasopharyngeal polyps treated with, 264
hemolysis treated with, 1235–1236
immune-mediated diseases treated with, 1255*t*–1256*t*
immune-mediated hemolytic anemia treated with, 1236
immune-mediated thrombocytopenia treated with, 1243
masticatory muscle myositis treated with, 451
pure red cell aplasia treated with, 1238–1240
Prednisone, 386*t*–388*t*, 934*t*
adverse effects of, 1225*t*
allergic rhinitis treated with, 266
azathioprine and, 1224
canine idiopathic polymyositis treated with, 1176
dosage of, 1222–1223, 1225*t*
endocrine disorders treated with, 896*t*–897*t*
granulomatous meningoencephalitis treated with, 1121*b*
hemolysis treated with, 1235–1236
immune-mediated diseases treated with, 1255*t*–1256*t*
description of, 1222–1223, 1222*t*
hemolytic anemia, 1236, 1350
polyarthritis, 1203–1204, 1204*t*, 1204*b*
thrombocytopenia, 1243
joint disease treated with, 1209*t*–1210*t*
lymphoplasmacytic rhinitis treated with, 269
mast cell tumors treated with, 1333
masticatory myositis treated with, 1252
myasthenia gravis treated with, 1251*t*
neurologic disorders treated with, 1185*t*–1186*t*
properties of, 1222, 1222*t*
steroid-responsive tremor syndrome treated with, 1122
systemic lupus erythematosus treated with, 1248–1249
Pregabalin, 1104
Pregnancy
cesarean section, 972–974, 974*f*
diagnosis of, 949–950, 949*t*, 950*f*
edema in, 967, 968*f*
fetal age determination, 950–951, 951*f*, 951*b*
fetal heart rate monitoring, 973*f*
gestational age, 950–951, 951*f*, 951*b*
loss of, 962
palpation detection of, 949–950
Pregnancy *(Continued)*
progesterone levels necessary for, 962–963
termination of
antiestrogens for, 959
antiprogestational agents for, 960
dexamethasone for, 960
dopaminergic compounds, 960
estrogens for, 959
overview of, 959–960, 959*f*
prostaglandins for, 960
thrombosis in, 967, 967*f*
ultrasound diagnosis of, 950, 950*f*
vaccination during, 961
Pregnancy toxemia, 967
Prehensile disorder, 391
Prekallikrein, 1387–1388, 1393
Preleukemic syndrome, 1312–1313
Premature ectopic rhythm, 38–39
Premature myometrial activity, 962
Premature ovarian failure, 956
Premature uterine activity, 962
Preprohormones, 13
Prerenal azotemia, 649, 686–687
Pressure gradient estimation, 30–31
Presyncope, 1–2
Presystolic gallop, 9
Preterm labor, 1034*t*–1036*t*
idiopathic, 962–963, 963*f*–964*f*
Prevacid. *see* Lansoprazole
Previcox. *see* Firocoxib
Priapism, 993–996, 994*f*–996*f*, 1034*t*–1036*t*
Prilosec. *see* Omeprazole
Primary adrenal insufficiency, 888–889
Primary autoimmune disease, 1211
Primary ciliary dyskinesia, 1023
Primary erythrocytosis, 1368, 1369*b*
Primary hepatic lipidosis, 561
Primary hyperparathyroidism, 758–763
clinical signs of, 759, 760*b*
definition of, 758–759
diagnosis of, 760–761, 762*f*
differential diagnosis of, 924, 925*f*
etiology of, 758–760
hypercalcemia caused by, 761*t*
physical examination of, 760
prognosis for, 763
signalment, 759
treatment of, 761–763
Primary hypoparathyroidism, 654*t*–655*t*, 763–766
clinical signs of, 764, 764*b*
diagnosis of, 764–765
etiology of, 763–764
hypocalcemia caused by, 765*t*
physical examination of, 764
prognosis for, 766
signalment, 764
treatment of, 765–766
Primary immune-mediated disorders, 1211
Primary splenic hemangiosarcoma, 1325*f*
Probiotics, 443
Procainamide
AV reciprocating tachycardia prevention using, 80–82
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
electrocardiographic changes associated with, 49*b*
indications for, 91–92
neurologic disorders treated with, 1185*t*–1186*t*
pharmacokinetics of, 92
toxic effects of, 92
Procarbazine, 1121*b*, 1185*t*–1186*t*
Prochlorperazine, 438, 438*t*, 515*t*–517*t*
Proctoscopy, 427
Prodrome, 1093
Productive cough, 282, 283*b*
Proestrus
canine
description of, 937, 938*t*, 939*f*
prolonged, 954–955
feline, 948
Progesterone, 942–943
Progesterone-secreting adrenal tumors, 893, 894*f*
Progestogens, 749
Proglycem. *see* Diazoxide
Progressive rear limb ataxia, 1146*f*
Progressive spinal cord dysfunction
description of, 1142–1156
diskospondylitis, 1143–1144, 1143*f*–1144*f*
infectious inflammatory disease, 1142–1143
neoplasia
clinical features of, 1145
description of, 1145–1147, 1145*f*
noninfectious inflammatory disease, 1143
spinal arachnoid diverticula, 1147–1148
subacute, 1142–1144
type II intervertebral disk disease, 1148
Proliferative glomerulonephritis, 678
PromAce. *see* Acepromazine
Propafenone
description of, 93
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Propantheline bromide, 97
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
Propecia. *see* Finasteride
Propentofylline, 1491
Propionibacterium acnes, 1497
Propofol
neurologic disorders treated with, 1185*t*–1186*t*
status epilepticus treated with, 1105*b*
Propranolol, 94
in cats, 90*t*–91*t*
characteristics of, 94*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
hypertension treated with, 217*t*
indications for, 94
pharmacokinetics of, 94
toxic effects of, 94
Proprioception, 1136
Propulsid. *see* Cisapride
Proscar. *see* Finasteride
Prostacyclin, 221
Prostaglandins, pregnancy termination using, 960
Prostate gland
bacterial prostatitis, 710–711, 710*f*
benign prostatic hyperplasia, 1001–1003, 1002*f*, 1034*t*–1036*t*
cystic benign prostatic hyperplasia, 1001–1003, 1002*f*
infections of, 1002–1003, 1002*f*, 1446
neoplasia of, 1003, 1003*f*
Prostatitis, 1441*t*
antibiotics for, 1441*t*
bacterial, 710–711, 710*f*
infectious, 1002–1003, 1002*f*
septic, 1003
Prostigmin. *see* Neostigmine methylsulfate
α_1-Protease inhibitor, 424
Protein
feline requirements for, 834–835
Greyhound levels of, 1362–1363
in urine, 665
in veterinary therapeutic diets, 904*t*–906*t*
Protein C, 222
Protein tyrosine phosphatase-like genetic mutation, 1179–1180
Protein-calorie malnutrition, 529–530, 529*f*
Protein-losing enteropathy, 495
causes of, 401*b*
diarrhea caused by, 399
fluid therapy in, 434
in soft-coated wheaten terriers, 497
Protein-losing nephropathy
antithrombin deficiency caused by, 223
diagnosis of, 1249–1250
fluid therapy in, 434
Protein-to-creatinine ratio, 661–662
Proteinuria, 678, 862
in chronic kidney disease, 681, 681*b*
clinical approach to, 681*b*
diagnostic tests for, 1218*t*–1219*t*
heartworm disease as cause of, 197
Proton pump inhibitors (PPIs), 439, 439*t*, 456
Protonix. *see* Pantoprazole
Prototheca zopfii, 484
Protothecosis, 484, 485*f*
Protozoal diseases, 965–966
systemic, 1430
Protozoal infections
American trypanosomiasis, 1525–1526
babesiosis, 154, 1514–1516
canine toxoplasmosis, 1525
cytauxzoonosis, 1516–1517
feline toxoplasmosis, 1521–1525
hepatozoonosis, 1517–1518
leishmaniosis, 1518–1520
neosporosis, 154, 1118*t*, 1127–1128, 1127*f*, 1520–1521
polysystemic, 1514–1531
toxoplasmosis. *see* Toxoplasmosis
Protozoal myocarditis, 153–154
Protozoal myositis, 1177–1178
Pseudocyesis, exaggerated, 957
Pseudocysts, perinephric, 656–657, 657*f*
Pseudohyperreflexia, 1047
Pseudohyponatremia, 918
Pseudopregnancy, 949, 957
Pseudorabies, 1541–1542
Pseudothrombocytopenia, 1389–1390
Psychogenic polydipsia, 655–656, 741*t*, 746–747
Psychomotor seizures, 1094
Psyllium, 445*t*
Psyllium hydrocolloid, 515*t*–517*t*
Puerperal hypocalcemia, 1034*t*–1036*t*
Puerperal tetany, 975
Pulmonary abscess, 343
Pulmonary arterial disease, 201–202
Pulmonary arterial hypertension, 18, 113
Pulmonary artery pressure, 102–103
Pulmonary artery systolic pressure, 30–31
Pulmonary capillary wedge pressure (PCWP), 52
Pulmonary carcinoma, 293*f*
Pulmonary edema, 356–358
cardiogenic
cough caused by, 3
in dogs, 18
in cats, 165
clinical features of, 356
degenerative atrioventricular valve disease as cause of, 121–122, 121*b*
diagnosis of, 357
etiology of, 356, 357*b*
furosemide for, 358
hypoalbuminemia as cause of, 358
lung stiffness caused by, 4
patterns of, 18
prognosis for, 358
treatment of, 357–358
vascular permeability as cause of, 357
Pulmonary eosinophilic granulomatosis, 201
Pulmonary fibrosis, idiopathic, 349–352
Pulmonary hypertension, 190–210
advanced imaging, 192
clinical features of, 354
clinical findings of, 191
clinicopathologic findings, 192
diagnosis of, 191, 354
diseases associated with, 193
in dogs, 193
echocardiographic findings, 192, 192*f*
electrocardiographic findings, 192

Pulmonary hypertension *(Continued)*
etiology of, 190–191, 353–354
heartworm disease as cause of, 193, 287
microthrombi in, 354–355
prognosis for, 192–193, 354
pulmonary thromboembolism as cause of, 224
radiographic findings, 191–192, 191*f*
with shunt reversal, 114–116, 115*f*
signs of, 130, 191
sildenafil citrate for, 116, 191, 354
treatment of, 192–193, 354
TRmax associated with, 30–31
Pulmonary infiltrates with eosinophils (PIE), 348
Pulmonary mycoses, 344
Pulmonary neoplasia, 352–353
bronchoalveolar lavage findings, 352*f*
clinical features of, 352
diagnosis of, 352–353, 352*f*
prognosis for, 353
radiographic findings, 366*f*
treatment of, 353
Pulmonary nodules, 296*f*
Pulmonary parenchymal disorders, 283*b*, 340–359
emergency management of, 381–382
eosinophilic lung disease, 348–349
parasites
Aelurostrongylus abstrusus, 345
Capillaria aerophila, 344
Crenosoma vulpis, 346
description of, 344–346
Paragonimus kellicotti, 344–345, 345*f*
pneumonias
bacterial. *see* Bacterial pneumonia
canine influenza, 340
definition of, 340
fungal, 344
fungal pneumonia, 344
viral, 340–343
pulmonary hypertension. *see* Pulmonary hypertension
pulmonary neoplasia. *see* Pulmonary neoplasia
toxoplasmosis, 343
Pulmonary thromboembolism
abnormalities associated with, 355*b*
clinical features of, 355
computed tomography pulmonary angiography of, 355–356
D-dimer measurements, 355
description of, 194, 224, 354–356
diagnosis of, 355–356
fibrinolytic agents for, 356
heartworm disease as cause of, 201–203, 224
pleural effusion caused by, 360
postadulticide, 201–203
prevention of, 356
prognosis for, 356
selective angiography of, 356
treatment of, 201–202, 356
Pulmonary toxicity, chemotherapy-induced, 1285–1286
Pulmonary vascular resistance, 190, 353–354
Pulmonary vasculature, 288
Pulmonary venous congestion, 18, 122–123
Pulmonary vessels, lobar, 17–18
Pulmonic stenosis
balloon valvuloplasty for, 108
β-blockers for, 108–109
clinical features of, 108
diagnosis of, 108
in dogs, 102*t*, 107
echocardiographic findings, 108, 110*f*
etiology of, 107–108
exercise restriction for, 108–109
murmur of, 11
pathophysiology of, 107–108
prognosis for, 108–109
radiographic findings, 103*t*, 108, 109*f*
Pulmonic stenosis *(Continued)*
single anomalous coronary artery associated with, 108
treatment of, 108–109
Pulse deficits, 79
Pulse oximetry
definition of, 318–319
indications for, 318–319
interpretation of, 319
method of, 319, 319*f*
oxygen saturation evaluations, 65
Pulsed wave Doppler echocardiography, 28–30, 29*f*–30*f*
Pulsus alternans, 6
Pulsus paradoxus, 6, 177–178
Pulsus parvus et tardus, 5, 106
Punctate chorioretinitis, 1522*f*
Pupillary light reflex, 1056*t*, 1084–1085, 1085*f*, 1086*t*
Pupils
description of, 1055, 1056*f*
size and symmetry evaluations, 1086
Puppies
biochemical parameters, 1018*t*–1019*t*
hypothyroidism in, 783
murmurs in, 101*f*
Pure low protein transudate, 407
Pure red cell aplasia, 1238–1240, 1239*t*, 1340–1341
Purine metabolism, 720*f*
Purring, 7, 7*f*
P wave, 26*t*
Pyelonephritis, 654*t*–655*t*, 667–668, 709, 741*t*, 1441*t*
Pyloric stenosis, 465
Pyloroplasty, 465
Pyoderma, 768–769
Pyogranulomatous splenitis, 1412*t*
Pyometra, 654*t*–655*t*
antibiotics for, 1441*t*
description of, 956*f*, 959, 983*f*
open, 1034*t*–1036*t*
treatment of, 1441*t*, 1446
Pyometra complex, 985–988, 986*f*–987*f*, 987*t*
Pyothorax, 371–374, 372*f*, 1441*t*, 1445
Pyrantel, 444*t*
Pyrantel pamoate, 515*t*–517*t*
Pyrantel/febantel/praziquantel, 444*t*
Pyridostigmine, 441, 515*t*–517*t*
Pyridostigmine bromide, 1171–1172, 1185*t*–1186*t*, 1251*t*, 1255*t*–1256*t*
Pyrimethamine, 1185*t*–1186*t*
Pyruvate kinase deficiency, 1347*t*
Pythiosis, 484
of alimentary tract, 420*f*, 472
Pythium insidiosum, 424, 472
Pyuria, 666, 666*f*, 667*b*

Q

QRS complex
abnormalities of, 46
description of, 25, 25*t*–26*t*
QT interval, 26*t*, 47
abnormalities of, 48*b*
prolongation of, 92
quinidine effects on, 92
Queen
breeding management of, 944–945
breeding soundness consultations in, 935–936
cystic endometrial hyperplasia/pyometra complex, 985–988, 986*f*–987*f*, 987*t*
gestational diabetes in, 967, 967*f*
infertility/subfertility in, 984, 984*b*
microbiology and, 984–985, 985*b*
labor in, 968
ovariohysterectomized, reproductive tract disorders in
chronic vestibulovaginitis, 980–982, 980*f*–982*f*
ovarian remnant syndrome, 982–983, 983*f*
ovulation inducement in, 949
Queen *(Continued)*
pregnancy in, 960–961. *see also* Pregnancy
puberty in, 948
Questran. *see* Cholestyramine
Quinidine
adverse effects of, 82–83
AV reciprocating tachycardia prevention using, 80–82
in cats, 90*t*–91*t*
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
electrocardiographic changes associated with, 49*b*
indications for, 92
pharmacokinetics of, 92
toxic effects of, 92
Quinolones, 1437*t*–1439*t*

R

Rabies
description of, 1533*t*–1535*t*
vaccination for, 1125–1126, 1454–1455
Radial nerve, 1158*t*
Radiation therapy
feline acromegaly treated with, 753
lymphoma treated with, 1301
nasal tumors treated with, 265
Radioactive iodine, 796*t*, 799–800, 799*f*, 803
Radiography. *see also* Thoracic radiography
abdominal, 419, 420*f*
of alimentary tract, 415
aspergillosis, 260
bacterial pneumonia findings, 353
cardiac, 14–18
chamber enlargement patterns, 15–16, 16*f*
cardiac tumors, 187
cardiomegaly, 15, 15*b*
caudal vena cava, 17
congenital heart disease, 103*t*
dilated cardiomyopathy findings, 142, 143*f*
dorsoventral view, 14
frontal sinus, 247, 248*f*
of gastric dilation/volvulus findings, 468*f*
gastric outflow tract obstruction findings, 419–420, 419*f*–420*f*
great vessels, 16–17
heartworm disease
in cats, 205*f*, 206
in dogs, 196
hepatobiliary system, 545–549, 546*f*–549*f*
hypertrophic cardiomyopathy, 160, 161*f*
idiopathic pulmonary fibrosis findings, 351*f*
intraoral, 248*f*
joint disease evaluations, 1193
of larynx and pharynx, 273, 274*f*
left atrium enlargement, 15–16
left ventricle enlargement, 16
lobar pulmonary vessels, 17–18
lower respiratory tract disorders, 286
lower urinary tract signs, 725–726
lymphoma, 1298
mediastinal masses, 364–366, 1291*f*
mediastinum, 365–366
mitral valve insufficiency, 123*f*
nasal aspergillosis, 260
nasal imaging using, 247–248, 248*f*–250*f*, 249*b*
neuromuscular system, 1064
Paragonimus kellicotti findings, 344
partial or intermittent chronic gastric volvulus, 469*f*
patent ductus arteriosus, 103, 103*t*
pericardial effusion findings, 178–179, 179*f*
pleural cavity, 364
pleural effusion findings, 360, 364, 365*f*
Radiography *(Continued)*
pneumothorax findings, 364–365, 365*f*
pulmonary hypertension findings, 191–192, 191*f*
pulmonary neoplasia findings, 366*f*
pulmonic stenosis findings, 108, 109*f*
pyothorax findings, 371
restrictive cardiomyopathy findings, 168–169, 169*f*
right atrium enlargement, 16
right ventricle enlargement, 16
spinal, 1064
stomach, 420–422, 421*f*
tetralogy of Fallot findings, 114
tracheal collapse findings, 336*f*
tricuspid dysplasia findings, 112
ureterolithiasis, 715*f*
urinary disorders, 671
ventricular septal defect findings, 110
ventrodorsal view, 14
vertebral heart score, 14–15, 14*f*
Radioisotopes, 661
Radiomimetics, 1272–1273
Radiotherapy. *see* Radiation therapy
Ramipril, 64*t*, 217*t*
Random plasma osmolality, 744–745
Ranitidine, 439–441, 439*t*, 515*t*–517*t*
Rapid-acting insulin analogs, 812
Rattlesnake vaccine, 1455
Reactive amyloidosis, 679
Reactive fibrosis, 55
Reactive lymphadenopathy, 1263–1264, 1408
Reactive polyarthritis, 1189, 1201–1202, 1202*f*
Recombinant human thyroid-stimulating hormone, 778–779
Rectal polyps, 503–504
Rectal prolapse, 504
Rectal temperature, of neonates, 1009*b*
Red blood cells
in Greyhounds, 1360
morphologic abnormalities of, 1345*t*
phagocytosis of, 1411–1412
in urinary sediment, 666, 666*f*
Reentrant supraventricular tachycardia, 39
Reflexes
bulbourethral, 1049*t*, 1050
crossed extensor, 1049–1050
cutaneous trunci, 1049*t*, 1050–1051, 1051*f*
evaluation of, 1049*t*
overview of, 1047–1051, 1049*t*
patellar, 1047, 1049*f*, 1049*t*
pelvic limb withdrawal, 1047–1049, 1049*f*, 1049*t*
perineal, 1049*t*, 1050, 1051*f*
pupillary light, 1084–1085, 1085*f*, 1086*t*
sciatic, 1049, 1049*t*, 1050*f*
thoracic limb withdrawal, 1049, 1050*f*
Refractometry, 664
Regenerative anemia, 1342–1343, 1344*f*, 1358*f*, 1426*t*
Regional lymphadenopathy, 1407–1408, 1410*t*
Reglan. *see* Metoclopramide
Regurgitation, 11
aspiration pneumonia secondary to, 346
definition of, 391
diagnostic approach to, 392–393, 392*f*
dysphagia and, 392
esophageal, 392
expectoration *versus*, 391–392
vomiting *versus*, 391–392
Relative erythrocytosis, 1368, 1369*b*
Relative hyperproteinemia, 1420
Remeron. *see* Mirtazapine
Remodeling, cardiac, 55
Renal amyloidosis, 194
Renal biopsy, 690
Renal calculi, 715*f*
Renal dysfunction, 131
Renal dysplasia, 693*b*

Renal failure
  definition of, 649
  hypercalcemia and, 760, 924
Renal glucosuria, 654*t*–655*t*
Renal insufficiency, 741*t*
Renal lymphoma, 1296–1297
Renal tubules
  backleak of, 688*f*
  urinalysis. *see* Urinalysis
Renin angiotensin, 1363–1364
Renin-angiotensin-aldosterone system (RAAS), activation of, 56, 120, 588
Renomegaly, 656–657
Reproductive disorders, drugs used in, 1034*t*–1036*t*
Reproductive practice job task, 936*b*
Respiratory acidosis, 318
Respiratory disorders, 1023, 1023*f*–1024*f*
Respiratory distress
  auscultation of, 285*f*
  breathing patterns in, 284
  definition of, 379
  lower respiratory tract disorders as cause of, 283–284
  orthopnea associated with, 379
  resulting from laryngeal diseases, 271
  signs of, 289*b*
  stress in animals with, 380*t*
  treatment of, 347–348
Respiratory noise, decreased, 7*f*
Respiratory patterns, 4, 4*f*
Respiratory tract
  infections of
    antimicrobial drugs for, 1441*t*, 1444–1445
    localization, 380*t*
  zoonoses, 1542
Resting nystagmus, 1109
Resting respiratory rate, 284
Restrictive cardiomyopathy
  in cats, 168–169, 169*f*
  clinical features of, 168
  diagnosis of, 168–169, 169*f*
  etiology of, 168
  pathophysiology of, 168
  treatment of, 169
Resuscitation, neonatal, 1007–1013, 1008*f*–1012*f*, 1008*b*–1010*b*, 1014*t*, 1016*t*, 1018*t*–1020*t*
Rete ovarii cysts, 956
Retention enemas, 445
Reticular interstitial pattern, 293
Reticulonodular patterns, 293
Retina
  lesions of, 1087–1088
  sudden acquired retinal degeneration, 1087
Retinal detachment, 791
Retinal hemorrhage, 791
Retrobulbar abscess, 1124*f*
Retrograde ejaculation, 1005
Retroorbital lymphoma, 1308*f*
Reverse cholesterol transport, 909
Reverse sneezing, 245, 271–272
Revolution. *see* Selamectin
Rheumatoid factor, 1194, 1206, 1217
Rhinitis
  bacterial, 259–260, 259*f*
  idiopathic, 266–269
  idiopathic canine chronic, 268–269
Rhinoscopy
  aspergillosis evaluations, 261
  description of, 250–251, 251*f*–252*f*, 253*b*
Rhinosinusitis, feline chronic, 266–268
  antibiotics for, 267–268
  clinical features of, 267
  diagnosis of, 267
  etiology of, 266–267
  radiographic signs of, 249*b*
  treatment of, 267–268, 267*b*
Rhinotomy, turbinectomy with, 244
Richter syndrome, 1317
Rickettsia felis, 1481, 1533*t*–1535*t*
Rickettsia rickettsii, 1440*t*, 1479, 1533*t*–1535*t*
Rickettsial diseases
  canine granulocytotropic ehrlichiosis, 1478–1479
  canine monocytotropic ehrlichiosis, 1473–1477
    clinical features of, 1474, 1474*t*
    diagnosis of, 1474–1476, 1475*f*, 1475*t*
    epidemiology of, 1473–1474
    etiology of, 1473–1474
    hypoalbuminemia and, 1475
    prevention of, 1477
    treatment of, 1476–1477
    zoonotic aspects of, 1477
  canine thrombocytotropic anaplasmosis, 1472–1473
  cytology of, 1430
  description of, 1128–1129
  feline monocytotropic ehrlichiosis, 1477–1478
  granulocytotropic anaplasmosis
    canine, 1469–1471
    feline, 1471–1472, 1472*f*
  polyarthritis, 1199–1200
  polysystemic, 1469–1484
  Rocky Mountain spotted fever, 1118*t*, 1128, 1199–1200, 1479–1480
  serologic tests for, 1194
Right atrial dilation, 107–108
Right atrium
  enlargement, 16
  hemangiosarcoma of, 182
Right bundle branch block (RBBB), 44, 45*f*, 46*b*
Right ventricle, enlargement, 16, 46*b*
Right ventricular hypertrophy, 108
Right-sided congestive heart failure, 142, 171, 181, 186–187
  fluid accumulation in, 6
  heartworm disease as cause of, 202–203, 206
  jugular vein distention and, 5, 5*f*
Right-sided heart failure
  fluid accumulation in, 6
  jugular vein distention and, 5, 5*f*
Right-to-left shunting, 111
Rigid endoscopy, 424
Rimadyl. *see* Carprofen
Robaxacin. *see* Methocarbamol
Rocky Mountain spotted fever, 1118*t*, 1128, 1199–1200, 1479–1480
Romanowsky stains, 1258
Rompun. *see* Xylazine
Ronidazole, 444*t*, 515*t*–517*t*, 1437*t*–1438*t*
R-on-T phenomenon, 82
Round cell tumors, 1261–1263, 1262*f*
Roundworms, 486–487, 486*f*, 1536
RR interval, 41
rt-PA, for arterial thromboembolism
  in cats, 227*b*, 229
  in dogs, 232
Rutin, 386*t*–388*t*

S

Saccular bronchiectasis, 290
S-adenosylmethionine, 571–572
Safe-Guard. *see* Fenbendazole
Salicylazosulfapyridine, 441
Salivary gland necrosis, 447
Salmon poisoning, 480
Salmonella spp., 1440*t*, 1533*t*–1535*t*, 1539
Salmonellosis, 481–482
Salt restriction, 72, 128–129
Sandostatin. *see* Octreotide
Sarcoma
  cytologic findings, 1260–1261, 1261*f*
  esophageal, 460
  fibrosarcoma, 1334
  hemangiosarcoma
    abdominal, 513
    canine, 1323*f*
    clinical features of, 1322
    clinicopathologic features, 1322
    clinicopathologic features of, 1322
Sarcoma *(Continued)*
    description of, 176, 178, 185, 1322, 1413
    diagnosis of, 1323–1324
    fine-needle aspiration of, 1323
    intraabdominal, 1323*f*
    primary splenic, 1325*f*
    prognosis for, 1324–1325
    treatment of, 1324–1325, 1324*f*
  injection site, 1334–1335, 1335*f*
  osteosarcoma
    appendicular, 1325–1326
    chemotherapy for, 1327, 1327*b*
    clinical features of, 1325–1326
    diagnosis of, 1326–1327, 1326*f*
    epidemiology of, 1325
    etiology of, 1325
    metastasis of, 1290*t*
    prognosis for, 1327–1328
    radiographic findings, 1326, 1326*f*
    round cells associated with, 1260–1261
    treatment of, 1327–1328
Scar tissue-related acquired epilepsy, 1096–1097
Schering-Plough. *see* Cloprostenol
Schiff-Sherrington posture, 1044, 1044*f*
Schistocytosis, 1345*t*
Schmidt's syndrome, 773
Sciatic nerve paralysis, 1158*t*
Sciatic reflex, 1049, 1049*t*, 1050*f*
Sclerosing cholangitis, 572
Scotty cramp, 1106
Screening neurologic examination. *see* Neurologic examination, screening
Scrotal dermatitis, 992, 992*f*
Scrotal edema, 1001*f*
Scrotal enlargement, 1000
Seborrhea, 768–769
Second heart sound, 8
Secondary autoimmunity, 1211
Secondary erythrocytosis, 1368, 1369*b*
Secondary hepatopathies, 616–617
Secondary hyperparathyroidism, 758
Secondary hypoadrenocorticism, 884, 886*t*
Secondary immune-mediated disorders, 1211
Second-degree atrioventricular block, 43–44, 44*f*, 88
Second-order neurons, 1090
Seizures
  alternative therapies for, 1104
  anticonvulsant therapy for
    chronic, 1101*b*
    phenobarbital, 1101–1102
  antiepileptic drug therapy for
    description of, 1100–1101
    diazepam, 1104
    for dogs, 1101*t*
    felbamate, 1104
    gabapentin, 1103–1104
    levetiracetam, 1103
    potassium bromide, 1102–1103
    pregabalin, 1104
    zonisamide, 1103
  classification of, 1094
  cluster, 1095
  components of, 1093
  descriptions, 1093–1094
  diagnosis of, 1096*f*, 1098–1100
  differential diagnosis of, 1095–1098
  disorders resulting in, 1094, 1095*b*
  extracranial causes of, 1094, 1095*b*, 1097–1098
  focal, 1094
  generalized, 1093–1094
  hypoglycemic, 808*b*
  in idiopathic epilepsy, 1095–1096
  intoxications that cause, 1099*b*
  intracranial causes of, 1095*b*, 1096, 1097*f*
  lidocaine-induced, 90–91
  localization of, 1094
  paroxysmal events and, 1093–1108
  partial, 1093–1094
Seizures *(Continued)*
  psychomotor, 1094
  recurrence prevention, 1105
Selamectin, 207
Selective angiocardiography, 52
Selective angiography, 356
Semen
  analysis of, 946–947, 946*f*
  canine, 946*f*
  collection of, 945–946, 945*b*
Semen peritonitis, 961–962, 961*f*
Seminoma, 996–997, 997*f*
Senile tremors, 1183
Sensitivity, 1434
Sensory evaluation, 1051–1052, 1052*f*
Sensory nerves, 1040–1041
Sentinel. *see* Milbemycin
Sepsis, abdominal, 443
Septic arthritis, 1193, 1197–1201, 1198*f*–1199*f*
Septic exudate
  pleural effusion, 361*t*, 362*f*, 363
  of pyothorax, 372
Septic peritonitis, 422, 510–512
  clinical features of, 510
  diagnosis of, 510–512, 511*f*
  etiology of, 510
  prognosis of, 512
  treatment for, 512
Septic polyarthritis, 1443–1444
Septic prostatitis, 1003
Septicemic plague, 1541
Serologic tests
  heartworm disease
    in cats, 205
    in dogs, 195
  joint disease, 1194
  lower respiratory tract disorders, 298
Serotonin receptor antagonists, 438*t*
Sertoli cell tumors, 991*f*, 997
Serum albumin concentration, 537–538
Serum amyloid A protein, 679, 683
Serum bile acid concentration, 535–536, 535*b*
Serum bilirubin concentration, 534–535
Serum biochemistry, 405–406, 412–413, 541–542, 541*t*–542*t*
Serum cholesterol concentration, 538
Serum cortisol, alimentary tract disease evaluations, 413
Serum liver enzyme activities, 532–534
Serum relaxin assay, 949–950
Serum urea nitrogen concentration, 538
Sexual differentiation disorders, 1005–1006
Shared vector zoonoses, 1543
Shiba dogs, enteropathy in, 497–498
Short bowel syndrome, 502
Shoulder, arthrocentesis method in, 1191*f*
Shunt reversal, pulmonary hypertension with, 114–116, 115*f*
Sialoadenitis, 447
Sialoadenosis, 447
Sialocele, 447
Sick sinus syndrome, 86–87, 87*f*
Sighthounds. *see* Greyhounds
Sigmoidoscope, 428
Signal aliasing, 31–32, 31*f*
Sildenafil, 386*t*–388*t*
Sildenafil citrate, pulmonary hypertension managed with, 116, 191, 354
"Silent atrium,", 87
Silent heat cycle, 953
Silica urolithiasis, 721–722, 722*f*
Simmetric dimethylarginine (SDMA), 1362
Simonsiella spp., 303–304, 304*f*
Single anomalous coronary artery, 108
Single thyroid lobe, 788, 788*f*
Sinus arrhythmia, 37, 40*f*
Sinus bradycardia, 37, 39*b*, 40*f*
  anticholinergic agents for, 86
  characteristics of, 86
  drugs that cause, 86

Sinus rhythms, 37, 40*f*
Sinus tachycardia, 37, 39*b*, 40*f*
  causes of, 79–80
Skeletal muscle, 1042
Skin infections, 1445
Sleep disorders, 1107–1108
Slide agglutination test, 1215–1216
Small airway obstruction, 329*b*
Small intestine
  bacterial overgrowth, antibiotics for, 1440*t*, 1442
  contrast-enhanced studies of, 422–423, 425*f*
  diarrhea, 399*t*, 400*f*
    dietary-responsive, 491–492
  enteropathy, antibiotic-responsive, 492
  imaging of, 419–423
  neoplasms of, 502–503
  ultrasonography of, 420–422, 421*f*
Small stature, 756*b*
Sneezing, 244–245
Sodium
  fractional clearance of, 664
  hypernatremia. *see* Hypernatremia
  hyponatremia. *see* Hyponatremia
  retention of, 684
Sodium bicarbonate, 690–691, 921*t*, 934*t*
Sodium levothyroxine
  hypothyroidism treated with, 783–784, 783*b*, 896*t*–897*t*
  thyrotoxicosis caused by, 784–785
Sodium nitroprusside, 63
Sodium pentobarbital, 1105*b*
Soft tissue infections, 1439*t*, 1445
Soft-coated Wheaton paroxysmal dyskinesia, 1106
Solitary lymphadenopathy, 1407–1408, 1410*t*
Solitary lymphoma, 1307
Solitary mass, 1288–1289, 1289*f*
Solu-Delta-Cortef. *see* Prednisolone
Somatostatin, 850*b*, 852, 896*t*–897*t*
Somogyi response, 825–826, 826*f*
Sotalol, 83–84, 95
  in cats, 90*t*–91*t*
  characteristics of, 94*t*, 95
  in dogs, 90*t*–91*t*
  dosage of, 90*t*–91*t*
Space-occupying lesions, of pharynx, 271–272
Specificity, 1432–1433
Specimens
  bronchoalveolar lavage, 309
  tracheal wash, 298, 301*f*
Sperm cells, 1004*f*
Sperm ejaculated, increase, 1034*t*–1036*t*
Spermatogenesis, defects of, 1005, 1005*f*
Sperm-rich fluid, 945–946
Spherocytes, 1233, 1234*t*, 1346–1348, 1346*f*
Spherocytosis, 1231, 1345*t*
Spina bifida, 1155
Spinal arachnoid diverticula, 1147–1148
Spinal articular cysts, 1147
Spinal cord
  anatomy of, 1039–1041
  fractures of, 1134*f*
  gray matter of, 1039
  lesions of, 1041, 1130–1133
    C1-C5, 1130, 1131*t*
    C6-T2, 1130–1131, 1131*t*
    diagnostic approach, 1132–1133
    L4-S3, 1131*t*, 1132
    neurologic findings in, 1131*t*
    T3-L3, 1131, 1131*f*, 1131*t*
  lower motor neuron signs, 1039–1040, 1039*f*, 1040*t*
  neoplasia of, 1142
  segments of, 1039*f*, 1132*f*, 1132*t*
  sensory pathways of, 1040–1041
  trauma to
    clinical features of, 1133
    description of, 1133–1135
    diagnosis of, 1133
    flowchart for, 1134*f*
Spinal cord *(Continued)*
    prognosis for, 1135
    treatment of, 1133–1134, 1134*f*
  upper motor neuron signs, 1040, 1040*f*
  white matter of, 1039
Spinal cord ataxia, 1046*b*
Spinal cord disorders, 1041*b*, 1130–1156
  acute intervertebral disk disease
    cervical disk extrusion, 1138*t*, 1139
    clinical features of, 1136, 1136*f*
    description of, 1135–1141
    diagnostic approach, 1136–1137, 1137*f*–1139*f*
    magnetic resonance imaging of, 1137
    myelography for, 1137, 1138*f*
    treatment of, 1137–1141
  atlantoaxial instability, 1142, 1154
  cauda equina syndrome, 1149–1151, 1149*f*–1151*f*
  cervical spondylomyelopathy, 1151–1153, 1152*f*–1153*f*
  common, 1131*b*
  degenerative myelopathy, 1148–1149
  fibrocartilaginous embolism, 1141–1142
  general considerations in, 1130
  hemorrhage, 1135
  infarction, 1135
  traumatic disk extrusions, 1141
Spinal cord dysfunction
  peracute or acute, 1133–1142
  progressive. *see* Progressive spinal cord dysfunction
Spinal dysraphism, 1155–1156
Spinal muscular atrophy, 1164
Spinal pain, 1053*f*–1054*f*, 1134*t*, 1143
Spinal radiographs, 1064
Spinal reflexes
  bulbourethral reflex, 1049*t*, 1050
  crossed extensor reflex, 1049–1050
  cutaneous trunci reflex, 1049*t*, 1050–1051, 1051*f*
  evaluation of, 1047–1051
  overview of, 1047, 1049*t*
  patellar reflex, 1047, 1049*f*, 1049*t*
  pelvic limb withdrawal reflex, 1047–1049, 1049*f*, 1049*t*
  perineal reflex, 1049*t*, 1050, 1051*f*
  sciatic reflex, 1049, 1049*t*, 1050*f*
  thoracic limb withdrawal reflex, 1049, 1050*f*
SPINK1, 621
Spironolactone
  chronic heart failure treated with, 64*t*, 67
  dilated cardiomyopathy treated with, 147
  onset of action, 67
Spleen
  abscesses of, 1412–1413
  biopsy of, 1416–1417
  blood storage in, 1413
  enlargement of. *see* Splenomegaly
  functions of, 1407
  masses of, 1413, 1415*f*
  radionuclide imaging of, 1416
  torsion of, 1413, 1416*f*
Splenectomy, 1228
Splenic fibrohistiocytic nodule, 1413–1414
Splenitis, 1412–1413, 1412*t*
Splenomegaly, 1407–1419
  anemia associated with, 1414–1415
  approach to, 1414–1418
  classification of, 1412*t*
  clinical features of, 1414
  clinicopathologic features of, 1414–1415
  congestive, 1412*t*
  cytologic evaluation of, 1416, 1417*f*
  definition of, 1411
  description of, 1382
  diffuse, 1409–1410
  disorders associated with, 1342*t*
  etiology of, 1411–1414
Splenomegaly *(Continued)*
  hyperplastic, 1411, 1412*t*
  imaging of, 1415–1416
  infectious, 1412*t*
  infiltrative, 1412*t*, 1413
  inflammatory, 1412*t*
  localized, 1411
  management of, 1418
  nonneoplastic causes of, 1413–1414
  pathogenesis of, 1411–1414
  pathogenetic classification of, 1412*t*
  signs of, 1410
Split heat cycle, 953–954
Spondylomyelopathy, 1065
Spontaneous intracranial hemorrhage, 1076
Spontaneous nystagmus, 1109
Spontaneous pneumothorax, 364–365, 376–377, 377*f*
Sporanox. *see* Itraconazole
Sporothrix schenckii, 1503*t*, 1542*f*
Sporothrix spp., 1533*t*–1535*t*, 1541
Sporozoites, 1520
Squamous cell carcinoma
  metastasis of, 1290*t*
  oral cavity, 448*t*
Squamous epithelial cells, 666, 667*f*
SRY gene, 1005
ST segment
  abnormalities of, 46–47, 48*b*
  definition of, 26*t*
  pseudodepression of, 47
Staining of specimens, 1258
Stanozolol, 336
Staphylococcus pseudointermedius, 1445
Statins, 913
Status epilepticus, 1098, 1104–1105, 1105*b*
Steatorrhea, 620
Stenotic nares, 279, 279*f*
Sterile hemorrhagic cystitis, 1284
Sternal lymphadenopathy, 926
Steroid-responsive meningitis-arteritis, 1118*f*, 1119–1123, 1119*b*
Steroid-responsive neutropenia, 1244
Steroid-responsive tremor syndrome, 1122
Stertor, 245, 271–272, 285
Stethoscope, traditional, 7, 7*f*
Stifle, arthrocentesis method in, 1191*f*
Stomach. *see also specific gastric entries*
  endoscopy of, 428*f*
  imaging of, 419–423
  radiographic imaging of, 420–422, 421*f*, 427*f*
  ultrasonography of, 420–422
Stomach disorders, 462–473. *see also specific gastric entries*
  bilious vomiting syndrome, 470
  gastric antral mucosal hypertrophy, 465, 466*f*
  gastric dilation/volvulus. *see* Gastric dilation/volvulus
  gastric foreign objects, 466–467
  gastric outflow obstruction/gastric stasis, 465–470
  gastritis. *see* Gastritis
  gastrointestinal ulceration/erosion, 470–471, 471*f*
  Helicobacter-associated disease, 464, 464*f*
  idiopathic gastric hypomotility, 469–470
  infiltrative gastric diseases, 471–472
  neoplasms, 471–472
  Ollulanus tricuspis causing, 465
  partial or intermittent chronic gastric volvulus, 469, 469*f*
  Physaloptera rara causing, 464–465
  pyloric stenosis, 465
  pythiosis, 420*f*, 472
Stomatitis, 450, 450*b*
  calicivirus-induced, 1496
  caudal, 1439*f*
Stomatocytosis, 1347*t*
Stool-softening agents, 445*t*
Strabismus, 1055–1057, 1058*f*, 1111*f*
Strain rate, 32
Stranguria, 735–736, 736*f*
Streptococcus group A, 1533*t*–1535*t*, 1542
Streptococcus pyogenes, 1542
Streptokinase, 227*b*, 229
Streptomycin, 1461–1462
"Stress" ulceration, 470
Stress-induced hyperglycemia, 833, 835, 837
Stress-induced neutrophilia, 1376
Stridor, 271, 285
Stroke. *see* Vascular accidents
Stromal tumor, 503
Strongyloides stercoralis, 1533*t*–1535*t*, 1536
Strongyloidiasis, 488
Struvite crystals, 668–669, 669*f*
Struvite uroliths, 718–719, 719*f*
Strychnine, 1099*b*
Stud dogs
  benign prostatic hyperplasia in, 1001–1003, 1002*f*, 1034*t*–1036*t*
  prostatic disorders in, 1001–1005
  testicular neoplasia in, 996–997, 996*f*–997*f*
Subaortic stenosis, 16–17
  β-blockers for, 107
  clinical features of, 106
  diagnosis of, 106–107
  dog breeds affected by, 102*t*
  echocardiography of, 106–107, 106*f*
  etiology of, 105–106
  pathophysiology of, 105–106
  prognosis for, 107
  radiographic findings, 103*t*
  severity of, 106
  treatment of, 107
Subarachnoid space, 1065
Subclinical bacteriuria, 705*t*, 706
Subfertility, infertility *versus*, 1003
Sublumbar lymphadenopathy, 1411*f*
Submucosal urethral bulking agents, 735
Sucralfate, 439–440, 439*t*, 515*t*–517*t*, 1255*t*–1256*t*
Sudden acquired retinal degeneration, 1087
Sulfadimethoxine, 444*t*, 515*t*–517*t*
Sulfasalazine, 515*t*–517*t*. *see also* Salicylazosulfapyridine
Sulfonamides, 781, 1439*t*
Sulfonylureas, 835
Summation gallop, 9
Superficial necrolytic dermatitis, 615
Suprascapular nerve, 1158*t*
Supraventricular premature complexes, 39
Supraventricular tachyarrhythmias
  acute therapy for, 80–82
  algorithm for, 81*f*
  mechanisms of, 78
  oral therapy for, 80
  refractory, 80
  vagal maneuver for, 82
Supraventricular tachycardias
  description of, 80
  electrocardiography of, 39
  reentrant, 39
Surgery
  canine thyroid neoplasia treated with, 803
  cardiac tumors treated with, 188
  cervical spondylomyelopathy treated with, 1153
  heartworm disease treated with, 207
  hyperthyroidism treated with, 798–799, 798*b*
Sustained atrial tachycardia, 42*f*
Swabs, nasal, 254, 259*f*
Swallowing reflex, 1060
Symmetric dimethylarginine, 659
Sympathomimetic drugs, 98
  canine chronic bronchitis treated with, 332
  in cats, 90*t*–91*t*, 327*b*
  in dogs, 90*t*–91*t*, 327*b*

Sympathomimetic drugs *(Continued)*
dosage of, 90*t*–91*t*
feline bronchitis treated with, 332
Syncope
cardiovascular causes of, 3
causes of, 2*b*
heart failure and, 1–3
test for, 2–3
Synovial fluid
collection and analysis of arthrocentesis for, 1189, 1190*f*–1191*f*
collection methods, 1190, 1190*f*
gross appearance, 1190–1192, 1192*f*
smear preparation, 1190, 1192*f*
culture of, 1193
description of, 1188–1189, 1189*t*
Synovial membrane biopsy, 1193
Syringomyelia, 1155, 1155*f*
Systemic arterial hypertension, 211–220
Systemic inflammatory response syndrome (SIRS), 432, 475
Systemic lupus erythematosus
antinuclear antibody test for, 1194, 1205, 1217, 1248
clinical features of, 1247
diagnosis of, 1194, 1247–1248
etiology of, 1247
lupus erythematosus test for, 1194, 1217, 1247
polyarthritis caused by, 1204–1205
signs of, 1248*t*
treatment of, 1248–1249
Systemic vasculitis, 1453
Systole, 8
Systolic anterior motion (SAM), 26
Systolic clicks, 9
Systolic murmurs
in cats, 159
description of, 9–11
Systolic time intervals (STIs), 27

T

T3. *see* Triiodothyronine
T4. *see* Thyroxine
Tachyarrhythmias
atrial fibrillation. *see* Atrial fibrillation
rapid irregular rhythms, 79
rapid regular rhythms, 79–80
sinus tachycardia, 79–80
supraventricular
acute therapy for, 80–82
algorithm for, 81*f*
mechanisms of, 78
oral therapy for, 80
refractory, 80
vagal maneuver for, 82
supraventricular tachycardia, 80–82
ventricular
acute therapy for, 82–84
algorithm for, 83*f*
in Boxers, 148
chronic oral therapy for, 84
description of, 82
refractory, 83–84
treatment of, 83*f*
Tachycardia, 37
atrial
causes of, 39
management of, 82
sustained, 42*f*
atrioventricular reciprocating, 44–45
paroxysmal AV reciprocating, 80–82
ventricular
acute therapy for, 82–84
chronic oral therapy for, 84
electrocardiography of, 41
intermittent paroxysms of, 42*f*
lidocaine for, 82
polymorphic, 41
treatment of, 82–84
Tachycardia-induced cardiomyopathy, 152
Tachypnea, 4
Tachyzoites, 1520
Tagamet. *see* Cimetidine
Tamsulosin, 733*t*–734*t*
Tapeworms, 487–488
Target organs, 211
Taurine, 151, 170–171
Telogen defluxion, 748*t*
Temporal muscle atrophy, 1223*f*
Tenesmus, 403–404, 403*b*, 1001
Tension pneumothorax, 376
Terbinafine, 386*t*–388*t*, 472, 1504*t*
Terbutaline sulfate, 386*t*–388*t*, 1034*t*–1036*t*
in cats, 90*t*–91*t*, 327*b*
description of, 98
in dogs, 90*t*–91*t*, 327*b*
dosage of, 90*t*–91*t*
uterine contractility suppression using, 962
Testes, canine, 996–997, 996*f*
Testicular neoplasia, 996–997, 996*f*–997*f*
Testicular parenchyma, 1001*f*
Testicular torsion, 991, 991*f*
Tetanus, 1181–1182, 1182*f*
Tetany
hypocalcemic, 928
puerperal, 975
Tetracyclines, 386*t*–388*t*, 1437*t*–1439*t*
Tetralogy of Fallot
clinical features of, 114
cyanosis caused by, 113–114
diagnosis of, 114
dog breeds affected by, 102*t*
etiology of, 113–114
pathophysiology of, 113–114
prognosis for, 114
treatment of, 114
Tetraparesis, 1045*t*
Tetraplegia, 1045*t*
Theophylline, 386*t*–388*t*
canine chronic bronchitis treated with, 327, 327*b*
feline bronchitis treated with, 332
idiopathic pulmonary fibrosis treated with, 351
Theriogenology, 935–952
definition of, 935
estrous cycle, 937–940, 938*t*. *see also* Estrous cycle; Estrus
prebreeding consultation, 935–937
Thiabendazole, 515*t*–517*t*
Thiacetarsamide, 200
Thiamine deficiency, 1078, 1115
Thiazide diuretics, 67
Thiobarbiturates, 49*b*
Thiopurine methyltransferase, 1223
Third-degree atrioventricular block, 43–44, 44*f*
Third eyelid protrusion, 1091, 1091*f*
Third heart sound, 9
Thoracic auscultation, 7, 285–286
Thoracic limb withdrawal reflex, 1049, 1050*f*
Thoracic radiography. *see also* Radiography
arrhythmogenic right ventricular cardiomyopathy, 171
arterial thromboembolism evaluations, 225
bacterial pneumonia findings, 343
caval syndrome, 202
chest tube placement verification using, 369
degenerative atrioventricular valve disease, 122, 123*f*
dorsoventral views of, 287
feline bronchitis, 330
general principles of, 287
lower respiratory tract disorders, 286
lungs
alveolar pattern, 290–292, 291*f*, 291*b*
atelectasis, 294, 294*f*
bronchial pattern, 290, 290*f*, 290*b*, 293*f*
cavitary lesions, 294, 295*f*
interstitial pattern, 292–293, 292*f*
lobes consolidation of, 293–294, 294*f*
Thoracic radiography *(Continued)*
pleural effusion, 360
radiographs of, 288–295
torsion of, 294–295
vascular patterns of, 288–290, 289*f*, 289*b*
Paragonimus kellicotti of, 345
peritoneopericardial diaphragmatic hernia, 174–175
pulmonary hypertension with shunt reversal, 115
pyothorax, 371
trachea, 287–288
vascular ring anomalies on, 116
ventrodorsal view of, 287
views of, 287
Thoracocentesis, 366–367
catheters for, 367
chylothorax treated with, 374
congestive heart failure treated with, 129
description of, 61
indications for, 366
pleural effusion treated with, 167, 360, 366
pneumothorax treated with, 345
spontaneous pneumothorax treated with, 377
technique for, 367
Thoracolumbar disk extrusion, 1138*t*, 1139–1141, 1140*f*, 1140*t*
Thoracoscopy, 312
with lung biopsy, 312
Thoracotomy, 367
exploratory, 373–374
Thorazine. *see* Chlorpromazine
Three-dimensional echocardiography, 33
Thrombin, 221–222
Thrombocytopenia
approach to, 1395–1396
causes of, 1393, 1395*b*
description of, 1278, 1345*t*
diagnostic tests for, 1218*t*–1219*t*
drug-associated, 1395
fever associated with, 1426*t*
immune-mediated
causes of, 1241*t*
classification of, 1240
clinical features of, 1240, 1242*f*
description of, 1396–1397
diagnosis of, 1240–1244, 1248*t*
etiology of, 1240
feline, 1244
immunosuppressive drugs for, 1243
physical examination of, 1240, 1242*f*
prognosis for, 1244
supportive care for, 1243–1244
treatment of, 1243
in lymphadenopathy, 1415
spontaneous bleeding caused by, 1387
Thrombocytosis, 1426*t*
Thromboelastography, 224, 231, 355, 1361, 1405*f*
Thromboembolic disease, 221–239
Thromboembolism
arterial
in cats, 224–230
anticoagulant therapy, 227*b*
antiplatelet therapy, 227*b*, 228
azotemia associated with, 225–226
cardiomyopathy as cause of, 224, 224*f*
causes of, 1405
clinical features of, 224–225, 225*f*, 226*b*
diagnosis of, 225–226
echocardiographic findings, 225
heparin for, 227*b*, 228
limb function after treatment for, 229–230
prognosis for, 226–230
prophylaxis against, 230
radiographic findings, 225
thrombolytic therapy for, 227*b*
treatment of, 226–230, 227*b*
Thromboembolism *(Continued)*
in dogs
clinical features of, 230–231
coagulation tests for, 231
diagnosis of, 231
diseases associated with, 230–233
echocardiographic findings, 231
physical examination findings, 231
prognosis for, 231–232
prophylaxis against, 232–233
radiographic findings, 231
thromboelastography for, 231
treatment of, 231–232
warfarin for, 232–233
prophylaxis against, 230, 232–233
caudal aortic, 1162–1163
coronary artery, 231
diagnosis of, 1405
diseases associated with, 223*b*
endothelial damage, 221
general considerations for, 221–224
in glomerular disease, 684–685
hypercoagulability secondary to, 223
in immune-mediated hemolytic anemia, 1237
pathophysiology of, 222–224
prevention of, 1237
pulmonary
abnormalities associated with, 355*b*
clinical features of, 355
computed tomography pulmonary angiography of, 356
D-dimer measurements, 355
description of, 194, 224, 354–356
diagnosis of, 355–356
fibrinolytic agents for, 356
heartworm disease as cause of, 201–203, 224
pleural effusion caused by, 360
postadulticide, 201–203
prevention of, 356
prognosis for, 356
selective angiography of, 356
treatment of, 356
sequelae of, 221
in spontaneous hyperadrenocorticism, 224
Thrombolysis, 222
Thrombolytic therapy, 227*b*
Thrombosis, 1405, 1405*f*
portal vein, 233
vena caval, 233
venous, 233–234
Thymomas, 1172
Thyroglobulin, 776*b*, 779
Thyroglobulin autoantibodies, 777, 956
Thyroid adenomas, 800
Thyroid carcinomas, 800
Thyroid gland
disorders of, 767–805
function tests, 774–779
antibody tests for lymphocytic thyroiditis, 779
baseline serum fT_4 concentration, 776–777
baseline serum thyroid-stimulating hormone concentration, 777–778, 778*f*
baseline serum triiodothyronine concentrations, 775–776, 776*b*
breed variations, 781–782
drugs that affect, 780–781, 781*t*
factors that affect, 779–782
overview of, 774–775, 775*f*–776*f*
thyroid stimulating hormone and thyrotropin-releasing hormone stimulation tests, 778–779
variables that affect, 777*t*
idiopathic atrophy of, 767
Thyroid hormones
autoantibodies, 769*t*, 776*b*
Greyhound levels of, 1363
secretion of, 774–775
Thyroid mass, 802*f*

Thyroid neoplasia, canine, 800–804
  cervical ultrasonography of, 801–802
  chemotherapy for, 803
  clinical features of, 800–802, 800*f*
  diagnosis of, 802
  etiology of, 800
  external beam radiation for, 803
  oral antithyroid drugs for, 803–804
  prognosis for, 804
  radioactive iodine for, 803
  signs associated with, 801*f*–802*f*, 801*b*
  surgery for, 803
  treatment of, 802–804, 802*f*
Thyroid scintigraphy, 794
Thyroidectomy, 796*t*, 798, 798*b*
Thyroid-stimulating hormone
  baseline serum concentration of, 777–778, 778*f*
  description of, 767
  Greyhound levels of, 1363
  recombinant human, 778–779
  serum concentration of, 777–778, 778*f*, 783
  stimulation tests, 778–779
Thyrotoxic cardiomyopathy, 790
Thyrotoxicosis, 784–785
Thyrotropin, 776*b*
Thyrotropin-releasing hormone
  description of, 767
  stimulation tests, 778–779
Thyroxine
  description of, 774–775
  free, 776–778, 776*b*, 778*f*, 787*f*, 792*f*, 793
  serum, 776*b*, 782, 787*f*, 791–793, 791*t*, 792*f*
Ticarcillin-clavulanate, 1437*t*–1438*t*
Tick paralysis, 1167*t*, 1169
Timolol, 94*t*
Tissue factor, 221, 1387
Tissue plasminogen activator, 222, 1388
Tissue procoagulants, 1401
To-and-fro murmurs, 11
Tocodynamometry, 962, 963*f*–964*f*, 969–974
Tocolytic agents, 962, 971*f*–972*f*
Tom, clinical conditions of, 990–1006
  balanoposthitis in, 992–993, 993*f*
  cryptorchidism in, 990–991, 991*f*
  paraphimosis in, 993–996, 994*f*
  persistent penile frenulum in, 992, 992*f*
  phimosis in, 993–996
  priapism in, 993–996, 994*f*–996*f*
  scrotal dermatitis in, 992, 992*f*
  testicular neoplasia in, 996–997, 996*f*–997*f*
  testicular torsion in, 991, 991*f*
  urethral prolapse in, 992
Tongue margin, 448*t*
Tongue tip necrosis, 697–698
Tonsil, 448*t*
Tooth root abscess
  carnassial, 245–246
  radiographic signs of, 249*b*
Torbugesic. *see* Butorphanol
Torbutrol. *see* Butorphanol
Torsades de pointes, 41
Torsemide, 66–67
Total dietary fiber, in veterinary therapeutic diets, 904*t*–906*t*
Total parenteral nutrition, for acute pancreatitis, 632
Toxemia, 967
Toxic hepatopathy, 580–582, 580*b*
Toxocara canis, 344, 1532–1536, 1533*t*–1535*t*
Toxocara cati, 1533*t*–1535*t*
Toxoplasma gondii, 298, 304*f*, 965–966, 1126, 1177, 1429, 1440*t*, 1445, 1521, 1522*f*, 1533*t*–1535*t*, 1537*f*, 1538
Toxoplasmosis, 965–966, 1118*t*
  canine, 1525
  central nervous system, 1126
  differential diagnosis of, 329*t*
  feline, 1521–1525
Toxoplasmosis *(Continued)*
  lung involvement, 343
  myocarditis caused by, 154
  treatment of, 1126
  zoonotic aspects of, 1524*b*
Trachea
  bronchoscopy of, 314*t*
  cervical, 287
  collapse of
    airway obstruction caused by, 380–381
    in cats, 334
    clinical features of, 334
    description of, 287
    diagnosis of, 334–336, 335*f*, 338
    etiology of, 333–334
    physical examination of, 334
    prognosis of, 337
    treatment of, 336–337
  cough associated with, 282
  disorders of, 283*b*, 321–339
    canine infectious tracheobronchitis. *see* Canine infectious tracheobronchitis
  examination of, 276
  hypoplastic, 288*f*
  radiographic diagnosis of, 288
  stenting of, tracheobronchomalacia, 336–337
Tracheal lumen, 288, 288*f*
Tracheal tubes, 384–385
Tracheal wash
  canine chronic bronchitis evaluations of, 326
  complications of, 298–300, 299*t*
  endotracheal technique for, 300–303
  feline bronchitis evaluations, 330–331
  heartworm disease evaluations, 206
  indications for, 298–300, 299*t*
  interpretation of results, 303–305, 304*f*
  specimen handling, 303, 303*f*
  techniques for, 300–303
  transtracheal technique for, 300–301, 301*f*–302*f*
Tracheobronchitis, canine infectious
  client communication challenges associated with, 321
  clinical features of, 322
  cough suppressants for, 323, 323*t*
  diagnosis of, 322–323
  etiology of, 321–322, 322*b*
  prevention of, 323–324
  prognosis for, 323
  treatment of, 323, 323*t*
  uncomplicated, 323
Tracheobronchomalacia, 381
  clinical features of, 334
  diagnosis of, 334–336, 335*f*
  etiology of, 333–334
  prevalence of, 334
  prognosis of, 337
  stanozolol for, 336
  tracheal stenting for, 336–337
  treatment of, 336–337
Traditional stethoscope, 7, 7*f*
Tramadol, 629*t*–630*t*, 974, 1196, 1197*t*, 1209*t*–1210*t*, 1268*t*, 1327*b*
Transcervical insemination, 947–948, 948*f*
Transendoscopic ultrasonography, 636
Transesophageal echocardiography, 32–33, 33*f*
Transfusion therapy, 1355–1358, 1357*t*
  complications of, 1358
Transfusion-associated lung injury (TRALI), 1358
Transient heart sounds, 7–9
  other, 9
Transient hypoparathyroidism, 764
Transitional cell carcinoma of bladder, 736
  metastasis of, 1290*t*
Transitional epithelial cells, 666–667, 667*f*
Transsphenoidal hypophysectomy, 753
Transtracheal catheters, 383*t*, 384
Transtracheal technique, for tracheal wash, 300–301, 301*f*–302*f*
Transudate pleural fluid, 361–363, 361*t*
Transudates, pathogenesis of, 519–521, 520*f*–521*f*
Transudative pericardial effusion, 177
Trauma
  diaphragmatic hernia caused by, 362–363
  head, 1075–1076
  laryngeal paralysis caused by, 277
  myocarditis caused by, 155
  peripheral vestibular disease caused by, 1114
  spinal cord. *see* Spinal cord, trauma to
  uterine, 976
Traumatic neuropathies, 1157, 1158*t*, 1159*f*
Traumatic pneumothorax, 376
Tremorgenic mycotoxins, 1099*b*
Tremors, 1183
Triaditis, 573
Triamcinolone, 1222*t*
Triatoma infestans, 1526
Tribrissen. *see* Trimethoprim-sulfadiazine
Trichomoniasis, 490–491, 490*f*
Trichuris vulpis, 485, 1536
Tricuspid dysplasia
  description of, 112
  dog breeds affected by, 102*t*
  echocardiographic findings, 112–113, 113*f*
  radiographic findings, 103*t*
Tricuspid insufficiency murmur, 11
Tricuspid regurgitation, 168
Trifexis. *see* Milbemycin
Trigeminal nerve, 1055, 1056*t*, 1057–1059, 1059*f*
  paralysis of, 1161–1162, 1162*f*
Triglycerides, 908
Triiodothyronine
  description of, 774–775
  free, 775*f*
  Greyhound levels of, 1363
  serum, 776*b*
  supplementation of, 793*f*
Trilostane, 749, 871–872, 872*f*, 896*t*–897*t*
Trimethoprim-sulfadiazine, 386*t*–388*t*, 444*t*, 515*t*–517*t*, 1126, 1185*t*–1186*t*, 1437*t*–1438*t*
Tritrichomonas foetus, 399, 413
Trochlear nerve, 1056*t*
Troponins
  cardiac, 13
  Greyhound levels of, 1363–1364
  I, 1363
Trypanosoma cruzi, 153–154, 1430, 1525–1526
Trypanosomiasis
  American, 1525–1526
  in dogs, 153–154
Trypomastigotes, 1526
Trypsin, 620
Trypsin activation peptide, 620
Trypsin-like immunoreactivity (TLI), 400*f*, 413, 538–539, 625–626, 639*b*
Trypsinogen, 621
Tube feedings
  enterostomy, 437
  gastrostomy, 436
  jejunostomy, 437
  nasoesophageal, 435, 437
  orogastric, 435
  pharyngostomy, 436
Tubular function, renal, 662–664, 663*t*
  fractional clearance of electrolytes, 664
  gradual water deprivation, 664
  osmolality, urine, 662–663
  urine specific gravity, 662–663
  water deprivation test, 663
Tumor(s)
  adrenal. *see* Adrenal tumors
  cardiac. *see* Cardiac tumors
  mast cell. *see* Mast cell tumors
  nasal. *see* Nasal tumors
  perianal gland, 506
Tumor lysis syndrome, 1276, 1286, 1286*f*
Tumor-associated erythrocytosis, 1368
Tunica albuginea, 994*f*
Turbinates, nasal
  computed tomography of, 250*f*
  radiographic imaging of, 247–248
Turbinectomy
  description of, 255
  rhinotomy with, 244
T wave
  abnormalities of, 48*b*
  description of, 26*t*, 47
Two-dimensional echocardiography, 20–22
  long-axis views, 21*f*, 23*f*
  in parasternal position, 20*f*–23*f*
  short-axis views, 20*f*, 22*f*
  speckle tracking, 32
  views on, 20–22
Tylan. *see* Tylosin
Tylosin, 443, 515*t*–517*t*, 1437*t*–1438*t*
Tympanic bullae, 247, 249*f*
Type I hypersensitivity, 1211, 1212*t*
Type II hypersensitivity, 1211–1212, 1212*t*
Type II intervertebral disk disease, 1148
Type III hypersensitivity, 1212, 1212*t*
Type IV hypersensitivity, 1212, 1212*t*
Tyrosine kinase inhibitors, 1333
Tyrosine kinase receptors, 1273

U

Ulcer(s)
  corneal, 258
  gastric, 426*f*
Ulcerative colitis
  granulomatous, 495
  histiocytic, 495
Ulnar nerve, 1158*t*
Ultra-low-fat diets, 435
Ultrasonography
  abdominal
    cancer staging using, 1288–1289
    hyperadrenocorticism evaluations, 862–864, 862*b*, 863*f*–865*f*
  acute kidney injury, 690*f*
  of alimentary tract, 415
  extrahepatic bile duct obstruction, 574*f*
  of hepatobiliary system, 549–553, 549*f*, 550*t*–551*t*, 551*f*–552*f*
  hypothyroidism in dogs, 774, 774*f*
  incidental adrenal masses on, 892
  of larynx and pharynx, 273
  lower respiratory tract disorders, 295, 296*f*
  lymphadenopathy, 1415
  neuromuscular system, 1064
  ovarian remnant syndrome findings, 983, 983*f*
  ovulation in bitch detected using, 943, 943*f*–944*f*
  pleural effusion evaluations, 360, 366
  postpartum endometritis, 977*f*
  pregnancy diagnosis using, 950, 950*f*
  priapism findings, 995*f*
  renal, 671
  septic prostatitis findings, 1003
  of small intestine, 420–422, 421*f*
  splenic mass, 1415*f*
  splenic torsion findings, 1416*f*
  splenomegaly, 1415
  of stomach, 420–422
  urinary incontinence, 731*f*, 736*f*
Umbilical hernias, 1020
Unasyn. *see* Ampicillin-sulbactam
Uncinaria stenocephala, 1533*t*–1535*t*, 1536
Unfractionated heparin, 228
Upper airway obstruction syndrome, 279, 280*f*
Upper motor neuron
  paresis, 1146*f*
  signs, 1039*f*–1040*f*, 1040

Upper respiratory infections, feline, 257–259
antibiotics for, 258, 1441*t*
clinical features of, 257
diagnosis of, 257–258
etiology of, 257
prevention of, 258–259
prognosis for, 259
treatment of, 258
Urate urolithiasis
in cats, 721
in dogs, 719–721, 720*f*, 720*b*
Urea, synthesis of, 658
Ureaplasma spp., 1441*t*, 1446, 1465
clinical findings of, 1465
diagnosis of, 1465–1466
epidemiology of, 1464–1465
etiology of, 1464–1465
prevention of, 1466
treatment of, 1466
zoonotic aspects of, 1466
Urecholine. *see* Bethanechol
Uremia, 649, 693, 697
Ureteral calculi, 715*f*, 716–719
Ureteral obstruction, 715
Ureteral stents, 716–717, 717*f*
Ureterolithiasis, 714–722
clinical signs of, 715, 715*f*
diagnostic imaging of, 715–716, 715*f*
medical treatment of, 716
surgical intervention for, 716–719
ureteral stents, 716–717, 717*f*
Ureters, ectopic, 730–732, 731*f*
Urethral bulking agents, 735
Urethral closure pressure, 735–736
Urethral obstruction, 725
Urethral occluder, 735*f*
Urethral plugs, 725, 725*f*
Urethral pressure profile, 672, 732*b*
Urethral prolapse, 992
Urethral sphincter mechanism incompetence, 732–735, 732*b*
Urethral stones, 736
Urethrocystoscopy, 672
Urethroliths, 712
Urinalysis, 544–545, 545*f*, 664–670
alimentary tract disease evaluations, 413
sediment examination, 665–670
Urinary bile acid concentration, 536
Urinary disorders
clinical approach to, 649–650
cystometrography of, 672
diagnostic imaging of, 671
dysuria, 652–653, 653*b*
hematuria, 650–652, 650*f*, 651*b*
history for, 649
microbiology of, 670–671
physical examination of, 649–650
polydipsia, 213, 649, 653–656, 654*t*–655*t*, 740–741, 741*t*
polyuria, 213, 653–656, 654*t*–655*t*, 740–741, 741*t*
radiography of, 671
renal biopsy of, 672–673
ultrasonography of, 671
urethrocystoscopy of, 672
urodynamic testing of, 672
Urinary incontinence
definitions of, 730–737
ectopic ureters as cause of, 730–732, 731*f*
overactive bladder as causes of, 736–737
overflow, 735–736
types of, 730–737
ultrasonography of, 731*f*, 736*f*
urethral closure pressure increases as cause of, 735–736
urethral sphincter mechanism incompetence, 732–735, 732*b*
Urinary tract, 1054
Urinary tract infections
in cats, 791
complicated, 705*t*
hyperadrenocorticism as cause of, 862
Urinary tract infections *(Continued)*
hyperthyroidism and, 791
microbiology of, 670–671
persistent, 705–706, 706*t*
refractory, 706*t*
relapsing, 706*t*
subclinical, 709
treatment of, 708–709, 1445–1446
Urinary tract zoonoses, 1542–1543
Urine
appearance of, 664
bilirubin in, 665
chemical properties of, 664–665
glucose in, 665
ketones in, 665
occult blood in, 665
pH, 664–665
physical properties of, 664
protein in, 665
sediment examination of, 665–670
casts, 667–668, 668*f*
crystals, 668–669, 669*f*–670*f*, 669*t*
epithelial cells, 666–667, 667*f*
organisms, 668, 669*f*
red blood cells, 666, 666*f*
white blood cells, 666, 666*f*
specific gravity of, 652, 662–664, 741, 743*f*, 745*f*, 861–862
Urine cortisol/creatinine ratio, 866*t*, 867, 867*f*–868*f*, 881, 881*t*
Urine protein-to-creatinine ratio, 661–662, 680–681, 698–699
Urodynamic testing, 672, 732
Urogenital disorders, 1025–1027, 1025*f*–1027*f*, 1441*t*
Urokinase, for arterial thromboembolism in cats, 227*b*, 229
Urokinase-type plasminogen activator, 1388
Urolith(s)
analysis of, 712
calcium oxalate, 717–718
removal of, 712–714, 713*f*–714*f*
struvite, 718–719, 719*f*
types of, 712
xanthine, 722
Urolithiasis, 712–723
calcium oxalate
dietary modifications for, 717–718, 718*b*
drug therapy for, 718
management of, 717*b*
prevention of, 717–718
cystine, 721–722
signs of, 712
silica, 721–722, 722*f*
urate
in cats, 721
in dogs, 719–721, 720*f*, 720*b*
xanthine, 722
Ursodeoxycholic acid
for lymphocytic cholangitis, 571–572
for neutrophilic cholangitis, 570
Ursodiol, 590
Usual interstitial pneumonia, 349–350
Uterine contractions
oxytocin effects on, 969–972
patterns of, 969
suppression of, terbutaline for, 962
Uterine inertia, 969
Uterus
postpartum disorders involving, 974–979
rupture of, 976
torsion of, 973*f*
trauma to, 976, 976*f*
Uveitis, lens-induced, 829

V

Vaccines and vaccinations
adverse reactions to, 1452
attenuated, 1451
autoimmunity and, 1214
Bordetella bronchiseptica, 1453, 1455
Borrelia burgdorferi, 1455
canine adenovirus, 1454–1455
Vaccines and vaccinations *(Continued)*
canine distemper virus, 1454–1455
canine infectious tracheobronchitis, 324
canine influenza, 1455
canine parvoviral enteritis, 478
canine parvovirus, 1454–1455
for cats, 1452–1454
Chlamydia felis, 1453
for dogs, 1454–1455
feline calicivirus, 258–259, 1453
feline herpesvirus, 258–259, 1453
feline immunodeficiency virus, 1454
feline infectious peritonitis, 1454
feline leukemia virus, 1453–1454
feline panleukopenia virus, 1453
immune response mechanism of, 1451–1455
immune-mediated hemolytic anemia secondary to, 1231
Leptospira interrogans, 1455
parainfluenza virus, 1455
pediatric, 1033, 1033*f*
rabies, 1125–1126, 1454–1455
rattlesnake, 1455
selection of, 1451–1452
types of, 1451
Vagal maneuver, 82
Vagina
artificial insemination through, 947
hyperplasia of, in bitch, 957–958, 958*f*
Vaginal cytology, 941*f*
Vaginal strictures, 980–982
Vaginitis, 1446
Vaginoscopes, 947–948, 948*f*
Vaginoscopy, 936–937, 936*f*–937*f*, 942, 943*f*
Vagolytic drugs, 97
Vagus nerve, 1056*t*, 1059–1060
Valium. *see* Diazepam
Valvular pulmonic stenosis, 9
Vascular accidents, 1076–1077
Vascular endothelial growth factor receptor, 1273
Vascular permeability edema, 357
Vascular rings
anomalies of, 116–117, 456–457, 458*f*
obstruction of, 452–453, 458*f*
Vasodilators
amlodipine, 71
heart failure treated with, 61–63, 64*t*, 71–72, 129
prazosin, 71
Vasopressin, 655–656
Vector borne disease, pregnancy loss and, 966
Vena caval syndrome. *see* Caval syndrome
Vena caval thrombosis, 233
Venipuncture, 1394
Venodilators, 71–72
Venous thrombosis, 233–234
Ventilation/perfusion ratio, 316
Ventilatory support, 385–386
Ventricular ectopy
in arrhythmogenic right ventricular cardiomyopathy, 148
Holter monitoring for, 143–144
Ventricular fibrillation, 41, 43*f*
Ventricular gallop, 9
Ventricular hypertrophy, 55
Ventricular outflow obstruction, 11, 105–109
Ventricular preexcitation, 44–45, 45*f*
Ventricular premature complexes, 77–79
compensatory pause associated with, 40
dilated cardiomyopathy and, 142
electrocardiography of, 40
treatment of, 83
Ventricular remodeling, 55
Ventricular septal defect
cardiopulmonary bypass for, 111
clinical features of, 110
diagnosis of, 110–111, 110*f*
dog breeds affected by, 102*t*
Ventricular septal defect *(Continued)*
echocardiographic findings, 110–111, 110*f*
electrocardiographic findings, 110
etiology of, 110
left-sided congestive heart failure associated with, 110
pathophysiology of, 110
prognosis for, 111
radiographic findings, 103*t*, 110
treatment of, 111
Ventricular tachyarrhythmias
acute therapy for, 82–84
algorithm for, 83*f*
in Boxers, 148
chronic oral therapy for, 84
description of, 82
refractory, 83–84
treatment of, 83*f*
Ventricular tachycardia
acute therapy for, 82–84
chronic oral therapy for, 84
electrocardiography of, 41
intermittent paroxysms of, 42*f*
lidocaine for, 82
polymorphic, 41
treatment of, 82–84
Ventricular wall stress, 55–56
Ventrodorsal view, 14
Verapamil
in cats, 90*t*–91*t*
characteristics of, 97
in dogs, 90*t*–91*t*
dosage of, 90*t*–91*t*
negative inotropic effects of, 97
Vertebral heart score (VHS), 14–15, 14*f*
Vertebral tumors, 1146
Very-low-density lipoproteins, 908
Vestibular ataxia, 1046*b*
Vestibular attacks, acute, 1116
Vestibulocochlear nerve, 1056*t*
Vestibulo-ocular reflex, 1056*t*
Vestibulovaginitis, chronic, 980–982, 980*f*–982*f*
Veterinary resources, for genetic disease, 936*b*
Veterinary therapeutic diets, 904, 904*t*–906*t*
Vetoryl. *see* Trilostane
Viagra. *see* Sildenafil citrate
Vibramycin. *see* Doxycycline
Vincristine, 1225*t*, 1229, 1255*t*–1256*t*
Viokase V, 440
Viral arthritis, 1201
Viral diseases, 1485–1501
canine distemper virus, 1485–1487
clinical features of, 1485–1486, 1486*t*
diagnosis of, 1125, 1486–1487
etiology of, 1485
medallion lesions from, 1486*f*
pathogenesis of, 1485
prevention of, 1487
signs of, 1124
treatment of, 1487
vaccination for, 1454–1455
zoonotic aspects of, 1487
feline coronavirus, 1488–1491
clinical features of, 1488–1489
diagnosis of, 1489–1490
enteric, 1488
epidemiology of, 1488
etiology of, 1488
prevention of, 1491
treatment of, 1490–1491
zoonotic aspects of, 1491
feline immunodeficiency virus. *see* Feline immunodeficiency virus
feline leukemia virus. *see* Feline leukemia virus
myocarditis in puppies caused by, 153
Viral enteritis, 443
Viral inclusion bodies, 1430
Viral myocarditis, 153
Viral pneumonias, 340–343
Virbac. *see* Aglepristone
Virbagen omega. *see* Interferon omega

Viruses, 1541–1542
Visceral larva migrans, 1532–1536
Visceral leishmaniasis, 1518–1519
Vision, 1055, 1056*f*
Vision evaluation, 1084
Vision loss, 1087–1089
  diagnostic approach to, 1087*f*
  Horner syndrome, 1089–1091, 1089*f*–1090*f*, 1089*b*, 1111*f*
  optic chiasm lesions, 1088
  optic disk lesions as cause of, 1087–1088
  optic nerve lesions as cause of, 1087–1088
  optic neuritis, 1087–1088, 1088*b*
  papilledema, 1088
  pupillary abnormalities and, 1084–1092
    general considerations in, 1084
  retinal lesions as cause of, 1087–1088
  sudden acquired retinal degeneration, 1087
Vitamin B, third eyelid protrusion, 1091, 1091*f*
Vitamin B_{12} (cobalamin), 515*t*–517*t*
Vitamin D, 759*t*, 765–766, 896*t*–897*t*, 928*b*, 934*t*
Vitamin K
  deficiency of, 1400
  forms of, 1400
Vitamins, serum concentrations of, 423–424
Voiding urohydropropulsion (VUH), 713–714, 714*f*
Volvulus
  gastric. *see* Gastric dilation/volvulus
  partial or intermittent chronic gastric, 469, 469*f*
Vomiting, 394–397, 395*f*
  acute, without hematemesis, 394–395
  antiemetics for, 438
  causes of, 394, 394*b*
  chemotherapy-related, 1280
  pancreatic disease and, 518
  regurgitation *versus*, 391–392, 391*t*
von Willebrand disease, 1356
von Willebrand factor, 772, 1355–1356, 1387, 1398–1399, 1398*f*
von Willebrand syndrome, 1398–1399
Voriconazole, 472, 1128, 1504*t*, 1507

W

Wandering pacemaker, 37, 40*f*
Warfarin
  arterial thromboembolism prophylaxis using, 229
  dosage of, 233, 233*t*
Water deprivation test
  dehydration during, 663
  description of, 653–655
  modified, for diabetes insipidus, 744, 744*t*
  tubular function, 663
Weakness
  esophageal
    acquired, 454–455, 454*f*
    congenital, 452–454, 453*f*
    description of, 393, 393*b*
  in heart failure, 1
  intermittent, 2–3, 2*b*
Weight loss
  in cats, 905*t*–906*t*
  commercial foods for, 904*t*–906*t*
  diabetes mellitus in dogs managed with, 816
Weight loss *(Continued)*
  in dogs, 904*t*
  gastrointestinal disorders, 405–407, 405*b*, 406*f*
  polyphagia with, 898–899, 899*t*
  rate of, 902
Weight reduction programs, 906
Wenckebach block, 43–44, 44*f*
West Nile Virus, 153
Wheelbarrowing, 1048*f*
Wheezes, 285–286
Whipworms, 485–486, 485*f*, 1536
White blood cell cast, 668*f*
White blood cell count, 1371
White blood cells
  in cerebrospinal fluid, 1071
  in urinary sediment, 666, 666*f*
Wobbler syndrome, 1065, 1151–1153, 1152*f*–1153*f*
Wolbachia pipientis, 193, 198
Wolff-Parkinson-White preexcitation, 44–45
Wright-Giemsa stain, 1258
Wyeth-Ayerst. *see* Metoclopramide

X

Xanthine uroliths, 722
Xanthomas, 910
X-linked muscular dystrophy, 1179
Xylazine, 49*b*, 515*t*–517*t*, 1185*t*–1186*t*

Y

Yersinia enterocolitica, 1533*t*–1535*t*
Yersinia pestis, 1460, 1461*b*, 1533*t*–1535*t*, 1541
Yorkshire Terrier, liver of, 585*f*

Z

Zantac. *see* Ranitidine
Zeniquin. *see* Marbofloxacin
Zinc sulfate, centrifugation, 1428*b*
Zithromax. *see* Azithromycin
Zoetis. *see* $PGF_{2\alpha}$
Zofran. *see* Ondansetron
Zonisamide, 1103, 1185*t*–1186*t*
Zoonoses, 1532–1545
  amoeba, 1538–1539
  bacteria, 1539
  cestodes, 1537
  ciliates, 1538–1539
  coccidians, 1537–1538
  definition of, 1532
  enteric, 1532–1539, 1533*t*–1535*t*
  flagellates, 1538–1539
  fungi, 1541
  genital tract, 1542–1543
  guidelines for avoiding transfer of, 1535*b*
  guidelines for pet owners to avoid transfer of, 1536*b*
  nematodes, 1532–1536, 1533*t*–1535*t*
  ocular, 1542
  respiratory tract, 1542
  shared environment, 1543
  shared vector, 1543
  urinary tract, 1542–1543
  viruses, 1541–1542
Zyrtec. *see* Cetirizine